Table 4. Age-Specific Prevalence of Exfoliation

Age Groups (yrs)	Exfoliation Glaucoma (Percentage, 95% CI)		
	Male	*Female*	*All*
40–49	0/338 (0.0, 0.0–0.0)	0/445 (0.0, 0.0–0.0)	0/783 (0.0, 0.0–0.0)
50–59	0/427 (0.0, 0.0–0.0)	0/532 (0.0, 0.0–0.0)	0/959 (0.0, 0.0–0.0)
60–69	2/324 (0.6, 0.0–1.47)	1/360 (0.3, 0.0–0.83)	3/684 (0.4, 0.0–0.94)
70–79	0/190 (0.0, 0.0–0.0)	0/238 (0.0, 0.0–0.0)	0/428 (0.0, 0.0–0.0)
≥80	2/55 (3.6, 0.0–8.59)	0/112 (0.0, 0.0–0.0)	2/167 (1.2, 0.0–2.85)
All subjects	4/1334 (0.3, 0.0–0.58)	1/1687 (0.1, 0.0–0.17)	5/3021 (0.2, 0.02–0.30)

CI = confidence interval.

parison among diverse epidemiological studies. Such nomenclature would also be applicable to SG, which is more complicated due to the variety of ocular hypertensive mechanisms involved.

In the present study, all subjects were screened for narrow angles using the van Herick method, which was reported to be highly specific in detecting narrow angles of Shaffer grade 2 or less, though some controversy existed.[33] Okabe et al reported 77% sensitivity and 94% specificity for the van Herick method in detecting eyes with Shaffer grade 2 narrow angles in Japanese.[34] Thus, some cases of Shaffer grade 2 narrow angle in the present study might not have been detected because gonioscopy was not performed in the screening examination. However, because the sensitivity and specificity of detecting Shaffer grade 1 narrow angles in Japanese were reported to be 93% and 98%, respectively,[34] such an extremely narrow angle must have been detected appropriately. Besides, the diagnosis of glaucoma was established based mainly on optic disc change and the VF. In all cases referred for the definitive examination, the ocular fundus was observed via a 2-mirror goniolens with the pupil dilated, except in narrow-angled eyes. All cases with poor-quality fundus IMAGEnet photographs were also referred for the definitive examination. Additionally, we applied an FDT screener to all participants for the screening VF test. The FDT screener has been reported to detect glaucomatous VF defects with high sensitivity and even earlier than conventional perimetries.[35–37] We did not employ red-free photography because the nerve fiber layer is observed quite easily even without it in a melanin-rich fundus such as seen in Japanese. Thus, the diagnosis of confirmed and suspected PACG was thought to be made with reasonable accuracy in the present study.

Racial or geographic differences in the prevalence of PAC or PACG are well known. Among Caucasians and African Americans, the prevalence of PACG has been reported to be relatively low. The Baltimore Eye Survey found a potentially occludable angle in 0.8% of Caucasians and 0.6% of African Americans, where an occludable angle was defined as at least 9 clock hours of the angle having a slit or closed appearance on gonioscopy, evidence of previous episodes of angle closure such as peripheral synechiae, or both.[38] The Melbourne Visual Impairment Project in Australia reported only a 0.1% prevalence of PACG diagnosed at the discretion of the ophthalmologists.[8] The Egna–Neumarkt Study conducted in northern Italy found a 0.6% prevalence of PACG in a population 40 years or older in which PACG was defined as glaucomatous optic neuropathy and chamber angle partly or totally closed or goniosynechiae extending to at least one third of the circumference, or with a very narrow angle clearly prone to occlusion.[10] In a Hispanic population 40 years or older, there was a 0.10% prevalence of PACG, which was defined as bilateral appositional angle closure combined with optic nerve damage.[28] In an African tribe, a 0.1% prevalence was found with PACG defined as glaucomatous optic neuropathy and an occludable drainage angle, meaning that the pigmented trabecular meshwork was visible for <90° in the primary position,[29] whereas, in a Tanzanian population, a 0.59% prevalence was reported with PACG defined as an occludable angle and one of the following in addition to Shaffer grade 2 or less in at least 8 clock hours in the fellow eye: IOP > 24 mmHg, structural optic disc abnormality, definite reliable VF damage, or a history compatible with an episode of acute angle closure.[39] By contrast, an Inuit population showed a surprisingly high prevalence of PACG/PAC, and 17% of those 50 years or older showed an occludable angle, defined as a trabecular meshwork not visible in 3 quarters of the angle and the ciliary body not visible in 2 quarters.[40]

