• Clinical Research •

Clues to prognosis in anterior ischemic optic neuropathy: an optical coherence tomography angiography study

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Abstract

● **AIM:** To investigate optic nerve vascularization in patients with anterior ischemic optic neuropathy (AION) during the first 3mo after onset, using comprehensive ophthalmic assessments combined with optical coherence tomography (OCT) and optical coherence tomography angiography (OCT-A).

● **METHODS:** A prospective longitudinal observational study was performed with a 3-month follow-up. Clinical data recorded included age, sex, laterality of ocular involvement, AION subtype, previous history of ischemic events, cardiovascular risk factors such as high blood pressure, dyslipidemia, diabetes mellitus, smoking status, obstructive sleep apnea, and systemic treatments received. Functional, structural, and vascular examinations, including best corrected visual acuity (BCVA), visual field, OCT, and OCT-A, were performed at baseline, 1, and 3mo.

● **RESULTS:** Twenty-two subjects included 12 patients with AION and 10 healthy controls were enrolled. Mean age was 63.75±8.32y in the AION group and 61.80±5.04y in the control group (P=0.365). Gender and laterality distributions were comparable. AION patients showed significantly decreased optic nerve head perfusion at baseline (P=0.024) and 1mo (P=0.033). OCT revealed early thickening and subsequent atrophy of the peripapillary retinal nerve fiber layer and macular layers. OCT-A vascular parameters correlated significantly with 1-month BCVA (r=0.800, P≤0.05) and 3-month structural outcomes (r=0.807-0.835, P≤0.05).

● **CONCLUSION:** Vascular parameters derived from OCT-A can act as predictive markers for medium-term visual and structural outcomes in patients with ischemic optic neuropathy.

● **KEYWORDS:** vascularization; optic nerve; anterior ischemic optic neuropathy; optical coherence tomography angiography

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INTRODUCTION

Anterior ischemic optic neuropathy (AION) is a severe and potentially devastating condition affecting the optic nerve. It is characterized by acute interruption of posterior ciliary arteries, stopping optic nerve head blood flow[1]. Initially, it presents with disc edema due to the neural tissue infarction, typically resolving over 6-11wk, subsequently leaving optic disc pallor and neuronal atrophy that can be quantitatively assessed by non-invasive optical coherence tomography (OCT). Ultimately, patients experience significant visual impairment and visual field defects.

AION is classified into two main categories: arteritic anterior ischemic optic neuropathy (A-AION), which has an immune-mediated origin, and non-arteritic anterior ischemic optic neuropathy (NA-AION), associated with vascular risk factors[2]. AION results from a complex interplay of systemic and local factors. Important systemic risk factors include high blood pressure, diabetes mellitus, dyslipidemia, and obstructive sleep apnea. Locally, the anatomical configuration of the optic nerve, particularly a small or crowded ("disc-at-risk") hypermetropic optic disc, significantly increases susceptibility to this pathology.

Prognosis markedly differs between A-AION and NA-AION. Patients with A-AION typically have a poorer visual prognosis; however, immunosuppressive therapy aimed at reducing arterial inflammation can restore blood flow and help prevent recurrence. Conversely, NA-AION patients, who generally

have a more favorable prognosis but currently lack effective treatment, may still experience spontaneous partial visual improvement in approximately half of the cases. Unfortunately, no reliable objective vascular criteria currently exist to predict this potential improvement.

With the advent of optical coherence tomography angiography (OCT-A), a novel approach has emerged for non-invasive examination of ocular microvascular changes. OCT-A allows detailed assessment of optic nerve perfusion and structural alterations, offering deeper insights into underlying pathophysiological mechanisms and their correlation with clinical outcomes. In this context, the primary objective of the present study is to evaluate the relationship between OCT-A-derived vascular parameters and their association with clinical and structural outcomes, ultimately enhancing understanding of disease mechanisms and informing therapeutic strategies.

PARTICIPANTS AND METHODS

Ethical Approval A prospective, longitudinal, observational study was conducted over a three-month follow-up period at the Miguel Servet University Hospital in Zaragoza, following approval from the Ethics Committee for Research of the Autonomous Community of Aragon (PI23/157) and informed consent from all subjects, in compliance with the principles outlined in the Declaration of Helsinki.

Inclusion Criteria Patients over 18 years of age who visited the emergency department or were treated at the Neuro-ophthalmology Unit of Miguel Servet University Hospital, Zaragoza, between October 2023 and March 2024 after being clinically diagnosed with AION (A-AION and NA-AION), and healthy control subjects without significant ophthalmological pathologies.

Exclusion Criteria High refractive errors, including high myopia (more than 6 diopters), high hyperopia and astigmatism (more than 3 diopters), best corrected visual acuity (BCVA) <0.05, diagnosis of glaucoma, intraocular pressure (IOP) corrected by pachymetry greater than 21 mm Hg, atypical optic nerves, active inflammatory ocular diseases, history of morphological vascular anomalies, respiratory insufficiency disorders, and pregnant or lactating women.

Follow-up examinations were performed during the first week of ischemic onset, and at 1 and 3mo, and included functional, structural, and vascular assessments. To reduce variability, all data were recorded, and each test was conducted by the same eye technician. An experienced neuro-ophthalmologist then reviewed all acquisitions and recordings.

Clinical data recorded included age, sex, laterality of ocular involvement, AION subtype, previous history of ischemic events, cardiovascular risk factors such as high blood pressure, dyslipidemia, diabetes mellitus, smoking status, obstructive sleep apnea, and systemic treatments received.

