Retinal blood flow reduction in normal-tension glaucoma with single-hemifield damage by Doppler optical coherence tomography

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Abstract

Aims—To evaluate the associations between retinal blood flow (RBF) and optical coherence tomography (OCT) structural measurements in normal-tension glaucoma (NTG) eyes with single-hemifield visual field (VF) damage by the Doppler OCT.

Methods—The Doppler OCT was used to measure temporal artery (TA) RBF and temporal vein (TV) RBF. Retinal nerve fibre layer thickness (RNFLT) was measured by spectral-domain OCT.

Results—Forty-three consecutive eyes of 43 patients with NTG with VF defect confined to a single hemifield and 24 eyes of 24 age-matched healthy subjects were studied. TA and TV RBF and RNFLT were reduced in the damaged hemisphere compared with the normal hemisphere (mean (SD), 3.61 (1.68) vs 5.86 (2.59) μL/min, p<0.001; 5.61 (2.51) vs 6.94 (2.83) μL/min, p=0.010; 69.0 (19.7) vs 99.7 (22.8) μm, p<0.001). Those values in the normal hemisphere of NTG eyes also decreased compared with the healthy hemisphere of the healthy eyes (8.40 (3.36) μL/min, p<0.001; 9.28 (4.47) μL/min, p<0.002; 122.8 (20.2) μm, p<0.001). Multivariate model showed that normal and damaged hemispheres and RNFLT were associated with RBF reduction.

In addition, the RBF in the normal hemisphere was lower than that in the healthy hemisphere even after adjusting for RNFLT.

Conclusion—In NTG eyes with single-hemifield damage, the RBF was significantly reduced in the damaged hemisphere compared with the normal one. The RBF decreased in the normal and damaged hemispheres of NTG eyes compared with the healthy hemisphere independent from RNFLT.

INTRODUCTION

Glaucoma is commonly defined as an optic neuropathy characterised by progressive loss of retinal ganglion cells and also associated with structural damage to the optic nerve and visual field (VF) loss.[1] In primary open-angle glaucoma (POAG), increased intraocular pressure (IOP) is considered the most important risk factor. However, in normal-tension glaucoma (NTG), the deterioration of the optic nerve fibres occurs under statistically normal IOP.[2] Although NTG is considered as a form of POAG and IOP is still widely recognised as a major risk factor for progression,[3] whether NTG and high-tension glaucoma differ in their pathogenesis remains controversial. Therefore, vascular factors (eg, vasospasms, small vessel disease or autoregulatory dysfunction) have been suggested to significantly contribute to the development and progression of glaucomatous optic neuropathy and VF loss.[4][5]

Blood flow can be regulated in response to changing metabolic demands and local vascular resistance.[4] When the demand for blood flow in the local tissue decreases, the blood flow is reduced through autoregulatory mechanisms. Previous studies have examined the relationship between the retinal vascular diameter and retinal nerve fibre layer (RNFL) thickness in patients with POAG. Jonas *et al*[6][7] reported that parapapillary retinal vessel diameters may reflect the demand of vascular supply in the corresponding superficial retinal area, and it decreases with advanced glaucomatous optic nerve damage. Similarly, Kim *et al*[8] demonstrated statistically significant associations between central retinal vessel diameters and RNFL defects in the quadrant in patients with NTG and that the vessel narrowing is due to the decreased demand for blood flow in the areas of the retina damaged by glaucoma. But Hwang *et al*[9] reported that there was no correlation or paradoxical correlation between blood flow and structure using the Doppler optical coherence tomography (DOCT) by the double circular scan method. Whether there is a correlation between blood flow and structure is still controversial.

Recently, a novel velocimetry technique using optical coherence tomography (OCT) technology, namely DOCT, has been developed.[10–12] OCT can detect morphological images and a Doppler shift of reflected light, which provides information regarding flow and movement.[13][14] We previously developed a DOCT instrument with novel software, referred to as a segmental scan method,[15–17] which enables continuous measurement of the retinal blood flow (RBF) in the retinal arterioles venules during one cardiac cycle.

In this study, we investigated the associations between RBF and structural measurements in normal and damaged hemispheres of NTG eyes with single-hemifield VF defects.

METHODS

Study population

A total of 43 Japanese patients with NTG with single-hemifield VF defect and 24 age-matched healthy subjects without retinal diseases participated in this study (1 April 2017 to 31 January 2020). Written informed consent was obtained from all subjects using the consent forms.