In Asian countries, the prevalence of PACG has been recognized to be intermediate. In southern India, 2 studies have been reported recently.[6,7] The Andhra Pradesh Eye Disease Study demonstrated, in participants 40 years or older, that prevalences of occludable angles without ACG and manifest PACG, defined as IOP of ≥22 mmHg or glaucomatous optic disc damage in the presence of an occludable angle, were 2.21% and 1.08%, respectively.[6] Whereas, according to a recent article from the Aravind Comprehensive Eye Survey, the prevalence of manifest PACG—defined as glaucomatous optic disc damage or glaucomatous VF defects with the anterior chamber angle partly or totally closed, appositional angle closure or synechiae in the angle, and absence of signs of secondary angle closure—was 0.5%.[7] The prevalence of PACG in Chinese residents in urban Singapore was reported to be 1.0%,[5] in a study where glaucoma was defined as glaucomatous optic neuropathy and an occludable drainage angle, and in which the pigmented/posterior trabecular meshwork could be seen for <90° of the angle circumference. In Mongolia,[4] the prevalence of occludable angles, defined as a pigmented trabecular meshwork that was not visible throughout ≥3

Glaucoma and Suspected Cases

Suspected Exfoliation Glaucoma (Percentage, 95% CI)		
Male	*Female*	*All*
0/338 (0.0, 0.0–0.0)	1/445 (0.2, 0.0–0.66)	1/783 (0.1, 0.0–0.38)
0/427 (0.0, 0.0–0.0)	0/532 (0.0, 0.0–0.0)	0/959 (0.0, 0.0–0.0)
0/324 (0.0, 0.0–0.0)	0/360 (0.0, 0.0–0.0)	0/684 (0.0, 0.0–0.0)
1/190 (0.5, 0.0–1.56)	0/238 (0.0, 0.0–0.0)	1/428 (0.2, 0.0–0.68)
0/55 (0.0, 0.0–0.0)	1/112 (0.9, 0.0–2.63)	1/167 (0.6, 0.0–1.77)
1/1334 (0.1, 0.0–0.21)	2/1687 (0.3, 0.07–0.53)	3/3021 (0.1, 0.0–0.22)

quarters of the angle circumference in the primary position, or PACG, defined as an occludable angle and a raised IOP and/or glaucomatous optic neuropathy, was reported to be 6.4% or 1.4%, respectively, which is higher than that in other Asian countries. In the present study, prevalences of PAC including PACG and suspected PACG, and PACG alone, were 1.3% and 0.6%, respectively. Clearly demonstrated was the effect of age on the prevalence for both PAC including PACG and suspected PACG, and PACG, but the effect of gender was only evident for the former category. The prevalence of PACG was numerically 3 times higher in females than in males (0.9% vs. 0.3%) in the present study, but the intergender difference did not reach a statistically significant level because of relatively small numbers of PACG diagnoses. Compared with other reports conducted in other Asian countries, the prevalence of PACG or PAC in Japanese tended to be lower, especially relative to the Mongolia or Andhra Pradesh study, but was still higher than in Caucasians or African Americans.

