Primary open angle glaucoma (POAG) is a chronic, progressive optic neuropathy that is characterized by the death of the retinal ganglion cells and their axons leading to a loss of visual function.1–2 Thus, an assessment of the retinal nerve fiber defects (NFLD) in eyes suspected of having glaucoma is important because the functional defects are permanent. Individuals with myopia have a higher risk of developing glaucoma than nonmyopic individuals, and myopia is a risk factor for POAG.3–4 It is important because the prevalence of myopia is increasing worldwide.5–7 In the early stage of glaucoma in myopic eyes, the NFLD and the corresponding visual field defects are more likely to be detected in the paracentral area.8–10 These defects can lead to central visual impairments which then result in a reduction of the visual acuity.

The results of earlier studies showed that the supra- and infratemporal thick retinal nerve fiber (RNF) bundles of myopic eyes were shifted toward the papillomacular line.11–13 This shift of the myopic RNF bundle can lead to paracentral NFLDs in glaucomatous myopic eyes because of its location. We have reported that the trajectory of the temporally-thick retinal nerve fiber bundles and retinal arteries can be described by a second degree polynomial equation. Our calculations showed that the curvature of the RNF trajectory was significantly correlated with the curvature of the retinal arterial trajectories in healthy eyes.14

However, it is difficult to detect the thicker RNF bundles in fundus photographs of glaucomatous eyes because the retinal nerve fiber layer thickness is reduced. Nevertheless, the RNF trajectories can be easily detected by examining the retinal artery trajectories. Therefore, we hypothesized that the supra- and infratemporal NFLDs would be located closer to the fovea when the retinal artery shifts toward the fovea in the early to intermediate stages of glaucoma. To test this hypothesis, we determined the relationship between the curvature of the retinal artery trajectory (RAT) and the position of the NFLD in patients with normal tension glaucoma (NTG).

METHODS

This was a retrospective clinical study. This study was approved by the Kagoshima University Hospital Ethics Committee. The details of the study are shown on a poster displayed in the outpatient waiting room. All subjects were diagnosed with NTG in the glaucoma clinic at Fukui-ken Saiseikai Hospital, Fukui, Japan, between December 1, 2009, and February 28, 2014. The medical records of all newly
Normal tension glaucoma was diagnosed when the intraocular pressure was consistently less than 21 mm Hg in eyes free of antiglaucoma medications, had characteristic glaucomatous optic nerve head damage, typical glaucomatous visual field defects, absence of neuroradiologic evidence of optic nerve damage, open iridocorneal angles, and no abnormal chamber angle structures by gonioscopic examinations. Patients with neurological comorbidities or abnormal neuroimaging findings were excluded. We defined a localized NFLD as a wedged-shaped defect encroaching on the optic disc.

The exclusion criteria were: mean deviation (MD) less than $-14$ dB on visual field testing to exclude advanced disease; earlier ocular pathology such as retinal disease, cataracts, or a history of ocular surgery; aged older than 70 years to rule out senile retinal nerve fiber layer (RNFL) atrophy; and cases where it was difficult to differentiate defects due to the low quality of the red-free photographs. During the RNFL analysis, eyes with indefinite localized NFLD due to abnormal retinal findings such as diabetic retinopathy, drusen, and epiretinal membranes were excluded. Eyes with diffuse RNFL atrophy detected in the red-free photographs, which could not be defined as a localized defect, were also excluded.

From 232 NTG patients, 88 eyes of 88 patients met the entry criteria. Fifty-six eyes had supratemporal NFLDs and 69 eyes had infratemporal NFLDs; and 37 eyes had both supratemporal and infratemporal NFLDs.

**Determination of RAT**

The curvature of the RAT was quantified by fitting it to a second-order polynomial equation as we described in detail. The retinal arteries and the center of the optic discs were identified in the color fundus photographs. The fovea-to-disc axis of the color fundus photographs were rotated to a vertical position. At least 20 points on the supra- and infratemporal retinal arteries were marked on the color fundus photographs (Fig. 1A). The $x$ and $y$ coordinates of each mark were then determined automatically by the ImageJ program (version 1.47, http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). The $x$ and $y$ coordinates in the color fundus photographs were converted to a new set of coordinates, $x$ and $y$, with the center of the disc as the origin. Finally, the converted coordinate data were fit to a second degree polynomial equation, $ay^2/bx + c$, using the curve fitting program of ImageJ.