All volunteers underwent a comprehensive ophthalmological examination, including a review of the medical history, best corrected visual acuity, slit-lamp biomicroscopy, IOP measurement through Goldman applanation tonometry, gonioscopy, ultrasound pachymetry, funduscopic examination using a 90-D lens, funds and optic disk photography. The axial length of each eye was measured using an A-mode ultrasound system (IOL Master 500; Carl Zeiss Meditec, Jena, Germany). Mean arterial blood pressure (MABP) and heart rate (HR) were measured using an electronic sphygmomanometer (EP-88 Si; Colin, Tokyo, Japan). MABP was calculated as 1/3 systolic blood pressure (SBP) +2/3 diastolic blood pressure (DBP). Mean ocular perfusion pressure (OPP) was calculated as 2/3 MABP – IOP.[18] Standard automated perimetry (SAP) was performed using the Swedish Interactive Threshold Algorithm standard 30–2 threshold test (Humphrey Field Analyzer 750 II-I; Carl Zeiss Meditec, Tokyo, Japan). Measurements of circumpapillary RNFL thickness (RNFLT) and macular ganglion cell complex thickness (GCCT) were performed using spectral-domain OCT (3D OCT-1 Maestro; Topcon Corp., Tokyo, Japan). Only good quality circumpapillary RNFL and macular ganglion cell complex images, defined by scans with a manufacture signal index 45, without segmentation failure or motion artefacts (ie, missing or blank areas), were included for the analysis.[19]

Inclusion criteria, common to both the healthy and NTG groups, consisted of reliable SAP defined as <20% fixation losses and <33% false-positive and false-negative errors, spherical equivalent refractive error between −6.00 and +3.00 D sphere, best corrected visual acuity of 20/40 or better, age 40 and 80 years, and no prior history of intraocular surgery.

Inclusion criteria for the healthy group were IOP 21 mm Hg, normal appearance of the optic nerve head and RNFL, normal SAP defined as a glaucomatous hemifield test within normal limits, and pattern SD (PSD) within 95% CI limits.

Inclusion criteria for the NTG group consisted of glaucomatous optic neuropathy and corresponding abnormal VF defined as abnormal glaucomatous hemifield test and PSD outside 95% normal limits. The patients required one normal visual hemifield, and the glaucomatous VF damage had to be confined to a single hemifield. All patients were familiar with SAP testing from earlier exposure to at least two VF examinations. The glaucomatous hemifield required the presence of a cluster of at least three contiguous test locations at p<0.05 on the pattern deviation plot, with at least one test location at p<0.01, except for the test locations in the most peripheral part. The sensitivity of each test location was converted to a linear scale of 1/Lambert (1/Lambert = $10^{0.1 \times dB\ value}$).[20] The retinal sensitivity (RS) values in 1/Lambert were calculated in each hemifield using the average of

38/76 VF locations. Finally, the average of the 1/Lambert scale was converted to the dB scale.

Exclusion criteria for both the groups were history of intraocular/laser surgery, existing retinal pathologies, non-glaucomatous optic neuropathy, uveitis, ocular trauma or diabetes. Participants with systemic hypertension were included unless they were diagnosed with hypertensive retinopathy. Participants with unreliable VF results and poor-quality spectral-domain OCT scans were excluded from this study.

RBF measurements of DOCT

As we previously described, the DOCT flowmeter is based on a commercially available spectral-domain OCT system (3D OCT-1 Maestro; Topcon Corp.) operated at an 800 nm wavelength range.

In DOCT, the flow velocity, $v(z)$, can be derived from the Doppler shift incurred by the moving blood:

$$v(\text{z}) = \frac{\Delta\Phi(z, \tau) \cdot \lambda_0}{4\pi \cdot n \cdot \tau} \cdot \frac{1}{\cos\theta}$$

where z is the depth location, is the phase difference at the same depth location between adjacent profiles after Fourier transform, λ_0 is the centre wavelength, n is the refractive index of blood, τ is the time interval between the adjacent profiles and θ is the Doppler angle between the flow vector and the incident probe beam.