In a previous epidemiological study conducted between 1988 and 1989 in Japan, it had been reported that the prevalence of PACG, defined as a closed or occludable angle and IOP $\geq$ 21 mmHg, was 0.34%.[25] If the same definition were adopted, the prevalence in the present study would be 0.23%, being comparable to the previous figure. However, there was no information regarding the prevalence of suspected PACG or occludable angles in the previous study.

In the present study, the overall prevalence of SG including exfoliation glaucoma was 0.5%. Exfoliation glaucoma was found to be the principal contributor to the prevalence of SG. However, the detection method in the present study included observation of only the pupillary margin and lens surface through undilated pupils. Because it was previously reported that exfoliation material may be missed in 10% to 20% of undilated eyes with exfoliation syndrome,[41,42] the prevalence of exfoliation glaucoma may have been underestimated in the present study. We also found that uveitic glaucoma is a common type of SG, and we confirmed that pigmentary glaucoma is rarely seen in Japan.[43] The epidemiology of SGs differs among various regions and races. Also, it is almost certain that the reported prevalence is affected by the accessibility to medical care and the prevalence of underlying conditions. The Egna–Neumarkt Study reported a 0.2% prevalence for aphakic glaucoma and 0.1% for SG.[10] In a Hispanic population 40 years or older, a 0.02% prevalence of SG was reported.[27] In Africans, the SG prevalence was reported as 0.15% in Tanzania[38] and 1.7% in South Africa, being mainly exfoliative and aphakic glaucoma.[28] In Asian countries, the Andhra Pradesh Eye Disease Study found a 0.28% prevalence for SG,[6,44] whereas, in the Aravind Comprehensive Eye Survey,[7] a higher prevalence for SGs was found: 0.4%, 0.06%, and 0.3% for pseudoexfoliation, absolute glaucoma, and other types of SGs, respectively. The Tanjong Pagar Study[5] in Singapore found a 0.5% prevalence for SGs (i.e., secondary pathologic process and glaucomatous optic neuropathy) in Chinese, in whom neovascular and lens-related forms were predominant and no exfoliation glaucoma cases were found. In Mongolia,[4] a 0.3% prevalence for SG comprised of exfoliation and uveitic glaucoma was reported. Thus, the prevalence and underlying conditions of SG vary even among the Asian regions and ethnicities.

Early-onset developmental or congenital glaucoma was not found in the present study. Because the prevalence of this type of glaucoma is 1 of 10 000 to 100 000 births,[45] this

Table 5. Age-Specific Prevalence of Exfoliation Syndrome Excluding Exfoliation Glaucoma and Suspected Cases

Age Groups (yrs)	Exfoliation Syndrome Excluding Exfoliation Glaucoma and Suspected Cases (Percentage, 95% CI)		
	Male	*Female*	*All*
40–49	0/338 (0.0, 0.0–0.0)	0/445 (0.0, 0.0–0.0)	0/783 (0.0, 0.0–0.0)
50–59	0/427 (0.0, 0.0–0.0)	2/532 (0.4, 0.0–0.90)	2/959 (0.2, 0.0–0.50)
60–69	3/324 (0.9, 0.0–1.98)	4/360 (1.1, 0.03–2.19)	7/684 (1.0, 0.27–1.77)
70–79	4/190 (2.1, 0.07–4.15)	4/238 (1.7, 0.05–3.31)	8/428 (1.9, 0.59–3.15)
≥80	2/55 (3.6, 0.0–8.59)	3/112 (2.7, 0.0–5.67)	5/167 (3.0, 0.41–5.57)
All subjects	9/1334 (0.6, 0.18–1.06)	13/1687 (0.9, 0.46–1.29)	22/3021 (0.8, 0.47–1.07)

CI = confidence interval.