From 232 NTG patients, 88 eyes of 88 patients met the entry criteria. Fifty-six eyes had supratemporal NFLDs and 69 eyes had infratemporal NFLDs; and 37 eyes had both supratemporal and infratemporal NFLDs.

**Measurements of Angle of Supra- and Infratemporal NFLDs**

The locations of the supratemporal and infratemporalNFLDs were quantified using the red-free fundus photographs. A reference line running from the center of the disc to the
center of the fovea was drawn. We defined the angle between the reference line and a line from the optic disc center to the point of the disc margin nearest the border of the superior NFLD as the supra-NFLD angle 1. The second method of measuring the NFLD angle was done by drawing a circle with a radius of one-half the distance between the optic disc center and the fovea, and a line was drawn between the intersecting point and the disc center. The angle between the line connecting the intersecting point and the disc center and the reference line was defined as the supra-NFLD angle 2.

FIGURE 2. Measurements of angle of the retinal NFLD. Reference line (longer straight line) extends from the center of the disc to the fovea. The angle between the reference line and a line from the optic disc center to the point of the disc margin nearest the border of the superior NFLD was defined as the supra-NFLD angle 1. The second method of measuring the NFLD angle was done by drawing a circle with a radius of one-half the distance between the disc center and the fovea, and determined the points where the circle intersected the nearest border of the superior NFLD. Then a line was drawn between the intersecting point and the disc center. The angle between the line connecting the intersecting point and the disc center and the reference line was defined as the supra-NFLD angle 2.

Statistical Analyses

All statistical analyses were performed with commercial software (SPSS statistics 19 for Windows; SPSS, Inc., IBM Corp., Somers, NY, USA). The correlations between the RAT, axial length, the supra-NFLD angles 1 and 2, and the infra-NFLD angles 1 and 2 were determined with the Spearman’s correlation analysis. To exclude the effects of the stage of glaucoma (MD value), we determined the correlation between the RAT and the supra-NFLD angle and the infra-NFLD angles by partial correlations. A value of $P < 0.05$ was considered to be statistically significant.

RESULTS

The demographic information of the patients is presented in the Table. The mean ± standard deviation of the age was 58.6 ± 8.3 years, and the mean refractive error (spherical equivalent) was $-4.44 ± 3.25$ diopters (D). The mean axial length was $25.4 ± 1.4$ mm, MD was $-4.53 ± 3.91$ dB, and the mean coefficient $a$ of the trajectory curve was $0.232 ± 0.073$.

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<th>Table. Patient Data</th>
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<td>Sex, male/female</td>
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<td>Spherical equivalent, D</td>
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The coefficient of determinant of the curve fitting was greater than 0.8 for all of the cases, which means that the second degree polynomial equation was a good fit with the shape of the RAT.

The mean supra-NFLD angle 1 was 50.3 ± 12.6°, and the mean infra-NFLD angle 1 was 34.6 ± 11.3°. The mean supra-NFLD angle 2 was 43.1 ± 11.1°, and the mean infra-NFLD angle 2 was 28.4 ± 8.5°. The steepness of the RAT, θ and the axial length were significantly and positively correlated (R = 0.61, P < 0.001). The retinal artery trajectory and the refractive error were significantly and negatively correlated (R = -0.54, P < 0.001; Figs. 3A, 3B).

