Retinal and Choroidal Microvasculature in Nonarteritic Anterior Ischemic Optic Neuropathy: An Optical Coherence Tomography Angiography Study

Edouard Augstburger,1,2 Pierre Zéboulon,1,3 Chafik Keilani,2 Christophe Baudouin,1–6 and Antoine Labbé1–6

1Department of Ophthalmology III, Quinze-Vingts Hospital, Paris, France
2Sorbonne Universités, UPMC Univ Paris 06, Paris, France
3Quinze-Vingts Hospital, DHU Sight Restore, INSERM-DHOS CIC, Paris, France
4INSERM, U968, Institut de la Vision, Paris, France
5CNRS, UMR_7210, Paris, France
6Department of Ophthalmology, Ambroise Paré Hospital, APHP, University of Paris Saclay, Boulogne-Billancourt, France

CONCLUSIONS. To analyze retinal and choroidal microvasculature in patients with nonarteritic anterior ischemic optic neuropathy (NAION) by using optical coherence tomography angiography (OCT-A).

METHODS. In this case-control retrospective observational study, patients with atrophic NAION (at least 3 months after onset of symptoms) and normal subjects underwent a complete ophthalmic examination including spectral-domain OCT, visual field (VF), and OCT-A. Whole en face image vessel density (wiVD) was used to assess retinal blood flow of the radial peripapillary capillaries (RPCs), circumpapillary RPC vessel density (cpVD), superficial capillary plexus (SCP), deep capillary plexus (DCP), and choriocapillaris (CC). Statistical correlations between wiVD measurements and visual acuity, VF parameters, retinal nerve fiber layer (RNFL), and combined thickness of retinal ganglion cell and inner plexiform layers were analyzed.

RESULTS. Twenty-four patients (26 eyes) with NAION and 24 age-matched normal controls (NCs) (24 eyes) were included. OCT-A showed significant reduction of the RPC wiVD (P < 0.0001) and the cpVD (P < 0.0001) in NAION eyes compared with NC and correlated with RNFL thickness (P = 0.002, P = 0.004), visual acuity (P = 0.042), and mean deviation of the VF (P = 0.001). Macular OCT angiograms showed capillary rarefaction in the SCP (P < 0.0001) and DCP (P < 0.0001) in the NAION group, both correlated with visual acuity (P = 0.02, P = 0.024). However, wiVD of the CC was not significantly different between the two groups in the peripapillary (P = 0.218) and macular (P = 0.786) areas.

Conclusions. OCT-A provided detailed visualization of the peripapillary and macular retinal capillary rarefaction, correlated with VF and visual acuity loss. OCT-A could be a useful tool for quantifying and monitoring ischemia in NAION.

Keywords: nonarteritic anterior ischemic optic neuropathy, OCT-angiography, microvascularization

Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common acute optic neuropathy in subjects older than 50 years, with an annual incidence ranging from 2.3 to 10.2/100,000 in the United States.1,2 It is classically characterized by a sudden and painless visual acuity loss, papilledema, and peripapillary hemorrhages. Pathogenesis remains incompletely understood, but all the available evidence indicates that NAION is associated with risk factors predisposing the optic nerve head (ONH) to ischemia: arterial hypertension,3 diabetes,3,4 obstructive sleep apnea,5,6 or a small cup to disc ratio also called “disc at risk.”7 In addition, triggering factors are described such as nocturnal hypotension8 or medications9,10 that induce transient hypoperfusion in the posterior ciliary circulation, causing a partial or total infarction of the ONH. Noticeable interindividual variations in blood supply of the ONH contribute to the various presentations of NAION.11 Currently, the severity assessment and the follow-up of NAION are based on repeated clinical examinations including best corrected visual acuity (BCVA) and visual field tests.11 Spectral-domain optical coherence tomography (SD-OCT) allows observation of damage to the neuronal structures such as the thinning of the peripapillary retinal nerve fiber layer (pRNFL) and the combined macular ganglion cell and inner plexiform layers (mGCIPL), which are considered relevant monitoring parameters in NAION.12 However, NAION is primarily a vascular disease, and there is no equivalent imaging device to study retinal vessels in clinical practice. Fluorescein angiography (FA) suffers from insufficient resolution for morphologic analysis of the different retinal vascular plexi.13,14