Table 6. Standardized Prevalence of Glaucoma and Suspected Cases in Patients over 40 Years (%)

	Male (95% CI)	Female (95% CI)	Overall (95% CI)
Glaucoma			
Primary open-angle*	4.1 (3.0–5.2)	3.7 (2.8–4.6)	3.9 (3.2–4.6)
Primary angle-closure	0.3 (0.0–0.7)	0.9 (0.5–1.3)	0.6 (0.4–0.9)
Secondary†	0.6 (0.2–1.0)	0.4 (0.1–0.7)	0.5 (0.2–0.7)
Early-onset developmental	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
All	5.0 (3.9–6.2)	5.0 (4.0–6.0)	5.0 (4.2–5.8)
Glaucoma including suspected cases			
Primary open-angle*	6.3 (5.0–7.6)	5.8 (4.7–6.9)	6.0 (5.1–6.8)
Primary angle-closure	0.5 (0.1–0.9)	1.1 (0.6–1.6)	0.8 (0.5–1.2)
Secondary†	0.7 (0.2–1.2)	0.6 (0.3–1.0)	0.7 (0.4–1.0)
Early-onset developmental	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
All	7.5 (6.1–8.9)	7.5 (6.3–8.7)	7.5 (6.5–8.4)

CI = confidence interval.
*Regardless of intraocular pressure.
†Including exfoliation glaucoma.

may be due to the relatively small number of subjects (3021) in the present study, and life expectancy, expected to be shorter with some forms of congenital glaucoma with systemic anomalies, might be also a contributing factor.

The present study and our study group's previous report[24] revealed that prevalences of all cases of glaucoma and glaucoma/suspected glaucoma are 5.0% (95% CI, 4.2%–5.8%) and 7.5% (95% CI, 6.5%–8.4%), respectively, in those 40 years or older in Japan. The prevalence of PACG or SG increased with age significantly. This, along with the similar trend for POAG,[24] means that glaucoma is an important health issue in the elderly population. The subtypes of various glaucomas differ among various ethnic groups. The ratio of the prevalence of POAG with normal IOP (i.e., normal-tension glaucoma) to that of all glaucoma was 72% (3.6%/5.0%) in our population. This high prevalence of normal-tension glaucoma is the most distinctive feature of glaucoma epidemiology in Japanese. Further research is needed to elucidate the cause of glaucomatous optic neuropathy in Japanese eyes with apparently normal IOP.

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LABORATORY INVESTIGATION

Topographic Characteristics of the Optic Nerve Head Measured with Scanning Laser Tomography in Normal Japanese Subjects

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Abstract

Purpose: Few studies have been performed regarding the topographic information obtained with the Heidelberg retina tomograph (HRT) in normal Japanese. In this study, we examined the factors influencing optic disc parameters and hemisphere symmetry obtained with the HRT in normal Japanese subjects.

Methods: Mean values and the standard deviation range for the main HRT parameters were evaluated in 223 eyes of 223 normal Japanese subjects. The influence of age, sex, and disc size on HRT topographic data was analyzed. The superior and inferior hemisphere topographic parameters were compared.

Results: Disc area showed a significant difference by sex ($P = 0.0493$). Rim volume ($r = -0.208$, $P = 0.019$), height variation contour ($r = -0.275$, $P = 0.001$), and mean retinal nerve fiber layer (RNFL) thickness ($r = -0.366$, $P = 0.001$) declined with age. All parameters except height variation contour and mean RNFL thickness showed a clinically significant correlation with disc size ($-0.159 < r < 0.719$, $P < 0.01$). Cup parameters in the superior hemisphere were significantly greater than those in the inferior hemisphere. In contrast, rim parameters in the superior hemisphere were significantly smaller than those in the inferior hemisphere.

Conclusions: Some factors, namely, sex, age, and disc size, affected the optic disc parameters in the HRT measurements. Possible parameter asymmetry between the two hemispheres should be considered in normal eyes. **Jpn J Ophthalmol** 2005;49:469–476 © Japanese Ophthalmological Society 2005

Key Words: influence factors, normal Japanese, optic nerve head, scanning laser ophthalmoscopy

Introduction

Recognition of optic disc changes is essential for diagnosing and monitoring glaucoma. The optic nerve head characteristics of normal eyes are known to be highly variable and usually reflect the subject's background and the techniques used to measure the optic disc.