A detailed description of blood flow measurement has been previously published.[15] Besides the measurement of the phase difference, the Doppler angle θ must be known to calculate the velocity. In the retina, most blood vessels run nearly parallel to the retinal surface, except at the area around the optic nerve head. As θ approaches 90°, the measured velocity becomes very sensitive to the accuracy of θ. To minimise this potential velocity measurement error, our Doppler blood flow measurements were performed where the Doppler angle θ is considerably <90°, at approximately 80°. Automated alignment software was integrated to seek the proper Doppler angle. Such autoalignment software traces the boundary of the internal limiting membrane in real time along the blood vessel to determine the Doppler angle. If the Doppler angle was out of range, the OCT beam was shifted farther away from the pupillary centre. This alignment was repeated until the estimated Doppler angle was calculated. The Doppler angle estimation routine was performed in locations where a pair of B-scan images was captured 100 μm apart across the blood vessels. This measurement was repeated eight times, and the median value was used to define the Doppler angle. Since the time interval for capturing a pair of B-scan images is only 10 ms, usually there are no eye motion artefacts. Obtaining the median value of eight repeated imaging measurements ensured more reliable and accurate results. DOCT imaging was performed for 2 s, followed by colour fundus imaging. The blood vessels were automatically detected and identified from the OCT structured and phase images. The vessel diameter was also measured using OCT phase images. The Image J software was used to describe the blood flow profile.

DOCT image acquisition and processing

The pupil was dilated with one drop of 0.5% tropicamide and 0.5% phenylephrine (Mydrin P; Santen Pharmaceuticals, Osaka, Japan). The participants rested for 10 min in a quiet room prior to the examination. After dilation of the pupils, the subjects were required to rest in the sitting position for at least 5 min in a quiet dimly lit room, where the temperature was maintained at 25°C. Subsequently, their blood pressure and HR were measured in the left arm. The RBF measurements were assessed after the blood pressure, HR and IOP measurements. The temporal arteries and veins having relatively straight segments and sufficiently far from the bifurcations were selected for the measurement of RBF.

Statistical analysis

The data were analysed using JMP software V.13.0.2 (SAS, Tokyo, Japan). The distribution of data was examined using the Shapiro–Wilk Test. Paired *t* tests were used to compare between the hemispheres corresponding to the normal and damaged hemifields in the same eye of the same patient with NTG. One-way analysis of variance followed by Tukey–Kramer honestly significant difference post-hoc test was used to compare the variables between healthy hemispheres of healthy subjects and normal hemispheres of patients with NTG. Multivariate regression analysis was used to investigate the associations between structural and RBF measurements of the damaged/normal hemispheres and SAP parameters in the corresponding hemifields. Univariate linear regression models were built using temporal artery (TA) RBF or temporal vein (TV) RBF as the dependent variable, and RNFLT, GCCT, RS and demographic ocular and systemic characteristic variables as the independent variables. Gender, axial length and factors that were significant in the univariate analyses ($p<0.05$) were then further included in the multivariable linear regression model. Logistic regression analysis was conducted to examine the impact of using topical and systemic medications on the TA RBF and TV RBF in NTG patients and healthy subjects.

RESULTS

The demographics of the study population are summarised in table 1. Forty-three eyes of 43 patients (men, 19; women, 24; mean (SD) age, 63.3 (9.8) years) and 24 eyes of 24 patients (men, 11; women, 13; mean (SD) age, 66.2 (6.1) years) were studied. There were no significant differences in age, gender, spherical equivalent, axial length, IOP, SBP, DBP, OPP, HR, proportion of hypertension or OCT-derived disk area measurements between healthy and NTG eyes. The mean (SD) of the VF mean deviation was −5.01 dB (3.83; range, −13.95 to 0.28 dB), and the mean (SD) VF PSD was 9.92 dB (4.15; range, 2.22 to 16.05 dB) in NTG eyes.

Figure 1 demonstrates a representative case of a patient with NTG with a single-hemifield VF defect (superior VF defect). It shows that reduced RNFLT (figure 1A,C) and GCCT (figure 1D), lower TA RBF and lower TV RBF (figure 1E,F) were observed in the inferior hemisphere compared with the superior hemisphere, which corresponded to the glaucomatous VF defects shown in the superior hemifield in the total and pattern deviation plots (figure 1B).