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.
This lack of resolution is related to intrinsic characteristics of angiography, which consists of a two-dimensional acquisition and generates a superposition of vascular structures. With the laser Doppler flowmeter, an 1\textsuperscript{5} reduced ONH blood flow has been described in NAION patients. Nevertheless, this technique is limited by a small field of view. Optical coherence tomography angiography (OCT-A) is a new noninvasive fast imaging method that maps vessels in three dimensions. It can show the different capillary networks of the retina, choroid, and ONH with high resolution.\textsuperscript{16} In two previous studies,\textsuperscript{17,18} our group has shown the value of vessel density analysis using OCT-A in glaucoma. Recently, it has been suggested that changes in the radial peripapillary capillary network observed with OCT-A might be useful to better characterize optic neuropathies,\textsuperscript{19} especially NAION.\textsuperscript{20,21} However, these studies include a small number of patients and do not provide a detailed analysis of the retinal and choroidal vasculature, whereas NAION is primarily an ischemic disorder. Therefore, the aim of the present study was to assess the ability of OCT-A to provide a quantitative analysis of peripapillary and macular vessel density, and to study the correlations with structural and functional parameters in patients with atrophic NAION.

**Patients and Methods**

**Patients**

This case-control retrospective observational study was conducted at the Quinze-Vingts National Ophthalmology Hospital in Paris, France, between March 2016 and May 2017. This study adhered to the principles outlined in the Declaration of Helsinki. All patients were informed about data collection and informed consent was obtained from each subject.

Patients followed up at the Quinze-Vingts National Ophthalmology hospital for NAION, between 3 months and 1 year before the study, were included. Diagnosis of NAION was established and based on sudden painless loss of vision in patients older than 40 years with papilledema associated or not with peripapillary hemorrhages, compatible visual field impairment, and normal C-reactive protein blood-based assay. The diagnosis was first made by an ophthalmologist from the hospital and then confirmed by one of the investigators. All patients were also examined in the internal medicine department to eliminate giant cell arteritis. In case of diagnostic uncertainty, a temporal artery biopsy was performed. All examinations were performed in the atrophic chronic phase, at least 3 months after the diagnosis, in order to wait for complete resolution of papilledema.\textsuperscript{2,2} Age-matched control subjects (NC group) were recruited during the same period. Inclusion criteria for NCs were BCVA better than 20/20, normal and symmetric clinical aspects of the ONH between the right and left eyes, and normal Humphrey SITA 24-2 visual field. Exclusion criteria for NAION and NC subjects were IOP > 21 mm Hg or a history of elevated IOP, significant systemic disorder, associated retinal or choroidal disease, history of ocular surgery other than cataract, any condition that could damage the optic disc (glaucoma, uveitis, or optic neuropathy), or neurologic disease.

NAION and NC subjects underwent a complete ophthalmologic evaluation of both eyes, including demographic data, a questionnaire on general risk factors for NAION (diabetes, high blood pressure, dyslipidemia, obstructive sleep apnea syndrome [OSAS], ischemic heart disease), an assessment of the BCVA according to the standardized ETDRS scale, slit-lamp anterior segment examination, applanation tonometry, and fundus examination. An automated visual field was performed (Humphrey Visual Field Analyzer, STA-Standard 24-2 program; Carl Zeiss Meditec, Dublin, CA, USA). The mean pRNFL four-quadrant thickness and the mean mGCIPL thickness were obtained with the Cirrus SD-OCT (Carl Zeiss Meditec). In case of bilateral atrophic NAION, both eyes were included but only one eye per NC subject was randomly selected for analysis.