Previous studies have suggested that factors such as age, race, and sex might affect optic disc characteristics in normal eyes.[1–3] Several semiquantitative or quantitative techniques of optic disc measurement have been employed in clinical practice and the laboratory. Evaluation of the cup/disc ratio using an ophthalmoscopic lens with slit-lamp biomicroscopy is subjective, and, although it is the most popular method, there is disagreement among glaucoma experts regarding the reliability of this technique.[4]

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See Appendix for the Heidelberg retina tomograph (HRT) study group members

Jpn J Ophthalmol
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The quantitative methods used in research include planimetric evaluation of stereoscopic photographs, digitized optic nerve image analyzers (e.g., the Rodenstock optic nerve head analyzer), and, more recently, the confocal scanning laser ophthalmoscope. These methods have markedly improved the consistency of the measurements. Results of semiquantitative evaluation of the cup/disc ratio differ from those of quantitative methods, especially in normal subjects,[5] and a previous study revealed an inconsistency between two different quantitative methods.[6]

The Heidelberg retina tomograph, a confocal scanning laser ophthalmoscope, has now become popular in glaucoma clinics because of its potential use in obtaining an objective and quantitative evaluation of the optic nerve head.[7–11] An accurate disc and nerve fiber layer complex measurement with the HRT enables the clinician to track glaucomatous changes during routine examinations. The latest version, ver.1.12 or later, of the HRT employs a classification program that enables the clinician to distinguish between normal and glaucomatous eyes using discriminant analysis.[12] To improve potential early glaucoma recognition with the HRT, we require detailed information about the characteristics of disc topography, cup/disc ratio side differences,[13] and hemispherical and segmental analyses[14] of normal eyes.

Racial differences in the normal optic disc have also been demonstrated by several previous studies.[1,15] Although several studies have described the optic nerve head topography obtained with the HRT in normal white subjects,[15,16] little is known about the topographic characteristics of optic discs of normal Japanese subjects. Moreover, little is known regarding the factors contributing to the characteristics of the optic disc or the symmetry of the disc sectors in the Japanese population. In the present study, we examined HRT images in a large number of normal Japanese, and studied the distribution pattern of each HRT parameter and the factors contributing to the parameters and hemisphere symmetry of the normal Japanese optic disc.

Subjects and Methods

Normal subjects were recruited from hospital staff members and their friends or family members, retired staff members, and visiting patients who met the inclusion criteria. All subjects were examined at Gifu University, Tokyo University, Niigata University, Hiroshima University, Nihon University, or the Yoshikawa Eye Clinic. The institutional review board of each institution approved this study. Informed consent was obtained from each subject.

The inclusion criteria for normal subjects were as follows: (1) no history of eye diseases except incipient age-related cataract; (2) no history of systemic diseases such as diabetes mellitus or hypertension; (3) no family history of glaucoma; (4) no history of intraocular surgery or neurological disease; (5) intraocular pressure less than 22 mmHg; (6) best-corrected visual acuity of 0.7 or better; (7) a spherical refraction between −5.0 D and +3.0 D and a cylinder correction within ±2.5 D; and (8) normal visual field with the Central 30-2 program of the Humphrey Field Analyzer 630 or Humphrey Field Analyzer II (Zeiss-Humphrey Systems, San Leandro, CA, USA) or program G1 or G2 of the Octopus perimeter (Interzeag, Schlieren, Switzerland).

Optic disc measurements were obtained with a Heidelberg retina tomograph (HRT version 2.11; Heidelberg Engineering, Heidelberg, Germany), the details of which have been reported elsewhere.[4–9] After the optic disc margin was outlined by an operator, stereometric disc and retinal nerve fiber layer (RNFL) parameters were calculated automatically. The reference plane, which was defined as being 50 μm below the retinal surface within the temporal 350°–356° sector, was used for determination of the two- and three-dimensional optic disc parameters.