Table 2 presents comparisons of the RNFLT, GCCT, RS and RBF parameters between the damaged and normal hemispheres, and normal hemispheres of NTG eyes and healthy hemispheres. Twenty-seven eyes with NTG showed VF defects confined to the superior hemifield. In eyes with NTG, the RNFLT was thinner in the damaged hemisphere than in the normal hemisphere (mean (SD), 76.6 (11.9) vs 92.7 (14.5) μm; p<0.001). The GCCT was thinner in the damaged hemisphere than the normal hemisphere (mean (SD), 69.0 (19.7) vs 99.7 (22.8) μm; p<0.001). The RS was reduced in the damaged hemisphere compared with the normal hemisphere (mean (SD), 25.2 (4.2) vs 29.3 (1.7) dB; p<0.001). Also, lower TA RBF (mean (SD), 3.61 (1.68) vs 5.86 (2.59) μL/min; p<0.001) and TV RBF (mean (SD), 5.61 (2.51) vs 6.94 (2.83) μL/min; p<0.001) were found in the damaged hemisphere compared with the normal hemisphere. We also compared the values in the hemisphere with apparently normal VF in NTG eyes with the healthy hemisphere in healthy subjects. We found that the RNFLT (mean (SD), vs 122.8 (20.3) μm; p<0.001), GCCT (mean (SD), vs 98.8 (6.5) μm; p=0.012), TA RBF (mean (SD), vs 8.40 (3.36) μL/min; p<0.001), and TV RBF (mean (SD), vs 9.28 (4.47) μL/min; p=0.002) were significantly reduced in the normal hemisphere of NTG eyes compared with the healthy hemisphere. The RS in the normal hemisphere of NTG eyes (mean (SD), 29.3 (1.7) dB) was reduced compared with the healthy hemisphere but did not reach a statically significant level (mean (SD), 30.0 (1.3) dB; p=0.187).

Table 3 demonstrates the associations between RBF and other measurements (RNFLT, GCCT and RS) in the normal and damaged hemispheres. The TA RBF and TV RBF were correlated with RNFLT (r=0.581, p<0.001 and r=0.311, p=0.043, respectively) and GCCT (r=0.463, p=0.002 and r=0.307, p=0.045, respectively) in the normal hemisphere but not with RNFLT (r=0.024, p=0.877 and r=0.087, p=0.578, respectively) and GCCT (r=0.007, p=0.963 and r=0.068, p=0.666, respectively) in the damaged hemisphere. There was no correlation between RS and TA or TV RBF in the damaged hemifield and corresponding hemisphere (r=0.147, p=0.347 and r = −0.108, p=0.489, respectively). Scatter plots illustrating the relationships between TA RBF and RNFLT for all hemispheres (r=0.628; 95% CI 0.507 to 0.717; p<0.001) are shown in online supplementary figure 1.

In the fully adjusted multivariable model, normal (ß = −1.70; p<0.001) and damaged hemisphere (ß = −2.94; p=0.005), and RNFLT (ß=0.33; p=0.021) were associated with TA RBF reduction (table 4). Similar results were observed in TV RBF of normal (ß = −1.75; p=0.022) and damaged hemisphere (ß = −2.37; p=0.028; online supplementary table 1).

DISCUSSION

In the present study, we observed that the RBF, RNFLT and GCCT were significantly reduced in the perimetrically normal hemisphere of NTG eyes compared with the healthy hemisphere values in the healthy eyes. Previous reports have evaluated the retinal vessel diameter or RBF in glaucomatous eyes and its association with RNFLT and VF defects.[6–8][21] However, to the best of our knowledge, this is the first report evaluating RBF volumes of NTG eyes with single-hemifield damage. The finding of early structural loss in the hemisphere with apparently normal VF is consistent with the literature that demonstrated

that eyes with SAP defects confined to a single hemifield have evidence of diffuse attenuation in RNFLT, GCCT and RS in apparently normal areas of the VF.[21–23]

Our study further supports previous data reported by Arend et al[24] who examined the effect of asymmetric altitudinal VF damage on retinal microcirculation obtained through fluorescein angiography in NTG eyes. The report revealed that the arteriovenous passage time in the hemisphere with more severe glaucomatous VF damage is significantly reduced compared with the opposite hemisphere, indicating that it reduced RBF in the hemisphere with VF damage. Our results also showed that RBF was reduced both in TA RBF and TV RBF in the hemisphere with VF defect compared with the one without VF defect.