Functional Tests BCVA was evaluated using Snellen charts after objective refraction measured by an autorefractometer (KR 800, Topcon, Japan) and subjective refraction using trial lenses. Contrast sensitivity was assessed with the Pelli-Robson test under controlled lighting conditions at 6 meters. Color vision perception was tested by counting correctly identified plates using the Ishihara test for near vision.

Visual field was assessed using Humphrey automated perimetry (Zeiss Meditec, Dublin, CA, USA), employing the Swedish Interactive Threshold Algorithm Standard (SITA Standard) strategy with the 30-2 program to evaluate the central 30° visual field relative to the macula, as it is the preferred method for studying altitudinal visual field defects characteristic of AION. Parameters recorded and analyzed included mean deviation (MD) in dB, pattern standard deviation (PSD) in dB, visual field index (VFI) percentage, false positives (FP), false negatives (FN), and fixation losses.

IOP was measured with Goldmann tonometry, corrected by pachymetry using the Ocuscan RxP contact pachymeter (Alcon Laboratories, Fort Worth, Texas, USA), which performs 10 measurements with a standard deviation below 5 μm, taking the mean value to minimize measurement error.

Structural Tests Neuroretinal thickness was evaluated using two OCT devices. Scans were performed using Spectralis OCT (Heidelberg Engineering, Germany) and Cirrus HD-OCT 5000 (Zeiss Meditec, Dublin, CA, USA), employing high-resolution protocols to ensure reproducibility and tracking functionality to assess the same retinal points over time in each patient. Protocols targeted monitoring axonal damage (through peripapillary retinal nerve fiber layer and macular analysis) and retinal involvement (*via* automated segmentation of the macular retinal layers). Macular sectors analyzed included superior, inferior, temporal, and nasal for OCT Cirrus, and the 9 sectors defined by the Early Treatment Diabetic Retinopathy Study: central, superior, inferior, nasal, and temporal (inner and outer rings) for OCT Spectralis. Optic nerve quadrants analyzed included superior, inferior, nasal, and temporal for OCT Cirrus, with additional superior and inferior temporal and nasal quadrants for OCT Spectralis.

Vascular Tests OCT-A was conducted to evaluate optic nerve perfusion and surrounding microvasculature. To ensure image quality and reproducibility, all scans were obtained in the morning with the patient seated and illuminate controlled. Images were reviewed by an ophthalmologist to rule out motion artifacts or segmentation errors. If any artifacts were detected, the image was discarded, and the acquisition was immediately repeated. Images were acquired using the AngioPlex® protocol available on the Cirrus HD-OCT 5000 (Zeiss Meditec, Dublin, CA, USA), and analyzed using specialized software that automatically segments vascular

networks within a 4.5 mm×4.5 mm cube centered on the optic nerve head. Vascular parameters such as perfusion percentage and flow index obtained from the radial peripapillary capillaries (RPC) network provided by the device were analyzed.

Simultaneously with OCT-A, pulse rate and oxygen saturation were monitored using a pulse oximeter (Sonosat F03P, Jiangsu Konsung Medical Equipment Co., Ltd., China), and blood pressure was measured using an automatic blood pressure monitor (OMRON Healthcare Co., Ltd., Kyoto, Japan).

All assessments were conducted in the morning to control for circadian rhythm-related variations.

Statistical Analysis Collected data were analyzed using IBM SPSS Statistics version 22.0, calculating means, standard deviations, and *P*-values for each variable. Normality was confirmed with the Kolmogorov-Smirnov test. Given that all variables were normally distributed, Student's *t*-test was applied to compare group means, and Pearson correlation analysis (considering only strong correlations $r>0.8$) was conducted to explore relationships among functional, structural, and vascular parameters. Statistical significance was set at $P\leq0.05$.

RESULTS

General Population Data The study population consisted of 22 subjects: 12 patients diagnosed of AION (both A-AION or NA-AION) and 10 healthy controls. The mean age of patients with AION was 63.75±8.32y, which did not significantly differ from the control group (61.80±5.04y; $P=0.365$). Gender (55% male) and eye laterality (50% right) distribution was homogeneous. NA-AION represented 91.6% of cases.

Regarding systemic factors, 45% of patients presented dyslipidemia and 13.6% were smokers. The 80% of patients did not have history of diabetes mellitus or obstructive sleep apnea, and only 4.5% of patients were receiving continuous positive airway pressure therapy. None of the participants exhibited ocular hypertension or morphological anomalies that might influence diagnostic outcomes.

Functional Results Both AION patients and control subjects had mild hyperopia and low astigmatism. Patients with AION exhibited significantly reduced BCVA at baseline (0.72±0.33 *vs* 0.97±0.05; $P<0.001$) compared to controls, with progressive recovery over three months (0.87±0.22; $P=0.069$). Similarly, contrast sensitivity and correct responses on Ishihara color vision test were reduced, achieving statistical significance by the third-month follow-up ($P=0.035$ and $P<0.001$, respectively). Patients with AION exhibited higher IOP values at one month (18.00±1.93 *vs* 16.00±1.77 mm Hg; $P=0.014$), although, they never reached levels indicative of ocular hypertension. From disease onset, patients with AION presented significantly worse MD values in automated perimetry testing (-9.25±9.19 *vs* -0.57±1.16 dB; $P<0.001$), with a stabilization trend observed at the third month ($P=0.243$). Nevertheless, the VFI remained consistently lower in patients throughout the study period. Furthermore, visual field reliability indices were significantly worse, particularly at disease onset ($P<0.001$; Table 1).

