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. 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, diabetes, obstructive sleep apnea, or a small cup to disc ratio also called “disc at risk.” In addition, triggering factors are described such as nocturnal hypotension or medications 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.

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. 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. 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.
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, 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. In two previous studies, our group has shown the value of vessel density analysis using OCTA in glaucoma. Recently, it has been suggested that changes in the radial peripapillary capillary network observed with OCTA might be useful to better characterize optic neuropathies, especially NAION. 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. 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, application tomometry, and fundus examination. An automated visual field was performed (Humphrey Visual Field Analyzer, SITA-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. 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.

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. The choriocapillaris (CC) was automatically individuated 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 χ² 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, 3–15 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 $R = 0.435$, $P = 0.028$, 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 ($R = -0.316$, $P = 0.116$). 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.

![Figure 1](http://arvojournals.org/) Correspondence between OCT-A findings with pRNFL thickness and visual field defect. (A) OCT-A en face image (the blue ring defines the circumpapillary region) segmented in the RPC layer shows a rarefaction of the capillary density in the superior peripapillary sector (arrows) corresponding to the blue areas in the color-coded map of wiVD (B). (C) Same OCT-A scan segmented in the pCC: there is a dense vascular network around the disc without any capillary rarefaction. (D) Late phase of FA: absence of leakage confirms the resolution of papilledema. (E) SD-OCT color-coded map and measurement (F) showing the pRNFL thinning (in red) in the superior sector corresponding to RPC rarefaction. (G) The automated visual field shows an absolute inferior scotoma matching the RPC and pRNFL defects.

**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.\textsuperscript{19,24–26} Concerning NAION, we observed, as previous authors\textsuperscript{20,21,27–30} have, low RPC vessel density in these subjects. This change has already been observed through delayed filling with FA.\textsuperscript{31,32} 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 the pRNFL are consistent with histologic studies, which have emphasized the metabolic dependence of axons with the peripapillary capillary bed.\textsuperscript{33} RPC forms a dense network within the RNFL\textsuperscript{34} and follows a parallel path to axons. These capillaries develop few anastomoses together and are the RNFL axons’ sole blood supply.\textsuperscript{35} These characteristics, coupled with the high energy demand of the unmyelinated axons of the RNFL,\textsuperscript{36} 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,\textsuperscript{12,38} secondary to the degeneration of peripapillary axons.\textsuperscript{39} SCP is located in the ganglion cell layer\textsuperscript{14} and the local ischemia induced by capillary rarefaction participates in the thinning of

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{En face OCT-A color-coded map of wiVD in an NC subject (left column) and three NAION subjects (right columns). (A) OCT-A in the RPC layer: compared to NC, NAION subjects show less vascularized areas (in blue) between the larger-caliber vessels emanating from the optic disc, which implies a lower wiVD. (B) OCT-A in the macular SCP and DCP (C) shows an overall rarefaction of the capillary mesh that predominates near larger vessels; in contrast, the capillaries near the central avascular zone form a perifoveal anastomotic ring and appear better preserved. SCP and DCP wiVD are smaller than in NC.}
\end{figure}
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

![Figure 3](image-url)

**Figure 3.** Correspondence between the various functional and anatomic examinations in a patient with NAION. A superior altitudinal scotoma (A) was associated with an inferior thinning of the pRNFL (B), and an inferior RPC alteration (C). The en face color-coded map segmented in the pCC (D) does not exhibit a capillary defect. At the macular level, a predominant thinning of the combined macular ganglion cell and inner plexiform layers (mGCCPL) was observed in the lower hemifield (E) associated with a depletion of the capillary mesh predominantly in the lower quadrants of the superficial (F) and deep capillary (G) plexi, without any mCC involvement (H).

### 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>
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<tbody>
<tr>
<td>Demographic characteristcs</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 characteristcs</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.
(due to swelling of the ischemic axons) compresses the capillaries located in the most superficial layers of the retina, which aggravates tissue ischemia in a vicious cycle. Several Doppler imaging studies have confirmed that the blood flow velocity is lower at the CRA on the affected side, without determining if this phenomenon is a partial cause or a result of NAION. It might be plausible that ONH edema, located within a rigid and narrow scleral canal, results in compression and slowing of blood flow in the retinal vessels. The combination of these ischemic phenomena generates a rarefaction of the capillary mesh without being as severe as in a primitive retinal vessel occlusion. Similar to what was described with OCT-A capillaries located in the most superficial layers of the retina, (due to swelling of the ischemic axons) compresses the capillaries, which aggravates tissue ischemia in a vicious cycle. Several Doppler imaging studies have confirmed that the blood flow velocity is lower at the CRA on the affected side, without determining if this phenomenon is a partial cause or a result of NAION. It might be plausible that ONH edema, located within a rigid and narrow scleral canal, results in compression and slowing of blood flow in the retinal vessels. The combination of these ischemic phenomena generates a rarefaction of the capillary mesh without being as severe as in a primitive retinal vessel occlusion. Similar to what was described with OCT-A 

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

<table>
<thead>
<tr>
<th></th>
<th>NAION (n = 26)</th>
<th>Controls (n = 24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA logMAR</td>
<td>0.48 ± 0.4</td>
<td>−0.03 ± 0.1</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Visual field parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean deviation, dB</td>
<td>−19.62 ± 7.1</td>
<td>0.11 ± 1.4</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Pattern standard deviation, dB</td>
<td>9.68 ± 3.8</td>
<td>1.80 ± 0.8</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Visual field index, %</td>
<td>41.42 ± 25.5</td>
<td>98.83 ± 1.5</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Foveal threshold, dB</td>
<td>25.46 ± 9.0</td>
<td>34.96 ± 2.18</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>ONH parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average pRNFL thickness, μm</td>
<td>70.89 ± 15.2</td>
<td>95.67 ± 10.76</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Circumpapillary RPC VD, % area</td>
<td>46.16 ± 6.3</td>
<td>65.77 ± 2.7</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>RPC wiVD, % area</td>
<td>45.99 ± 5.6</td>
<td>57.50 ± 3.5</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Choriocapillaris wiVD, % area</td>
<td>61.56 ± 3.0</td>
<td>62.52 ± 2.0</td>
<td>0.218</td>
</tr>
<tr>
<td>Macular parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average mGCCP thickness, μm</td>
<td>60.66 ± 10.7</td>
<td>84.08 ± 8.4</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Superficial capillary plexus wiVD, % area</td>
<td>44.73 ± 4.5</td>
<td>50.74 ± 3.8</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Choriocapillaris wiVD, % area</td>
<td>64.76 ± 2.9</td>
<td>64.90 ± 1.8</td>
<td>0.786</td>
</tr>
<tr>
<td>Data are given as mean ± standard deviation. dB, decibel; mGCCP, macular ganglion cell-inner plexiform layer; VD, vessel density.</td>
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</table>

### 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>BCVA logMAR</td>
<td>0.650*</td>
<td>0.408*</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001*</td>
<td>0.039*</td>
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</tbody>
</table>

* Statistically significant.
studies are necessary to determine if OCT-A can be a useful tool to distinguish between NAION and AION. 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 DCP12 and CC. New algorithms to remove these artifacts are currently being developed.35 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

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References