Previous reports have evaluated the retinal vessel diameter in NTG eyes and its association with RNFLT. Kim et al found a strong association between decreased peripapillary arteriole diameter and RNFLT in the corresponding hemifield in eyes with NTG.[8] Our study also observed a significant correlation between RBF and structural measurements in the normal hemisphere (table 3), and in the hemisphere of total subjects (online supplementary figure 1). The loss of retinal ganglion cells may cause a decrease in the RBF via autoregulatory mechanisms by responding to a decreased regional demand for oxygen.[67][25–27] This hypothesis is supported by the observation that retinal vessel narrowing is found in various forms of optic nerve damage and is not specific to glaucoma.[25][26][28–30] There was no correlation between RBF, structural measurement and RS in the damaged hemisphere (table 3). Takusagawa et al[31] reported that focal capillary dropout could be visualised in the superficial vascular complex (SVC) but not in the intermediate capillary plexus (ICP) and deep capillary plexus (DVP) in the glaucomatous eyes using a projection-resolved OCT-A. The lack of correlation with RNFLT, GCCT and RS in the damaged hemisphere suggests that measurements of RBF in the damaged hemisphere may mainly reflect the blood flow demands of the tissues that are less associated with glaucoma, for example, the ICP and DVP.

Previous reports have evaluated the relationship between total RBF, RNFLT and RS in glaucoma eyes using DOCT by a double circular scan method.[9][21] Hwang et al[9] reported that there was no correlation or paradoxical correlation between blood flow and structure. Sehi et al[21] evaluated total RBF in both normal and damaged hemispheres of POAG with VF defects confined to a single hemifield, and reported that the reduced RBF in the abnormal hemisphere was significantly associated with thinner RNFLT and GCCT in the same hemisphere, but there was no significant association between these parameters in the normal hemisphere. These results are contrary to the results of our study. The differences in the DOCT measurement method (double circular scan and segmental scan method; total venous vessels and only temporal arteriovenular vessel measurement) and in the target patients (POAG and NTG) may have been the cause of this discrepancy. Further studies are needed to confirm the relationship between RBF and structural measurements in glaucoma.

Several studies applying OCT angiography (OCTA) into POAG with single-hemifield VF damage have documented a relationship between SAP RS and vessel density measurements in the overall peripapillary region.[32][33] Yarmohammadi et al[33] reported that circumpapillary and perifoveal vessel density significantly correlated with SAP RS in both the normal and

damaged hemifield and corresponding hemisphere. In our study, RS and TA RBF were significantly correlated in the normal hemifield and corresponding hemisphere but not in the damaged hemifield and corresponding hemisphere. OCTA evaluates RNFL specific vascular morphology (SVC), whereas DOCT evaluates RBF in the inner retina (SVC +ICP + DCP). Therefore, RS may not correlate with RBF measured by DOCT in damaged hemispheres with thinner RNFLT. In cases of glaucoma in which the RNFL is thin enough to cause VF impairment, it is clinically useful to evaluate RNFL-specific blood factors, such as OCTA.

The multivariate regression analysis (table 4 and online supplementary table 1) revealed that the hemisphere in NTG was associated with blood flow reduction independent from structural loss (RNFLT and GCCT). Our results support previous reports.[9][34] Yarmohammadi *et al*[34] reported that OCTA vessel density was more strongly correlated with the severity of VF loss than RNFLT, and decreased vessel density was significantly associated with severity of VF damage independent of the structural loss in POAG. Similarly, Hwang *et al*[9] reported that there was a close link between reduced RBF and VF loss in glaucoma that is largely independent of structural loss. Considering these reports and our results, blood flow factor may be independent of structural loss in glaucoma.

Sehi *et al*[21] used DOCT by a double circular scan method to evaluate total venular RBF in both normal and damaged hemispheres of POAG with VF defects confined to a single hemifield. The results showed that both total venular RBF and OCT measurements (mean RNFLT and GCCT) were reduced in the hemisphere corresponding to the abnormal hemifields compared with the opposite hemisphere in glaucoma eyes. The double circular scan method can measure whole blood flow by measuring all venous blood vessels in the retina. Because the double circular scan method evaluates whole RBF, the method has an advantage, especially in situations when comparing whole RBF between individuals. On the other hand, the advantages of the segmental scan method are: (1) the arterial blood flow can be measured; (2) the retinal artery and vein pulsate, and the segmental scan method can obtain the waveform by continuously measuring one heartbeat, so that the blood flow can be measured more accurately; (3) measuring only the blood flow of the temporal arteriovenular with the thickest RNFL might be more indicative of glaucoma status. The double circular scan method measures whole blood flow, but also includes parts of nasal quadrant that are less likely to be associated with glaucoma. Meanwhile, the segmental scan method has several disadvantages: measurement of all retinal arteriovenular vessels is time consuming, and the reproducibility is poor for vessels<50 μm. Therefore, we selected four temporal vessels (TA and TV) per eye. Because our study measures only the largest retinal arteriovenular, the blood flow in the blood vessels branching in the optic disc region may have been underestimated.