Structural Results Structural analysis of the optic nerve head was performed using two OCT devices. Both instruments revealed an increased thickness in all peripapillary retinal nerve fiber layer (pRNFL) sectors in AION patients at disease onset. With the Cirrus OCT, this increase was statistically significant across all sectors, whereas OCT Spectralis showed significant thickening in fewer sectors. At one month, OCT Cirrus maintained significant thickening in the inferior sector, and both devices identified a trend shift toward atrophy in superior and temporal sectors. The inferior sector displayed prolonged thickening before transitioning to significant thinning, while the superior sector was the first to show significant atrophy by the third month. Subsequently, atrophy was confirmed at three months by both OCT devices: in the superior sector (Cirrus) and in the superior nasal sector (Spectralis; $P\leq0.001$; Figure 1A).

OCT Spectralis provided further structural analysis by individually assessing the macular retinal ganglion cells through segmentation of their axons within the macular retinal nerve fiber layer (mRNFL) and their somas within the ganglion cell layer (GCL). Interestingly, Spectralis OCT revealed early and uniform atrophy of the GCL from disease onset, remaining stable up to the third month ($P\leq0.001$). In contrast, mRNFL initially exhibited thickening in early stages (inner-superior and outer temporal; $P\leq0.001$), later evolving toward atrophy (outer nasal and outer inferior sectors; $P\leq0.001$; Figure 1B; Table 2).

Structural Vascular Results Patients with AION exhibited significantly reduced optic nerve head perfusion compared to healthy controls, as measured by OCT-A at disease onset (43.50%±1.93% *vs* 44.95%±1.50%; $P=0.024$) and at one month follow-up (42.75%±3.32% *vs* 44.70%±1.34%; $P=0.033$). Additionally, patients showed elevated pulse rates (76.83±12.36 *vs* 65.78±11.14 bpm; $P=0.017$) and reduced oxygen saturation (97.42%±2.10% *vs* 98.56%±0.51%; $P=0.035$) at disease onset compared to controls. However, these vascular parameters did not remain statistically significant at subsequent evaluations. The flow index was slightly lower, and blood pressure was slightly higher among AION patients, but these differences did not reach statistical significance at any time point during follow-up (Table 3).

Finally, an analysis was performed to identify functional, structural, and vascular parameters exhibiting strong and significant correlations in patients with AION, and to identify vascular parameters capable of predicting visual prognosis three months after the ischemic event.

Table 1 Functional test

Functional tests	Groups	Baseline	*P*	1mo	*P*	3mo	*P*
Refraction							
Sphere (D)	Control	0.75±1.47	0.803	0.63±1.54	0.941	0.71±1.58	0.855
	AION	0.62±1.14		0.59±0.88		0.61±1.05	
Astigmatism (D)	Control	-0.64±0.28	0.618	-0.76±0.43	0.312	-0.79±0.32	0.166
	AION	-0.56±0.52		-0.56±0.49		-1.02±0.50	
Axis (°)	Control	93.19±32.04	0.749	101.00±37.24	0.379	95.25±33.21	0.706
	AION	98.17±49.28		87.63±28.35		90.73±25.28	
Visual acuity							
BCVA (Snellen)	Control	0.97±0.05	<0.001[a]	0.98±0.05	0.070	0.97±0.05	0.069
	AION	0.72±0.33		0.75±0.35		0.87±0.22	
Uncorrected	Control	0.69±0.31	0.047	0.64±0.28	0.461	0.67±0.29	0.461
	AION	0.43±0.33		0.55±0.33		0.53±0.41	
Contrast sensitivity	Control	1.65±0.13	0.101	1.75±0.31	0.119	1.72±0.17	0.035
	AION	1.59±0.19		1.60±0.31		1.45±0.51	
Ishihara test	Control	0.98±0.03	0.238	0.99±0.02	0.505	1.00±0.00	<0.001[a]
	AION	0.96±0.05		0.98±0.03		0.96±0.05	
IOP (mm Hg)	Control	16.60±2.06	0.601	16.00±1.77	0.014[a]	16.15±1.94	0.264
	AION	17.00±2.09		18.00±1.93		17.00±2.31	
Pachymetry (μm)	Control	550.95±36.14	0.454	548.35±38.89	0.844	555.20±39.62	0.960
	AION	538.83±54.39		544.75±53.19		555.85±28.69	
Adjusted IOP (mm Hg)	Control	16.60±2.06	0.601	16.00±1.77	0.014[a]	15.15±1.94	0.364
	AION	18.00±2.09		18.00±1.93		16.00±2.31	
Visual field 30-2							
MD (dB)	Control	-0.57±1.16	<0.001[a]	-0.45±0.91	<0.001[a]	0.08±1.63	<0.001[a]
	AION	-9.25±9.19		-6.49±3.73		-7.50±10.06	
PSD (dB)	Control	2.08±0.65	<0.001[a]	1.91±0.45	<0.001[a]	2.52±1.37	0.243
	AION	6.75±2.89		6.89±3.74		3.81±3.43	
VFI (%)	Control	98.85±1.18	<0.001[a]	98.63±2.24	<0.001[a]	99.18±0.95	<0.001[a]
	AION	75.60±28.96		87.33±10.42		77.23±32.18	
FP (%)	Control	3.00±3.55	0.047	2.47±2.72	0.269	3.53±4.58	0.682
	AION	6.60±5.96		1.17±1.16		2.92±3.04	
FN (%)	Control	1.30±2.10	<0.001[a]	1.63±2.79	<0.001[a]	3.35±4.38	0.199
	AION	18.00±13.20		15.50±7.66		6.92±9.92	
FL	Control	0.08±0.08	0.022	0.11±0.08	0.454	0.09±0.07	0.147
	AION	0.19±0.16		0.15±0.19		0.71±1.58	

BCVA: Best-corrected visual acuity; IOP: Intraocular pressure; AION: Anterior ischemic optic neuropathy; MD: Mean deviation; PSD: Pattern standard deviation; VFI: Visual field index; FP: False positives; FN: False negatives; FL: Fixation losses; D: Diopter. [a]Statistical significance which outperforms the Bonferroni correction for multiple comparisons ($P \leq 0.003$) when we compared healthy group *vs* AION group. Baseline: 1wk.