**OCT-A Data Acquisition and Processing**

All subjects were examined with the OCT-A (RTVue XR100 Avanti; Optovue, Inc., Fremont, CA, USA): a 6 × 6-mm macular cube scan centered automatically on the fovea and a cube scan measuring 3 × 3 mm centered automatically on the optic disc were performed. Images were acquired by using an 840-nm superluminescent diode performing 70,000 A-scans per second and providing an axial resolution of 5 μm. Vertical and horizontal scanning raster volumetric acquisitions were combined to provide a single final image. To minimize motion-related artifacts, the instrument has an eye tracker system for pupil movements during acquisition and a motion correction program. A split-spectrum amplitude decorrelation algorithm was used for blood flow detection within the selected tissue volume.\textsuperscript{14} Automatic segmentation was used to analyze the different vascular networks. Two consecutive scans were performed for each eye. The scan showing the highest signal strength index (SSI) was used for analysis. Images with an SSI < 45, aberrant segmentation, or movement-related artifacts were excluded.\textsuperscript{18}

Vessel density was calculated by measuring the percentage of vascular areas with blood flow on en face angiograms in relation to the whole surface in the selected regions. Peripapillary region parameters were measured as follows (Fig. 1): (1) whole en face image vessel density (wvD) was calculated from the 3 × 3-mm cube scan automatically segmented in the radial peripapillary capillary (RPC) and peripapillary choriocapillaris (pCC) zones and (2) the circum-papillary RPC vessel density (cpvD) was measured within a 750-μm-wide elliptic ring automatically generated around the optic disc. Macular parameters were measured as follows (Figs. 2, 5): wvD was obtained from a 6 × 6-mm chororetinal scan segmented in the superficial capillary plexus (SCP), the deep capillary plexus (DCP), and the macular choriocapillaris (mCC). The SCP was automatically defined between 3 μm beneath the internal limiting membrane and 16 μm below the inner border of the inner plexiform layer (IPL), and the DCP between 16 and 70 μm below the inner border of the IPL.\textsuperscript{23} The choriocapillaris (CC) was automatically individualized from 31 to 60 μm below the retinal pigment epithelium.

**Statistical Analysis**

All data are presented as mean ± standard deviation. BCVA was converted to a log of the minimum angle of resolution (logMAR). A Mann-Whitney bilateral test was used for continuous data and a χ\textsuperscript{2} test for categorical data. Correlations were tested by using the Spearman correlation coefficient. P values < 0.05 were considered statistically significant. XLSTAT 2017 software was used for statistical analysis.

**Results**

In the NAION group, 26 eyes from 24 subjects (two cases of bilateral NAION) with optic atrophy were included. The mean interval between the onset of disease and inclusion was 6.1 ± 3.5 months (range, 3–13 months). In the NC group, 24 eyes from 24 normal subjects were included. There was no significant difference in age, sex, prevalence of diabetes, self-reported history of OSAS, ischemic heart disease, and
dyslipidemia between the two groups. Prevalence of hypertension was significantly higher in the NAION group ($P = 0.0002$). IOP did not differ between the two groups. The percentage of small cup to disc ratio ($<0.3$) was higher in the NAION group than the NC group (70.8% vs. 12.5%, $P < 0.0001$). None of the NAION patients had undergone cataract surgery during the year before the development of NAION. The demographic and clinical data of the NAION and NC groups are summarized in Table 1.