Trained operators in each institution obtained HRT images three times through undilated pupils. Mean HRT topographic images having less than 30 μm of average variability were used for the analysis. One operator (HU) drew a contour line to determine the optic disc margin on all HRT images obtained. A contour line was drawn as coincident with the inner border of the scleral ring (the Elschnig ring), or with the outer border rim edge when the Elschnig ring was unclear. Data from deformed discs (e.g., markedly tilted, morning glory-like, disc drusen, microdiscs, megalodiscs) or poor-quality images were excluded from the database. For each subject, if both eyes met the inclusion criteria, one eye was randomly selected for the analyses, except for the side difference analysis.

We determined the following HRT stereometric parameters: disc area, cup area, cup-to-disc area ratio, cup volume, rim volume, height variation contour, cup shape measure, mean RNFL thickness, and RNFL cross-sectional area. The mean ± SD and range of each disc parameter were calculated, and the distribution pattern was evaluated using the Kolomogorov-Smirnov test.

Influences on the main HRT parameters, sex, age, and optic disc size, were evaluated using the Bonferroni-Dunn test for sex and Spearman's rank correlation test for age and optic disc size. Comparison between the superior and inferior hemisphere symmetry of the HRT parameters was carried out using the Wilcoxon signed-ranks test. The interocular difference in HRT parameters was also calculated in 174 subjects in whom good-quality HRT images had been obtained in both eyes.

A P value of less than 0.05 was considered statistically significant.

Results

From the initial database of 248 subjects (448 eyes), 223 subjects (124 women, 99 men) (223 eyes) were selected for this study. Twenty-five subjects were excluded because of their poor-quality images or unsatisfied inclusion criteria. The mean (±SD) age was 45 years ± 17.5 years (range, 15 to 76 years), and the mean refractive error (spherical equivalent) was −1.8 D ± 2.8 D (range, −4.75 D to +2.5 D).

Morphometric Data for the Optic Disc

The normal optic disc parameters obtained with HRT are shown in Table 1. Histograms of all HRT parameters, except cup volume, show a normal distribution curve (Fig. 1) by the Kolomogorov-Smirnov test. The histogram for cup volume is positively skewed.

Influence of Sex, Age, and Optic Disc Size on HRT Parameters

Disc area was larger in men than in women ($P = 0.049$). Other HRT disc parameters showed no significant intersex differences (Table 2). The rim volume ($r = -0.208$, $P = 0.019$), height variation contour ($r = -0.275$, $P = 0.0011$), RNFL cross-sectional area ($r = -0.348$, $P = 0.006$), and mean RNFL thickness ($r = -0.366$, $P = 0.001$) declined with age. The cup shape measure showed a significant positive correlation with age ($r = 0.153$, $P = 0.023$). No other parameters significantly correlated with age (Table 3).

All parameters, except the height variation contour and the mean RNFL thickness, showed significant correlations with disc size (Table 4). Cup area showed the strongest correlation ($r = 0.72$, $P = 0.01$) with disc size in normal eyes.

Symmetry Analysis Between Superior and Inferior Disc Hemispheres

HRT parameters in the superior and inferior disc hemispheres are summarized in Table 5. The cup area, cup-to-disk area ratio, cup volume, mean RNFL thickness, and

Table 1. Summary of Heidelberg retina tomograph (HRT) disc parameters in the present study (number of eyes = 223)