At disease onset, BCVA and pRNFL inferior sector thickness, measured by OCT Cirrus, correlated significantly with the flow index (r=0.800 and r=0.902, respectively; $P \leq 0.05$). One month after onset, BCVA remained significantly correlated with the flow index (r=0.837; $P \leq 0.05$). At three months, perfusion index was significantly correlated with RNFL thickness in the superior-nasal and superior sectors (r=0.835 and r=0.807, respectively; $P \leq 0.05$) and macular GCL thickness, both measured by OCT Spectralis (r=0.832; $P \leq 0.05$), highlighting structural implications. No strong significant correlations were found between visual fields and OCT-A parameters.

DISCUSSION

The primary objective of this study was to analyze optic nerve vascularization in patients diagnosed with AION and to determine the correlation among various functional, structural and vascular parameters through ophthalmological assessment using OCT-A during the initial three months following disease onset.

NA-AION is the most common subtype, typically described as being more frequent in hyperopic males aged around 50y. This predominance of NA-AION was also observed in our cohort; however, our sample displayed a homogeneous

Table 2 Structural test using Spectralis optical coherence tomography of control and AION groups and comparison of both groups in three different times: in baseline (1wk), 1, and 3mo of follow-up

OCT Spectralis	Groups	Baseline	*P*	1mo	*P*	3mo	*P*
Peripapilar RNFL (µm)							
Global	Control	103.55±13.22	0.016	102.75±12.49	0.895	101.00±12.94	0.058
	AION	130±42.44		100.67±36.31		83.86±30.82	
Superior nasal	Control	125±22.72	0.112	123.85±22.53	0.708	119.33±20.36	<0.001
	AION	159.11±88.39		119.17±38.09		83.29±42.29	
Nasal	Control	66.10±10.89	0.036	67.15±01.08	0.977	67.83±11.06	0.793
	AION	83.22±31.22		67.33±21.87		69.29±15.30	
Inferior nasal	Control	137±17.68	0.050	139.60±17.30	0.677	137.17±17.53	0.179
	AION	161.89±49.21		133.83±54.85		121.29±40.74	
Inferior temporal	Control	113.30±26.90	0.387	110.50±23.28	0.511	104.83±19.89	0.704
	AION	140.67±88.37		119.67±46.10		99.00±57.61	
Temporal	Control	87.25±22. 21	0.050	83.20±15.43	0.849	81.83±16.89	0.070
	AION	121.67±70.14		81.50±28.50		63.43±31.57	
Superior temporal	Control	145.20±28.87	0.274	147.80±28.65	0.516	144.33±29.67	0.017
	AION	170.78±94.96		135.17±70.94		100.57±55.15	
Macular RNFL (µm)							
Central	Control	13.40±1.98	0.941	13.60±1.73	0.206	13.55±2.01	0.132
	AION	13.50±2.55		12.38±3.29		12.21±3.04	
Inner nasal	Control	21.40±2.58	0.154	22.20±1.91	0.402	21.25±1.86	0.021
	AION	23.40±4.94		21.38±3.16		19.43±2.50	
Outer nasal	Control	47±5.73	0.148	48.60±4.33	0.161	47.55±4.19	<0.001
	AION	58.60±15.33		45.00±8.99		39.71±9.71	
Inner superior	Control	23.80±2.93	<0.001	24.45±2.48	0.051	22.95±3.34	0.251
	AION	24.80±2.74		22.25±2.82		21.57±3.43	
Outer superior	Control	37.80±4.29	0.126	38.10±4.30	0.579	37.20±3.76	0.010
	AION	40.70±5.58		36.75±8.51		30.93±9.29	
Inner temporal	Control	17.70±1.56	0.020	17.85±1.08	0.159	17.60±0.99	0.319
	AION	19.20±1.68		18.63±1.68		17.07±2.02	
Outer temporal	Control	19.60±1.27	<0.001	19.60±1.14	0.121	19.20±1.10	0.854
	AION	20.56±0.73		30.38±1.18		19.29±1.59	
Inner inferior	Control	26.25±3.13	0.490	27.25±1.80	0.010	26.05±1.50	0.041
	AION	25.30±4.19		23.00±4.14		23.86±4.27	
Outer inferior	Control	40.05±5.15	0.685	40.70±3.63	0.367	40.75±3.97	<0.001
	AION	41.00±7.44		38.25±10.74		33.64±8.57	
Center	Control	2.80±3.19	0.536	4.00±4.83	0.184	3.40±4.25	0.331
	AION	3.80±6.16		1.38±3.89		5.14±6.06	
Center min	Control	0.55±1.76	0.722	0.30±1.13	0.464	0.25±1.18	0.801
	AION	0.00±0.00		0.00±0.00		0.36±1.33	
Center max	Control	26.80±4.44	0.163	26.10±2.40	0.245	27.90±6.76	0.797
	AION	30.90±11.32		28.13±6.77		27.36±4.70	
Macular GCL (µm)							
Central	Control	17.25±5.19	0.941	18.15±5.16	0.030	18.10±5.22	0.137
	AION	17.08±7.44		13.25±4.89		15.14±6.04	
Inner nasal	Control	51.00±4.62	0.034	51.25±5.02	0.028	51.50±5.34	0.023
	AION	45.25±9.99		42.88±14.41		43.50±13.66	
Outer nasal	Control	38.55±4.82	0.148	38.15±4.95	0.308	38.20±5.21	0.112
	AION	36.17±3.54		35.88±5.91		34.64±7.50	
Inner superior	Control	52.25±4.79	<0.001	52.10±4.99	<0.001	52.35±4.83	<0.001