Mean thickness of pRNFL, RPC wiVD, and cpVD wiVD were significantly lower in the NAION group than the NC group ($P < 0.0001$ for all; Table 2). There was no difference between the two groups regarding the pCC wiVD. In NAION patients, OCT-A en face projection images segmented on the RPC layer showed extended areas where vessel density between the large caliber vessels was lower than in the NCs (Figs. 1–3). These areas corresponded to thinner zones of the pRNFL (Fig. 1). Accordingly, a strong correlation was found between RPC wiVD and cpVD depending on the mean pRNFL thickness ($R = 0.582$, $P = 0.002$ and $R = 0.549$, $P = 0.004$, respectively) (Table 3). Significant correlations were also found between cpVD and pRNFL thickness in the superior and inferior sectors ($R = 0.650$, $P < 0.001$ and $R = 0.408$, $P = 0.059$, respectively) (Table 4). In the macular area, NAION eyes showed significant mGCIPL thinning and significantly lower SCP and DCP wiVD ($P < 0.0001$ for all comparisons) (Table 2). No difference in the mCC wiVD was found between the two groups (Table 2).

BCVA was significantly correlated with RPC wiVD ($R = -0.404$, $P = 0.042$), SCP wiVD ($R = -0.456$, $P = 0.02$), and DCP wiVD ($R = -0.045$, $P = 0.024$). There were no correlations between BCVA and pRNFL and mGCIPL thickness ($R = -0.208$, $P = 0.306$ and $R = -0.069$, $P = 0.736$, respectively), but correlations between mean deviation (MD) and pRNFL and mGCIPL thickness were significant ($R = 0.481$, $P = 0.014$ and $R = 0.433$, $P = 0.028$, respectively). RPC wiVD and cpVD were significantly correlated with all visual field parameters, especially RPC wiVD with MD ($R = 0.605$, $P = 0.001$) and visual field index (VFI; $R = 0.660$, $P < 0.001$). There was no statistically significant correlation between mGCIPL and SCP wiVD ($R = -0.516$, $P = 0.116$). Similarly, no correlation between pCC wiVD and mCC wiVD was found with the other parameters. Table 3 summarizes correlations between the different parameters measured with OCT-A and clinical parameters.

**DISCUSSION**

This OCT-A study showed three main results concerning NAION: (1) rarefaction of RPC was strongly correlated with BCVA, thickness of the pRNFL, and visual field parameters; (2)
macular vessel density was lower in SCP and DCP and correlated with BCVA; and (3) there was no difference concerning vessel density in the pCC and mCC.

Rarefaction of RPC in OCT-A has been reported as a major factor associated with severity of optic neuropathies. Concerning NAION, we observed, as previous authors have, low RPC vessel density in these subjects. This change has already been observed through delayed filling with FA. However, the insufficient resolution of FA images and the absence of quantification have limited the value of this analysis in clinical practice. The strong statistical correlations found between the decrease of RPC wiVD and cpVD with the thinning of pRNFL are consistent with histologic studies, which have emphasized the metabolic dependence of axons with the peripapillary capillary bed. RPC forms a dense network within the RNFL and follows a parallel path to axons. These capillaries develop few anastomoses together and are the RNFL axons' sole blood supply. These characteristics, coupled with the high energy demand of the unmyelinated axons of the RNFL, make them particularly vulnerable to ischemia. This vascular supply is suggested by the correspondence in the topography of RNFL defect and capillary rarefaction (Fig. 1; Table 4). In accordance, we found a scotoma in the corresponding visual field area, whose depth and location were correlated with the impairment of pRNFL and RPC (Figs. 1, 3).

We also found lower vessel density of macular capillaries in the SCP and DCP. Macular involvement in NAION has already been known through the early thinning of mGCIPL secondary to the degeneration of peripapillary axons. SCP is located in the ganglion cell layer and the local ischemia induced by capillary rarefaction participates in the thinning of...
In a recent case-control OCT-A study on 13 NAION patients, Liu et al. do not observe lower parafoveal vessel density (calculated for the ring-shaped area between a 1- and 3-mm radius from the center of the macula), while we found a difference for a wider macular area (6 × 6 mm). This result is consistent with the observations that capillary rarefaction predominates near the large retinal vessels of the arcades and less at the parafoveal areas where the capillary network converges and forms an anastomotic ring (Fig. 2). The topography of these areas of lower vascular density at the posterior pole seems to be contiguous with the ischemic zones around the optic disc (Figs. 1–3), which is easily explained by the interconnection of the different capillary networks. The fact that the fovea is less affected by ischemia could explain the relative preservation of the visual acuity in these patients despite severe visual field alterations.