Parameter	Mean ± SD	Range
Disc area (mm^2)	2.167 ± 0.485	0.896–4.086
Cup area (mm^2)	0.595 ± 0.362	0.009–2.073
Cup/disc area ratio	0.261 ± 0.121	0.007–0.595
Rim area (mm^2)	1.567 ± 0.328	0.403–2.814
Height variation contour (mm)	0.401 ± 0.110	0.177–0.850
Cup volume (mm^3)	0.144 ± 0.156	0–1.330
Rim volume (mm^3)	0.416 ± 0.138	0.141–0.784
Mean cup depth (mm)	0.225 ± 0.093	0.044–0.600
Maximum cup depth (mm)	0.628 ± 0.199	0.137–1.211
Cup shape measure	−0.209 ± 0.078	−0.446–0.001
Mean RNFL thickness (mm)	0.266 ± 0.081	0.050–0.505
RNFL cross-sectional area (mm^2)	1.362 ± 0.417	0.151–2.488

RNFL, retinal nerve fiber layer.

Table 3. Effect of age on HRT parameters

Parameter	*R*	*P**
Disc area (mm^2)	0.053	0.434
Cup area (mm^2)	0.057	0.394
Cup/disc area ratio	0.069	0.302
Rim area (mm^2)	0.004	0.953
Height variation contour (mm)	−0.275	0.001
Cup volume (mm^3)	0.069	0.301
Rim volume (mm^3)	−0.208	0.019
Mean cup depth (mm)	−0.004	0.994
Maximum cup depth (mm)	−0.101	0.131
Cup shape measure	0.153	0.023
Mean RNFL thickness (mm)	−0.366	0.001
RNFL cross-sectional area (mm^2)	−0.348	0.006

*Spearman's coefficient of rank correlation.

Table 4. Influence of optic disc size on HRT parameters

Parameter	Correlation	*P**
Cup area (mm^2)	0.719	0.010
Cup/disc area ratio	0.504	0.001
Rim area (mm^2)	0.601	0.001
Height variation contour (mm)	−0.081	0.231
Cup volume (mm^3)	0.636	0.001
Rim volume (mm^3)	0.214	0.001
Mean cup depth (mm)	0.457	0.001
Maximum cup depth (mm)	0.309	0.001
Cup shape measure	0.418	0.001
Mean RNFL thickness (mm)	−0.159	0.018
RNFL cross-sectional area (mm^2)	0.180	0.076

*Spearman's coefficient of rank correlation.

Table 2. Comparison of optic disc morphometry by sex

Parameter	Men (99 eyes)	Women (124 eyes)	*P**
Disc area (mm^2)	2.239 ± 0.505	2.110 ± 0.463	0.049
Cup area (mm^2)	0.615 ± 0.382	0.579 ± 0.346	0.467
Cup/disc area ratio	0.260 ± 0.120	0.262 ± 0.122	0.896
Rim area (mm^2)	1.613 ± 0.334	1.531 ± 0.319	0.056
Height variation contour (mm)	0.402 ± 0.122	0.399 ± 0.100	0.858
Cup volume (mm^3)	0.153 ± 0.174	0.137 ± 0.141	0.455
Rim volume (mm^3)	0.428 ± 0.146	0.408 ± 0.132	0.267
Mean cup depth (mm)	0.224 ± 0.089	0.227 ± 0.097	0.795
Maximum cup depth (mm)	0.629 ± 0.191	0.628 ± 0.205	0.978
Cup shape measure	−0.212 ± 0.074	−0.207 ± 0.081	0.691
Mean RNFL thickness (mm)	0.263 ± 0.087	0.267 ± 0.075	0.709
RNFL cross-sectional area (mm^2)	1.375 ± 0.439	1.352 ± 0.399	0.691

Values represent mean ± SD.
*Bonferroni-Dunn test.