The present study has several limitations. First, the use of topical and systemic medications during the course of this study may have potentially affected the RBF.[35] Several reports have indicated that the use of topical beta blockers decreases RBF.[36] Furthermore, another report suggested that the use of topical carbonic anhydrase inhibitors increased RBF in patients with glaucoma.[37] The full list of the topical and systemic medications has been provided in online supplementary table 2. Logistic regression analysis showed that none of the topical and systemic medications were statistically associated with average TA RBF and TV RBF in

NTG and healthy eyes (p>0.05). However, this might be due to the small sample size. The results of this study might not completely have eliminated the effects of eye drops. Second, we could not measure all retinal arteries and veins since the reproducibility is poor for vessels less than 50 μm. To calculate all arterial blood flow, technical problems must be solved.

CONCLUSION

In NTG eyes with single-hemifield damage, the RBF was found to be significantly reduced in the damaged hemifield and corresponding hemisphere. RBF reduction and thinner RNFLT and GCCT were also observed in the normal hemisphere of NTG eyes. The reduced RBF was associated with thinner RNFLT and GCCT in the normal hemifield and the corresponding hemisphere, but not in the damaged hemifield and the corresponding hemisphere. Multivariate regression analysis suggested that blood flow attenuation may be independent from structural loss in NTG.

Supplementary Material

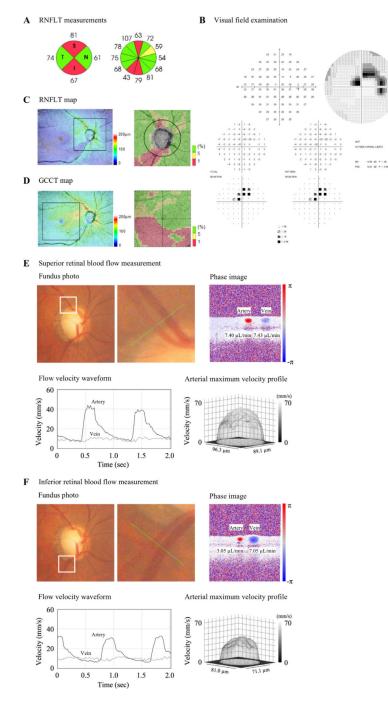Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A representative case of normal-tension glaucoma with superior visual field defect. (A) Retinal nerve fibre layer thickness (RNFLT) measurements. (B) Visual field examination. (C) RNFLT map. (D) Ganglion cell complex thickness (GCCT) map. (E) Superior retinal blood flow (RBF) measurement. The upper left image shows the fundus photograph, the white line square shows the next photograph and the green line shows the measurement location. The upper right image shows the phase image. The lower left image shows the velocity waveform of the average velocity in the blood vessel, the black line shows the artery

and the grey line shows the vein. The lower right image shows the velocity profile at the maximum velocity in the artery. (F) Inferior RBF measurement. Reduced RNFLT, GCCT, lower temporal artery RBF, and temporal vein RBF were observed in the inferior hemisphere compared with the superior hemisphere, which corresponded to the glaucomatous visual field defects shown in the superior hemifield in the total and pattern deviation plots. In the Topcon RNFLT deviation map, areas with RNFLT thinner than the fifth percentile and the first percentile of the normative database were marked in yellow and in red, respectively. dB, decibel; GHT, glaucoma hemifield test; I, inferior; MD, mean deviation; N, nasal; PSD, pattern SD; S, superior; T, temporal.