Retinal capillaries depend on the central retinal artery (CRA) and therefore should not be affected by the abnormal posterior ciliary artery (PCA) flow in NAION. The mechanism by which they are altered is multifactorial. Papilledema

Table 1. Demographic and Ophthalmic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>NAION (n = 24)</th>
<th>Controls (n = 24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>66.9 ± 10.1</td>
<td>66.0 ± 9.2</td>
<td>0.579</td>
</tr>
<tr>
<td>Male/female</td>
<td>16/8</td>
<td>16/8</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>29.1</td>
<td>12.5</td>
<td>0.28</td>
</tr>
<tr>
<td>Self-reported history of OSA, %</td>
<td>12.5</td>
<td>0</td>
<td>0.10</td>
</tr>
<tr>
<td>Ischemic heart diseases, %</td>
<td>12.5</td>
<td>4</td>
<td>0.60</td>
</tr>
<tr>
<td>Arterial hypertension, %</td>
<td>70.8</td>
<td>20.8</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>50</td>
<td>29.2</td>
<td>0.23</td>
</tr>
<tr>
<td>Ophthalmic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>14.1 ± 3.4</td>
<td>13.4 ± 3.9</td>
<td>0.526</td>
</tr>
<tr>
<td>% Cup/disc &lt; 0.3</td>
<td>70.8</td>
<td>12.5</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

Data are given as mean ± standard deviation. IOP, intraocular pressure; OSA, obstructive sleep apnea.

* Statistically significant.
in central retinal vein occlusions, we found a correlation between the lower SCP and DCP density, and visual acuity.\textsuperscript{47} This rarefaction has never been observed in FA, certainly due to the limitations of this technique in terms of resolution and its ability to differentiate the vascular plexus.\textsuperscript{13,14}

No alteration of the vessel density in the CC was found in OCT-A. However, in a recent study of six patients with acute NAION, Sharma et al.\textsuperscript{21} have found a reduction of the VD in the peripapillary choroid layer as compared to healthy controls. As discussed by the authors, this reduction in flow density could have been due to segmentation errors, as they used a manual segmentation to quantify vessel density. Moreover, analyses were performed during the acute stage of NAION. Retinal edema might induce an underestimation of choriocapillary vessel density and explain the difference with healthy controls. Several authors\textsuperscript{11,32,46} have confirmed with FA the absence of choroidal circulation abnormality in NAION, unlike arterial anterior ischemic optic neuropathy in which a choroidal filling defect can be observed in the territory of occluded PCAs. NAION results from transitory hypoperfusion, not from permanent occlusion, which may explain why we observed no reduction in vessel density measured with OCT-A. However, this study did not include a comparative group with subjects presenting arteritic anterior ischemic optic neuropathy (AAION). In two recent case reports of AAION in giant cell arteritis, Rougier et al.\textsuperscript{49} and Balducci et al.\textsuperscript{50} demonstrated that choroidal ischemia seen on FA was also well defined with OCT-A. Larger comparative studies are needed to confirm the role of OCT-A in differentiating choroidal ischemia.