Spearman’s and Partial Correlation Coefficients Between Axial Length, RAT, and Supra- and Infra-NFLD Angles

The axial length was not significantly correlated with the supra-NFLD angle 1 (R = -0.22, P = 0.11; Fig. 3C) and the infra-NFLD angle 1 (R = -0.20, P = 0.09; Fig. 3D). However, the axial length was significantly correlated with the infra-NFLD angle 2 (R = -0.26, P = 0.035; Fig. 3A), but not significantly correlated with the supra-NFLD angle 2 (R = -0.24, P = 0.069; Fig. 3E). The steepness of the RAT, θ, was significantly and negatively correlated with the supra-NFLD angle 1 (R = -0.27, P = 0.041; Fig. 3E) and angle 2 (R = -0.28, P = 0.040; Fig. 3F), but not significantly correlated with the infra-NFLD angle 1 (R = -0.06, P = 0.61; Fig. 3F) and angle 2 (R = -0.21, P = 0.078; Fig. 3F).

To eliminate the effect of the stage of glaucoma on these results, we excluded the effects on the MD values. The partial correlation between the retinal artery trajectory and the supra-NFLD angle 1 was improved (R = -0.36, P = 0.007). However, the correlation between the RAT and the infra-NFLD angle 1 was not significant even after excluding the effect of the MD value (R = -0.10, P = 0.41). The partial correlation between the RAT and the supra-NFLD angle 2 was also improved (R = -0.35, P = 0.015); however, the correlation between the RAT and the infra-NFLD angle 2 was not significant even after excluding the effect of the MD value (R = -0.22, P = 0.070).

**DISCUSSION**

The results of earlier studies showed that arcuate scotomas often appear at paracentral areas in the early and intermediate stage of myopic glaucoma.8–10 A representative case of an eye with a steep and narrower RAT and an eye with a flatter and wider RAT are shown in Figure 5. Both the localized supratemporal NFLD (white arrows) was closer to the fovea (yellow dot) and the retinal arteries (red curve) were also closer to the fovea.

The stage of glaucoma may have affected the results. To exclude the effects of the stage of glaucoma, we determined the correlation between the RAT and supra-NFLD angle and the infra-NFLD angle using partial correlation. The correlation between the RAT and the supra-NFLD angle was improved after eliminating the effects of the MD value. This means that the localized supratemporal NFLDs were closer to the fovea in eyes in which the major retinal arteries were located closer to the fovea regardless of the severity of the visual field defects.

The steepness of the RAT was significantly correlated with the supra-NFLD angle but not significantly correlated with the infra-NFLD angle. One possible explanation for this may be that the average supra-NFLD angle 1 (50.3°) was narrower than the average infra-NFLD angle 1 (50.3°), and that the range of the infra-NFLD angle 1 (5.3 to 58.9°) was narrower than supra-NFLD angle 1 (5.0 to 76.4°). On the other hand, these results indicate a more clinically important point that the infratemporal NFLDs have a tendency to appear nearer the fovea. This is because the fovea is more likely to be located below a horizontal line through the center of the optic disc. Nerve fiber layer defects closer to the fovea can be easily detected as a parafoveal scotoma or serious vision problem. Therefore, infraNFLDs should be carefully examined regardless of the RAT and the axial length.

The supratemporal artery trajectory was not differentiated from the inferoretinal artery trajectory, but they were examined as a combined trajectory. An earlier study showed that the superior and inferior RNFL trajectories were different, and they were only weakly correlated in an individual.19,20 On the other hand, our earlier study showed that the angle of foveo-disc/supratemporal artery and the angle of foveo-disc/inferoretinal artery were significantly correlated among individuals.13,14 Our preliminary study showed that they were correlated with the RAT (e.g., the RAT and the angle of foveo-disc/supratemporal artery [R = -0.585, P < 0.001]) and RAT and the angle of foveo-disc/inferoretinal artery [R = -0.56, P < 0.001]). Therefore, the present analysis using the combined RAT is reasonable to a certain extent. This issue needs to be interpreted carefully and further investigation is ongoing.

The curvature of the RAT and axial length were significantly and positively correlated, but the correlation coefficient of 0.61 was not so high. Additionally, the axial

![Figure 4](https://example.com/f4.png)

**FIGURE 4.** Scatterplots of the axial length and (A) the supra-retinal NFLD angle 2 or (B) the infra-NFLD angle 2. Scatterplots of the steepness of the RAT and (C) the supra-NFLD angle 2 or (D) the infra-NFLD angle 2.