Table 1

Demographics of the study population

Variable	Healthy eyes (n=24)	NTG eyes (n=43)	P value
Age, mean (SD; 95% CI), years	66.2 (6.1; 63.6 to 68.7)	63.3 (9.8; 60.3 to 66.3)	0.201 [*]
No of men/women	11/13	19/24	0.897 [†]
VF defect location, no of superior/inferior	–	27/16	
Spherical equivalent, mean (SD; 95% CI), D	−0.55 (2.13; −1.45 to 0.35)	−1.51 (2.44; −2.26 to−0.76)	0.112 [*]
Axial length, mean (SD; 95% CI), mm	23.8 (1.1; 23.4 to 24.3)	24.1 (1.3; 23.7 to 24.5)	0.324 [*]
IOP, mean (SD; 95% CI), mm Hg	15.7 (3.0; 14.4 to 16.9)	15.3 (2.5; 14.5 to 16.1)	0.598 [*]
SBP, mean (SD; 95% CI), mm Hg	131.1 (9.5; 127.1 to 135.1)	130.3 (9.6; 127.3 to 133.2)	0.742 [*]
DBP, mean (SD; 95% CI), mm Hg	77.1 (9.6; 73.1 to 81.2)	78.0 (11.3; 74.5 to 81.5)	0.744 [*]
MOPP, mean (SD; 95% CI), mm Hg	47.7 (6.0; 45.2 to 50.3)	48.3 (6.9; 46.2 to 50.5)	0.726 [*]
HR, mean (SD; 95% CI), beats/min	65.8 (7.6; 62.5 to 69.0)	65.5 (8.5; 62.9 to 68.1)	0.892 [*]
Hypertension, No. (%)	5 (21)	6 (14)	0.466 [†]
SAP MD, mean (SD; 95% CI), dB	0.48 (1.33; −0.09 to 1.04)	−5.01 (3.83; −6.20 to −3.84)	**<0.001** [*]
SAP PSD, mean (SD; 95% CI), dB	1.79 (0.41; 1.62 to 1.96)	9.88 (4.13; 8.61 to 11.15)	**<0.001** [*]
Disc area, mean (SD; 95% CI), mm^2	2.21 (0.43; 2.03 to 2.39)	2.32 (0.60; 2.13 to 2.50)	0.449 [*]
Rim area, mean (SD; 95% CI), mm^2	1.15 (0.50; 0.94 to 1.36)	0.59 (0.30; 0.50 to 0.68)	**<0.001** [*]

Boldface indicates statistically significant difference.

[*] Calculated as unpaired t-test, with p<0.05 considered to be statistically significant.

[†] Calculated as χ^2 test, with p<0.05 considered to be statistically significant.

dB, decibel; DBP, diastolic blood pressure; HR, heart rate; IOP, intraocular pressure; MD, mean deviation; MOPP, mean ocular perfusion pressure; NTG, normal-tension glaucoma; PSD, pattern SD; SAP, standard automated perimetry; SBP, systolic blood pressure; VF, visual field.

Table 2

Comparisons of variables between normal and damaged hemispheres in normal-tension glaucoma (NTG) eyes; and normal hemisphere of NTG eyes and healthy hemisphere of healthy eyes

Variable	NTG eyes, mean (SD)			Healthy eyes, mean (SD)	
	Damaged hemisphere, n=43	Normal hemisphere, n=43	P value[*]	Healthy hemisphere, n=48	P value[†]
RNFLT, μm[‡]	69.0 (19.7)	99.7 (22.8)	**<0.001**	122.8 (20.2)	**<0.001**
GCCT, μm	76.6 (11.9)	92.7 (14.5)	**<0.001**	98.8 (6.5)	**0.012**
RS, dB	25.2 (4.2)	29.3 (1.7)	**<0.001**	30.0 (1.3)	0.187
TA RBF, μL/min	3.61 (1.68)	5.86 (2.59)	**<0.001**	8.40 (3.36)	**<0.001**
TA diameter, μm	76.0 (13.8)	84.2 (13.5)	**<0.001**	97.1 (13.9)	**<0.001**
TA average velocity, mm/s	12.8 (4.1)	15.4 (4.7)	**0.003**	17.1 (5.7)	0.111
TA maximum velocity, mm/s	26.5 (8.7)	31.6 (10.6)	**0.007**	33.7 (10.7)	0.308
TA minimum velocity, mm/s	5.2 (2.1)	6.7 (2.7)	**0.001**	7.7 (3.5)	0.109
TV RBF, μL/min	5.61 (2.51)	6.94 (2.83)	**0.010**	9.28 (4.47)	**0.002**
TV diameter, μm	112.5 (15.2)	115.1 (18.9)	0.409	120.3 (19.1)	0.168
TV average velocity, mm/s	9.5 (3.7)	10.4 (3.9)	0.184	12.7 (4.6)	**0.007**

Boldface indicates statistically significant difference.