Table 2 Structural test using Spectralis optical coherence tomography of control and AION groups and comparison of both groups in three different times: in baseline (1wk), 1, and 3mo of follow-up (continued)

OCT Spectralis	Groups	Baseline	*P*	1mo	*P*	3mo	*P*
	AION	45.25±9.06		42.00±12.33		43.71±12.61	
Outer superior	Control	36.30±4.34	<0.001	35.60±3.56	0.017	36.15±4.37	<0.001
	AION	32.25±3.01		31.38±3.56		30.64±6.31	
Inner temporal	Control	47.35±4.86	<0.001	47.30±5.32	<0.001	47.50±4.63	<0.001
	AION	41.25±7.51		36.75±10.19		37.93±11.08	
Outer temporal	Control	38.30±5.01	<0.001	37.65±5.93	0.017	38.35±5.04	<0.001
	AION	30.92±4.50		31.00±7.03		31.71±6.69	
Inner inferior	Control	52.40±4.19	<0.001	52.00±4.17	0.012	52.15±4.44	0.019
	AION	47.08±6.05		44.63±10.54		44.86±12.21	
Outer inferior	Control	32.40±3.97	0.480	32.00±4.20	0.637	32.25±4.13	0.445
	AION	31.33±4.27		31.25±2.49		31.00±5.29	
Center	Control	6.40±5.57	0.536	6.60±6.79	0.153	6.80±6.24	0.977
	AION	7.83±7.32		2.88±3.31		6.86±4.42	
Center min	Control	1.20±1.61	0.226	1.30±2.18	0.643	1.30±2.27	0.437
	AION	0.58±0.79		0.88±1.73		0.79±1.18	
Center max	Control	44.65±8.66	0.146	44.05±8.68	<0.001	44.90±9.30	0.111
	AION	39.42±11.05		30.63±12.19		38.86±12.18	

OCT: Optical coherence tomography; RNFL: Retinal nerve fiber layer; GCL: Ganglion cell layer; AION: Anterior ischemic optic neuropathy. We have applied the Bonferroni correction for multiple comparison in OCT parameters of the macular RNFL and GCL, and we have considered significant differences under *P* value of 0.004 for these parameters and 0.007 for peripapilar RNFL.

Table 3 Vascular tests of control and AION groups and comparison of both groups in three different times: in baseline (1wk), 1, and 3mo of follow-up

Vascular tests	Groups	Baseline	*P*	1mo	*P*	3mo	*P*
OCT-A							
RNFL (μm)							
Superior	Control	121.85±20.79	0.047	122.70±21.18	0.574	119.00±22.26	0.040
	AION	153.80±63.01		116.50±30.30		96.17±33.71	
Nasal	Control	69.35±16.62	<0.001[a]	70.75±13.20	0.650	64.63±10.93	0.961
	AION	100.30±34.86		74.67±30.80		64.42±11.05	
Inferior	Control	118.60±17.74	0.016	117.70±16.48	<0.001[a]	115.81±16.33	0.213
	AION	158.70±66.36		140.67±62.08		104.75±29.18	
Temporal	Control	70.25±14.75	0.018	70.00±13.36	0.135	74.50±17.46	0.151
	AION	90.70±30.10		44.70±21.43		65.67±12.68	
Perfusion (%)	Control	44.95±1.50	0.024[a]	44.70±1.34	0.033[a]	44.89±1.60	0.081
	AION	43.50±1.93		42.75±3.32		43.33±3.08	
Flow index	Control	0.43±0.04	0.253	0.42±0.03	0.194	0.42±0.10	0.799
	AION	0.39±0.13		0.38±0.16		0.41±0.06	
Blood presure (mm Hg)	Control	10.11±2.65	0.238	10.18±2.71	0.189	10.27±2.41	0.414
	AION	11.40±3.29		11.81±3.32		11.06±3.18	
Beats per minute (bpm)	Control	65.78±11.14	0.017[a]	71.28±14.85	0.133	76.22±12.93	0.974
	AION	76.83±12.36		81.33±8.47		76.38±14.76	
O_2 saturation	Control	98.56±0.51	0.035[a]	95.94±2.98	0.576	97.72±1.07	0.214
	AION	97.42±2.10		97.67±1.36		98.15±0.69	

We have applied the Bonferroni correction for multiple comparison in OCT-A parameters of the RNFL, and we have considered significant differences under *P* value of 0.012 for these parameters. OCT-A: Optical coherence tomography angiography; RNFL: Retinal nerve fiber layer; O_2: Oxygen; bpm: Beats per minute; AION: Anterior ischemic optic neuropathy. [a]Statistical significance (*P*≤0.05 and 0.012 for RNFL parameters of the OCT-A).