### Table 3. Spearman Coefficient Correlation Matrix for Peripapillary and Macular Vessel Density and Other Variables

<table>
<thead>
<tr>
<th></th>
<th>BCVA logMAR</th>
<th>Visual field parameters</th>
<th>ONH parameters</th>
<th>Macular parameters</th>
<th>Visual field index, %</th>
<th>Mean mGCIPL thickness, μm</th>
<th>Mean pRNFL thickness, μm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean deviation, dB</td>
<td>Pattern standard deviation, dB</td>
<td>Visual field index, %</td>
<td>Foveal threshold, dB</td>
<td>Average mGCIPL thickness</td>
<td>Average pRNFL thickness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\bar{x} \pm SD)</td>
<td>(\bar{x} \pm SD)</td>
<td>(\bar{x} \pm SD)</td>
<td>(\bar{x} \pm SD)</td>
<td>(\bar{x} \pm SD)</td>
<td>(\bar{x} \pm SD)</td>
</tr>
<tr>
<td><strong>BCVA logMAR</strong></td>
<td>0.48 ± 0.4</td>
<td>(-19.62 ± 7.1)</td>
<td>9.68 ± 3.8</td>
<td>41.42 ± 23.5</td>
<td>25.46 ± 9.0</td>
<td>70.89 ± 15.2</td>
<td>46.16 ± 6.3</td>
</tr>
<tr>
<td><strong>Visual field parameters</strong></td>
<td>(-0.03 ± 0.1)</td>
<td>0.11 ± 1.4</td>
<td>1.80 ± 0.8</td>
<td>98.83 ± 1.5</td>
<td>34.96 ± 2.18</td>
<td>95.67 ± 10.76</td>
<td>57.50 ± 3.3</td>
</tr>
<tr>
<td><strong>ONH parameters</strong></td>
<td>(&lt;0.0001^*)</td>
<td>(&lt;0.0001^*)</td>
<td>(&lt;0.0001^*)</td>
<td>(&lt;0.0001^*)</td>
<td>(&lt;0.0001^*)</td>
<td>(&lt;0.0001^*)</td>
<td>(&lt;0.0001^*)</td>
</tr>
<tr>
<td><strong>Macular parameters</strong></td>
<td>(0.0001^*)</td>
<td>(0.0001^*)</td>
<td>(0.0001^*)</td>
<td>(0.0001^*)</td>
<td>(0.0001^*)</td>
<td>(0.0001^*)</td>
<td>(0.0001^*)</td>
</tr>
</tbody>
</table>

Data are given as mean ± standard deviation. dB, decibel; mGCIPL, macular ganglion cell–inner plexiform layer; VD, vessel density.

* Statistically significant.

### Table 4. Spearman Coefficient Correlation Matrix for cpVD and pRNFL Thickness in Superior and Inferior Sectors

<table>
<thead>
<tr>
<th></th>
<th>Superior cpVD</th>
<th>Inferior cpVD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Superior pRNFL thickness</strong></td>
<td>(0.650^*)</td>
<td>0.159</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>(&lt;0.001^*)</td>
<td>0.436</td>
</tr>
<tr>
<td><strong>Inferior pRNFL thickness</strong></td>
<td>(0.211)</td>
<td>0.408^*</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>(0.299)</td>
<td>0.039^*</td>
</tr>
</tbody>
</table>

* Statistically significant.
OCT-A Study of the Chorioretinal Capillaries in NAION

studies are necessary to determine if OCT-A can be a useful tool to distinguish between NAION and AAION. Finally, these results should be analyzed by taking into account current limits of the technology: automatic segmentation imperfections and flow projection artifacts could induce overestimation of the measurements and alter the visibility of DCP and CC. New algorithms to remove these artifacts are currently being developed. To limit these biases, we did not manually change the segmentation, but we excluded the images that seemed aberrant so that the NAION and NC groups could be compared.

To the best of our knowledge, this study is the first showing alterations of different retinal capillary plexi in NAION. Retinal vessel densities quantified in the peripapillary and macular areas were significantly correlated with visual function parameters. OCT-A is therefore a new tool that should participate in the assessment of ischemia severity in NAION patients. Further studies and technologic improvements are needed to clarify its role in the diagnosis and follow-up of this pathology in clinical practice.

Acknowledgments

The authors thank Amélie Beaugrand, MD, for initial data gathering.

Disclosure: E. Augstburger, None; P. Zéboulou, None; C. Kellani, None; C. Baudouin, None; A. Labbé, None

References