![Figure 5](https://example.com/f5.png)

**FIGURE 5.** The retinal artery trajectories (red curve), fovea (yellow dot), and the border of the retinal NFLD (white arrows) in red-free fundus photographs. An eye with a narrow retinal artery trajectory is shown in (A), and an eye with wider retinal artery trajectory is shown in (B). Localized supratemporal NFLD is closer to the fovea in the eye with a narrow retinal artery trajectory.
length was not significantly correlated with the supra-NFLD angle 1 ($R = -0.22$, $P = 0.11$), angle 2 ($R = -0.24$, $P = 0.069$), and the infra-NFLD angle 1 ($R = -0.20$, $P = 0.09$). This would suggest that there is an inconsistency between the RAT and the axial length or the presence of unknown factors. One possibility would be the presence of paradoxical eyes that are defined as those with a short axial length with myopic fundus changes (e.g., conus, elliptic optic disc, and greater RAT). Or there may be eyes with a longer axial length with few myopic fundus changes and lower RAT (Fig. 3A). An earlier study showed that there were large variations in the axial lengths at birth. Thus, a long axial length at birth does not necessarily mean that the axial length will be longer after attaining full growth. More specifically, even though two eyes have the same axial length as adults but differed at birth, the degree of elongation must have been different between these eyes during the growth period. This may affect the trajectories of the arcade arteries. Therefore, when assessing the NFLDs, not only the axial length but also the RAT should be considered.

In the clinic, ophthalmoscopic examinations and fundus photography are still important methods to study myopic eyes. However, it is difficult to identify the RNF bundles and NFLDs in myopic eyes because the RNF bundles are obscured by a fundus with low pigmentation. In Caucasians, the fundus in low pigmented eyes may further enable this phenomenon. Even in more pigmented eyes, such as Asian eyes, it is not easy to detect the RNF bundles in myopic eyes because of the lower pigmentation in eyes with high myopia. In a previous study, the distribution and peaks of the retinal nerve fiber layer thickness coincided well with that of the temporal retinal artery. Therefore, it is possible that the retinal artery trajectory can be a good way to monitor the location of NFLDs even when the RNF bundles are not clearly observed.

It should be emphasized that we do not argue that NTG is a unique disease entity, and that the present findings are specific to NTG and not POAG. We studied only NTG patients, and thus the findings and conclusions should be applied only to NTG patients. The study population was limited to NTG in this study because the majority of Japanese glaucoma patients have NTG. Considering the nature of glaucoma, NTG and POAG most likely belong to the same disease spectrum, and similar findings can probably be observed in both diseases. This issue needs further investigation.

There are several limitations in this study. First, because of its retrospective nature, we cannot exclude the possibility of selection bias. For example, the cases without clear images were excluded from the present analysis. This can lead to an inevitable bias. Second, epidemiological studies have shown that the Japanese population is one of the most myopic populations, and the mean and standard deviation of the refractive error of this study was $-4.44 \pm 3.25$ D. Thus, our results describe the characteristics of myopic eyes, and might not hold for nonmyopic populations. Third, there are many factors which affect the trajectories of the retinal artery (e.g., the size, shape, and torsion of the eye). The effect of the eye torsion was minimized by using a second-degree polynomial approach and by using the fovea-optic disc axis as a vertical landmark in measuring the retinal artery trajectory and NFLD angles. In addition, the magnification effect should not have altered angular measurements and trajectories. However, this does not apply to the cases in which irregular magnification is present. Thus, we cannot definitely determine whether the differences in the magnification affected our results. These limitations should be remembered in interpreting the results.

In conclusion, localized supratemporal NFLDs were closer to the fovea as the retinal arteries shifted toward the fovea in NTG patients. Thus, the trajectory of the temporal retinal artery can be used as one predictor of the proximity of the NFLDs to the fovea. In patients, the trajectories of the temporal retinal artery should be taken into account when assessing myopic glaucomatous eyes.

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References