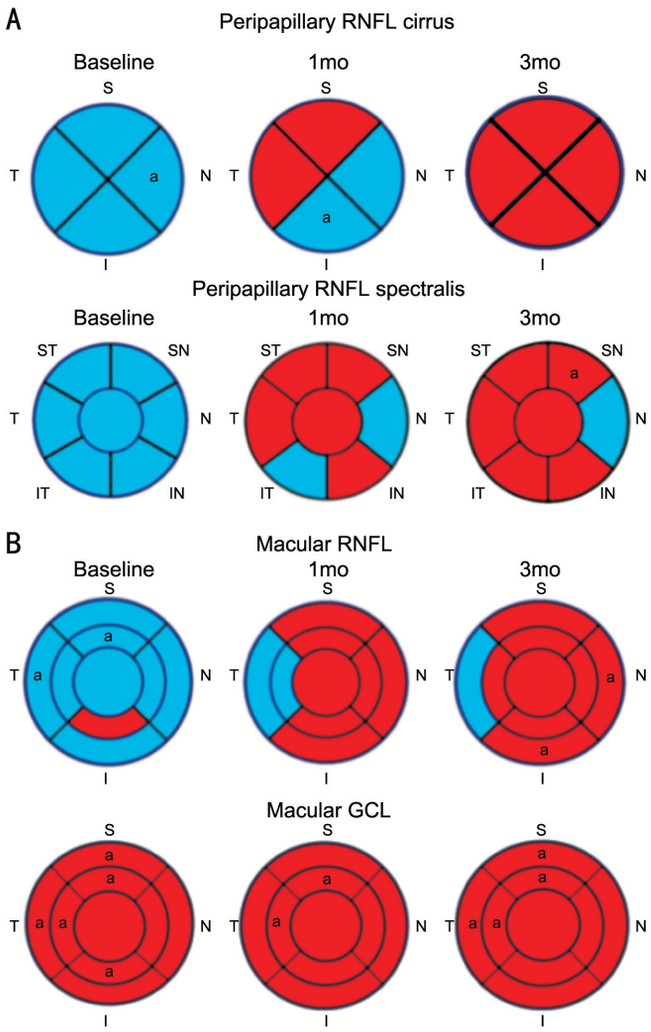

Figure 1 Neuroretinal structural analysis in patients with anterior ischemic optic neuropathy using OCT A: Optic nerve head structural assessment using retinal nerve fiber layer (RNFL) thickness, measured by OCT Cirrus and OCT Spectralis. B: Macular analysis of retinal ganglion cell axon (macular RNFL) and soma (GCL) thickness using OCT Spectralis. Colours: In blue: Thickening of the layer; In red: Thinning of the layer. GCL: Ganglion cell layer; mRNFL: Macular retinal nerve fiber layer; S: Superior; T: Temporal; I: Inferior; N: Nasal; SN: Superior nasal; IN: Inferior nasal; OCT: Optical coherence tomography. [a]Statistical significance (P≤0.05). Baseline: 1wk.

sex distribution. Regarding cardiovascular risk factors, most patients did not present the traditionally described conditions, with dyslipidemia being the most prevalent risk factor[3-4]. These discrepancies may reflect local demographic characteristics.

Functional evaluation demonstrated that BCVA was lower in the AION group from baseline, with slight improvement by the third month[5]. Visual field defects persisted throughout follow-up, although global sensitivity indices showed some improvement by month three, even approaching values seen in healthy controls regarding pattern standard deviation. These findings suggest that pattern standard deviation may serve as an early prognostic parameter of visual field recovery and visual quality. Conversely, contrast sensitivity and color perception remained impaired up to three months, indicating these functional parameters may recover less completely or at a slower rate. This could indicate different mechanisms of visual recovery (neural *vs* vascular). Perhaps vascular failure is more related to the loss of BCVA, whereas neural damage established after ischaemia causes deterioration of inner retinal cells (parvocellular cells, *etc*.) resulting in worse colour or detail perception.

Neuroretinal structural changes in the optic nerve head were analyzed using the pRNFL protocol with two different OCT devices (Cirrus and Spectralis). Both OCT systems provided highly similar and statistically significant results at disease onset (1wk) and at the three-month follow-up.

The optic nerve head is supplied by two posterior ciliary arteries supplying the superior and inferior poles. At one month we observed a shift toward atrophy in the superior sectors of the pRNFL, while the inferior sectors remained thickened. Coincident with our study, several papers demonstrated loss of peripapillary capillary layers and retinal nerve fibers predominantly in the superior sectors. And changes in vascular, immune and neural structures correlated with visual field defects[6-8]. Up to one month, there seems to be a transient period during which therapeutic interventions could be particularly effective in protecting the retinal ganglion cells in the lower sector of the optic disc. By the third month, the initial pRNFL edema had resolved, progressing to significant atrophy, reflecting the degenerative process associated with AION[9-10].

Additionally, the analysis of the GCL revealed a uniform thinning from the onset of the ischemic event (1wk). Based on our findings, early vascular damage leads to GCL atrophy, which remains stable by the third month and is likely irreversible. This retinal ganglion cell damage coincided with impairments in color vision and contrast sensitivity, functions primarily mediated by ganglion cells[11].

Studies in animal models of ischemic optic neuropathy show that ganglion cell loss occurs in two phases: a rapid initial phase (first 2wk) and a slow and sustained phase. This indicates that degeneration is not linear, but starts with massive apoptosis followed by progressive degeneration, possibly by atrophy of the supporting tissue or late apoptosis. In addition, after an experimental ischemic event, optic disc swelling and fluorescein leakage are observed, evidencing acute perfusion disturbance on day 1. And spectral-domain optical coherence tomography (SD-OCT) revealed significant thickening of the GCL on day-1 after ischemia followed by gradual thinning that plateaued by week-3[12]. Our study revealed correlation between microvascular reduction and thinning of pRNFL (at

baseline -1wk- and 3mo) and GCL (3mo) directly supports this causal relationship.