[*] Paired t-tests were used to compare the variables between the normal hemisphere and the hemisphere corresponding to the visual field defect in the same eye with NTG. P<0.05 is considered to be statistically significant.

[†] One-way analysis of variance followed by Tukey–Kramer Honestly Significant Difference post-hoc test was used to compare the variables between healthy hemispheres and normal hemispheres of NTG, with p<0.05 considered to be statistically significant.

[‡] Measured in superior (46°–135°) and inferior (226°–315°) quadrants.

RNFLT, retinal never fibre layer thickness; GCCT, ganglion cell complex thickness; RS, retinal sensitivity; TA, temporal artery; RBF, retinal blood flow; TV, temporal vein.

Table 3

Associations between retinal blood flow (RBF) and other parameters in each hemisphere in normal-tension glaucoma eyes

Variable	RNFLT, µm*		GCCT, µm		RS, dB	
	r (95% CI)	P value†	r (95% CI)	P value†	r (95% CI)	P value†
Normal hemifield and corresponding hemisphere						
TA RBF, µL/min	0.581 (0.340 to 0.751)	**<0.001**	0.463 (0.189 to 0.670)	**0.002**	0.348 (0.053 to 0.587)	**0.022**
TV RBF, µL/min	0.311 (0.011 to 0.559)	**0.043**	0.307 (0.007 to 0.556)	**0.045**	0.104 (−0.203 to 0.392)	0.509
Damaged hemifield and corresponding hemisphere						
TA RBF, µL/min	0.024 (−0.278 to 0.322)	0.877	0.007 (−0.294 to 0.307)	0.963	0.147 (−0.161 to 0.428)	0.347
TV RBF, µL/min	0.087 (−0.219 to 0.378)	0.578	0.068 (−0.237 to 0.361)	0.666	−0.108 (−0.396 to 0.198)	0.489

Boldface indicates statistically significant difference.

*
Measured in superior (46°–135°) and inferior (226°–315°) quadrants.

†
Calculated as Pearson correlation coefficient, with p<0.05 considered to be statistically significant.

RNFLT, retinal never fibre layer thickness; GCCT, ganglion cell complex thickness; RS, retinal sensitivity; TA, temporal artery; TV, temporal vein.

Table 4

Influence of factors on temporal artery retinal blood flow

Factor	Univariate analysis			Multivariate analysis		
	Coefficient	95% CI	P value	Coefficient	95% CI	P value
Age, per year	−0.01	−0.08 to 0.06	0.781	–	–	–
Gender, female	0.68	0.12 to 1.24	**0.018**	0.73	−0.22 to 1.68	0.129
Axial length, mm	−0.67	−1.12, to 0.21	**0.005**	−0.22	−0.61 to 0.17	0.263
IOP, mm Hg	−0.02	−0.23 to 0.19	0.194	–	–	–
SBP, mm Hg	0.03	−0.05 to 0.07	0.855	–	–	–
DBP, mm Hg	0.01	−0.05 to 0.06	0.783	–	–	–
MOPP, mm Hg	0.01	−0.07 to 0.10	0.738	–	–	–
HR, beats/min	−0.01	−0.07 to 0.06	0.972	–	–	–
Hypertension	0.40	−0.34 to 1.14	0.284	–	–	–
RS, dB	0.39	0.24 to 0.54	**<0.001**	−0.03	−0.21 to 0.16	0.781
RNFLT,*, per 10 μm	0.61	0.46 to 0.76	**<0.001**	0.33	0.05 to 0.60	**0.021**
GCCT, per 10 μm	1.11	0.77 to 1.45	**<0.001**	0.07	−0.37 to 0.51	0.747
Group						
Healthy hemisphere	Reference			Reference		
Normal hemisphere	−2.54	−3.64 to 1.43	**<0.001**	−1.70	−2.87 to 0.52	**<0.001**
Damaged hemisphere	−4.79	−5.90 to 3.68	**<0.001**	−2.94	−4.61 to 1.26	**0.005**

Boldface indicates statistically significant difference.

*Measured in superior (46°–135°) and inferior (226°–315°) quadrants.

IOP, intraocular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MOPP, mean ocular perfusion pressure; HR, heart rate; RS, retinal sensitivity; RNFLT, retinal never fibre layer thickness; GCCT, ganglion cell complex thickness.