The ability of SD-OCT to segment and measure individual retinal layers is the technological cornerstone that makes it possible to investigate the timing of thinning in the AION in patients. Without this precision, the distinction between cell body and axon thinning would be unfeasible. Different studies in humans have demonstrated an early thinning of the GCL. De Dompablo *et al*[13] reported significant minimal ganglion cell-inner plexiform layer (GCIPL) thinning as early as 2.2d after symptom onset, with more than 50% of affected eyes showing thinning within the first week. Kupersmith *et al*[14] observed a permanent reduction in GCL thickness within the first month, with some patients developing thinning within 2 to 3wk. A key prospective study by Akbari *et al*[15] concluded that GCIPL thinning was first evident at 1mo after the onset of AION symptoms and persisted for at least 3mo. In our study and coinciding with previous studies, thinning of the GCL was detected from the onset of symptoms (1wk), the greatest loss of thickness was observed at 1mo and stabilization of atrophy at 3mo.

The variability in the time to onset of GCIPL thinning (from a few days to a month) between different studies is a critical finding. This discrepancy can be attributed to differences in the OCT methodologies employed, including the different devices (*e.g.*, Avanti SD-OCT *vs* Cirrus OCT *vs* Spectralis Heidelberg) and the layer segmentation algorithms used. This underscores that while ganglion cell (GC) thinning is consistently early, the accuracy of its detection may depend on the specific technology used.

Although OCT is invaluable in detecting both acute edema and chronic atrophy, early edema may mask early RNFL loss, highlighting the advantage of GCL as a more reliable irreversible neuronal injury biomarker in the acute phase[9]. In addition, early-stage GCIPL thickness appears to have long-term predictive value by correlating with visual acuity. This confers GCIPL greater sensitivity and specificity for early detection of irreversible damage. Other studies also demonstrated that the decrease in GCL thickness occurs earlier than the thinning of peripapillary RNFL in AION, the latter not being detectable until the third month after the ischemic event. The most pronounced thinning of GCIPL+inner plexiform layer (IPL) was observed in the subacute phase (1-2mo), while RNFL only began to show significant thinning around the third month, when the thinning of GCIPL+IPL has largely stabilized, with minimal further reduction after this period, as in our study[15].

In summary, the early thinning pattern of the GCL preceded structural changes in both peripapillary and macular RNFL, suggesting that GCL atrophy may serve as an earlier biomarker of neuronal damage and visual dysfunction in AION. The importance of dendritic integrity in optic neuropathy disease models has been established through the observation that loss of complexity in RGC dendritic trees occurs prior to axonal loss[16]. Our findings demonstrate that GCL atrophy occurs early and remains stable, while RNFL first thickens and then atrophies. This is consistent with the pathology of AION and is useful as a key difference between the two structural biomarkers. In this way we can use the biomarkers in the evolution of AION to confirm the diagnosis, to monitor evolution and with prognostic value. While there is some variability in the exact timing of the onset of GCIPL thinning between studies, the evidence suggests that it may begin as early as a few days after the ischemic event, with rapid and significant loss observed in the first few weeks to one to two months. This early detection capability is crucial for the design and implementation of future neuroprotective strategies, as the "window of opportunity" to intervene and potentially preserve visual function appears to be very narrow, likely within the first month from symptom onset.

OCT-A has proven to be a valuable tool for studying AION, enabling a detailed assessment of the optic nerve microvasculature and its relationship with functional outcomes[17]. The findings are consistent with previous studies highlighting reduced peripapillary perfusion as an early marker of ischemic damage[18].

In this regard, AION patients exhibited a significant reduction in optic nerve perfusion compared to healthy controls from disease onset up to one-month post-ischemic event (P<0.05), but by the third month, perfusion values had normalized to levels comparable to controls.

At the beginning of the disease there is a decrease in perfusion due to a possible combination of vascular insufficiency and compartment oedema that would further limit perfusion. When the oedema disappears after 3mo, vascular parameters normalize, although with a tendency to decrease *vs* control. This could be due to a reduced need for neuroretina tissue as suggested by previous authors who used the same device (OCT-A AngioPlex®)[19]. These authors analyzed the superficial peripapillary vascularization in eyes with acute non-arteritic anterior ischemic opitc neuropathy (NAION; <1wk) and at 3mo (atrophic stage), significant correlation was found between the mean GCIPL thinning and the microvascular reduction from the acute to the atrophic stages. On the contrary, other authors such as Akbari *et al*[15] and Fard *et al*[20], reported that ganglion cell loss does not occur at presentation in NAION eyes, to support that macular vasculature abnormalities occurred before detectable macular GCL atrophy. However these vascular analyses were focus on macula area, and ours is on the optic nerve[21-23].

In this study, systemic parameters such as blood pressure, pulse and oxygen saturation were assessed. At the onset of the disease, patients tended to have higher blood pressure and pulse levels and lower oxygen saturation, although without reaching hypoxic levels[24]. However, at 3mo all these parameters stabilized with continued systemic treatment after diagnosis[25].

At the third-month follow-up, vascular normalization (in both perfusion percentage and flow index) was observed, accompanied by structural sequelae and a decline in visual quality regarding color perception and contrast sensitivity. However, BCVA showed improvement, and PSD returned to normal values in perimetric analysis. This suggests that psychophysical tests with more subjective interpretation, such as visual acuity and perimetry, exhibited a tendency toward improvement, possibly influenced by compensatory mechanisms.

This study supports the clinical utility of OCT-A in identifying altered perfusion patterns and their correlation with functional and structural parameters. The positive correlation (r=0.83; P≤0.01) between perfusion and BCVA highlights the importance of vascular factors in AION prognosis, suggesting that vascular changes serve as early indicators of functional status. Additionally, a strong vascular-structural correlation was observed, particularly in the superior pRNFL sector and macular GCL, where atrophy was detected at the third-month follow-up. This indicates that when a patient with AION has upper pRNFL sector damage, the visual prognosis is likely to be worse 3mo after the event. At the clinical level, this assessment is useful for several reasons. First, it serves as a visual prognosis, since the initial visual acuity offers an indication of the extent of final structural damage. Second, if vascularization does not normalize between 1 and 3mo, it may be advisable to extend the study to investigate other possible pathologies and conduct complementary tests. Third, it supports differential diagnosis, with early involvement of ganglion cells being a key factor. Fourth, in cases of suspected simulators who report low subjective visual acuity but show initial structural and vascular integrity without subsequent atrophy, it provides valuable information.

While vascular parameters stabilized at three months, progressive atrophy of the pRNFL and GCL persisted, indicating that structural changes play a crucial role in disease progression and may be influenced by other factors beyond vascular restoration. The results show that optic nerve perfusion was reduced at baseline (1wk from disease onset) and at one month, but normalized at three months, similarly for BCVA. However, structural atrophy persisted. Nowadays, we have no way of knowing what the cause is, although these findings suggest that normalization of perfusion after the acute episode allows partial functional recovery of vision, and that there is therefore an association between neuroretinal perfusion and the ability to discriminate letters. While such reperfusion fails to recover the structural damage associated with those hours without adequate vascularization of the deeper layers of the retina.

These findings suggest that future therapeutic strategies for AION should focus on early vascular intervention combined with neuroprotection at intermediate and late stages, as vascular recovery alone does not appear to prevent neurodegeneration[19-21].

This study has certain limitations, including a relatively small sample size and a follow-up period restricted to three months. The small sample size led us to apply strict inclusion and exclusion criteria; therefore, the results may not be applicable to patients with amblyopia or posterior pole disorders, such as advanced myopia. Future research with larger cohorts and long-term follow-up, possibly using artificial intelligence and image processing, would be necessary to validate these findings and assess their clinical applicability. Results are obtained from both NA-AION (most of our sample) and A-AION subtypes, but these have distinct pathophysiological mechanisms, risk profiles, and clinical courses. Combining them in a single analysis could have introduced pathophysiological heterogeneity, bias vascular imaging outcomes, as A-AION typically causes more extensive ischemic damage. From another perspective, integrating additional diagnostic techniques, such as electrophysiology, could further complement OCT-A findings. Another limitation is that all tests were performed in the morning to minimize circadian variations, so it would be useful to assess whether optic nerve perfusion and/or oxygen saturation fluctuates throughout the day and whether this affects the reproducibility of the results[24]. The eye is a dynamic system, and its physiological parameters exhibit significant fluctuations due to circadian variability in IOP[26], optic nerve vascularization[27], neuroretina structure and oxygen saturation. To avoid misinterpretation and to ensure that the changes detected truly reflect disease progression, consistency in the timing of measurements is desirable. IOP and mean ocular perfusion pressure show a significant diurnal change. Ocular tissue perfusion must remain stable to ensure metabolic activity, despite fluctuations in perfusion pressure[28]. On the other hand, a small but statistically significant increase in optic nerve head vascular density has also been observed in the afternoon compared to the morning in healthy eyes. This diurnal variability in optic nerve vascularity could mean that this area experiences periods of increased or decreased perfusion throughout the day, which could contribute to its susceptibility to damage, especially if vascular autoregulation is compromised[27]. In our cohort, vascular normalization was

observed at 3mo, suggesting that a definitive stop did not occur, but rather a dysregulation of the arterioles in the optic nerve head that created an imbalance in the flow and energy demands to the retinal tissue. Cardiovascular risk factors create fibrosis and alteration of pericytes[29], making the vessels less flexible and insufficient to cope with nocturnal blood pressure drops[30]. Finally, some studies using SD-OCT (specifically Spectralis) have reported small but statistically significant diurnal variations in RNFL thickness in nasal, inferior, and inferonasal sectors, with values tending to be lower in the afternoon[31]. This reinforces the idea that neuro-vascular chronobiology is a relevant factor in the pathogenesis of optic neuropathies and that its detailed study is fundamental to better understand the progression of these conditions. This study is multifactorial as it analyzes functional, structural, and vascular changes and is therefore exposed to the existence of circadian variations, which means that the values obtained would not be fixed points, but dynamic ranges that change throughout the day. Creating longitudinal measurements throughout the day would help to better understand the pathophysiology. Knowledge of circadian variation requires rigorous standardization of measurements, but the reality of clinical practice makes 24-hour measurements “not feasible”. Practical solutions are needed without imposing undue burden on patients or health systems[26]. New artificial intelligence (AI)-aided metrics and algorithms that not only measure thickness or density but also quantify the amplitude and phase of circadian rhythms of ocular parameters could help.

In conclusion, OCT-A enables the identification of significant vascular alterations in AION patients, with direct implications for visual prognosis. Beyond providing a more precise diagnosis, it may also play a role in monitoring and guiding therapeutic decisions. This study reinforces the integration of OCT-A into clinical practice as a standard tool for evaluating and tracking AION, potentially improving patient care and outcomes by offering objective biomarkers, such as GCL thickness at disease onset and vascular recovery at three months, as key prognostic indicators.

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