Jpn J Ophthalmol
Vol 49: 469–476, 2005

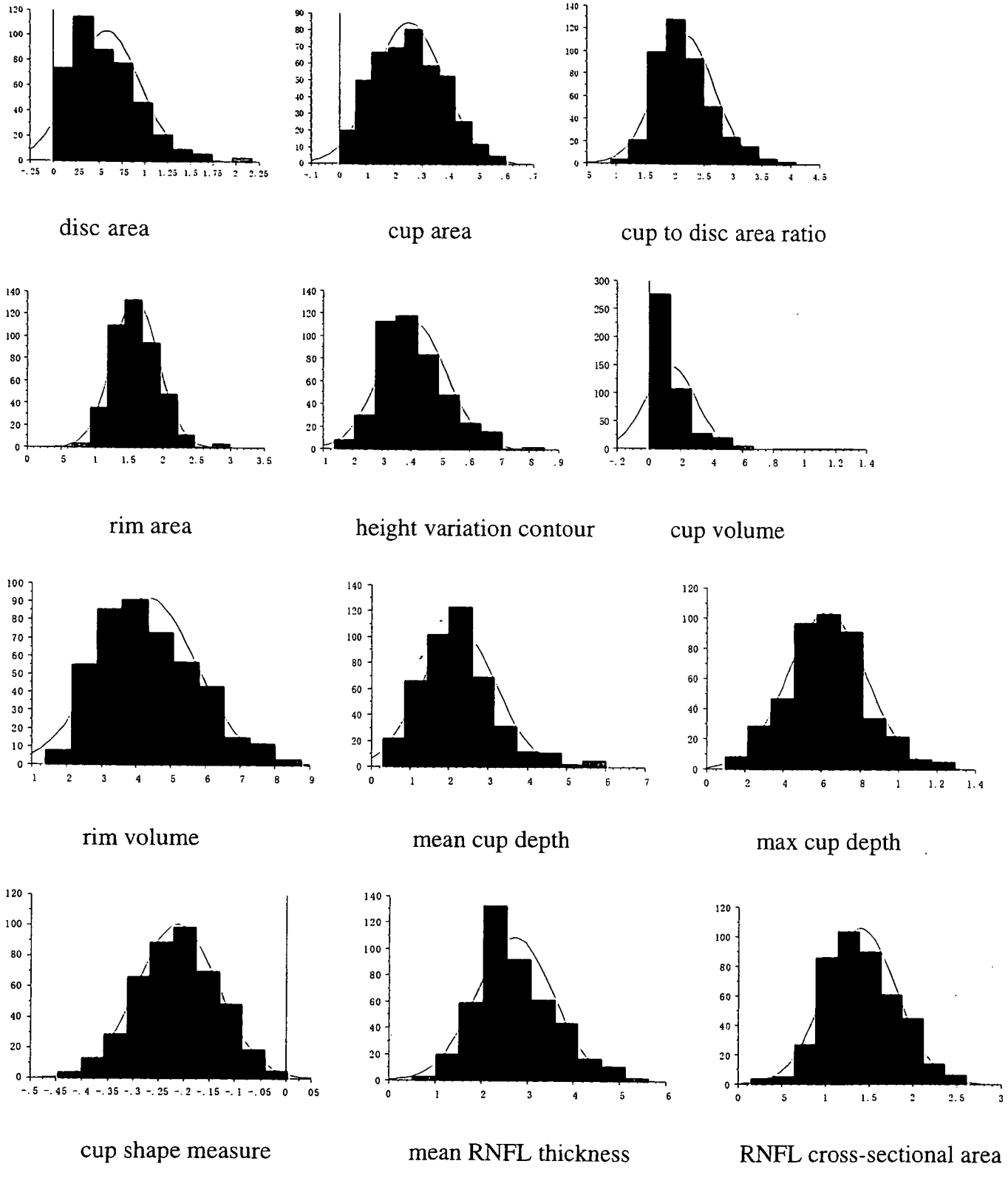

Figure 1. Distribution patterns of Heidelberg retina tomograph (HRT) parameters in normal Japanese were analyzed using the Kolomogorov-Smirnov test. All HRT parameters except cup volume show a normal distribution. Cup volume skews to the left.

Table 5. Symmetry analysis between superior and inferior disc hemispheres in HRT

Parameter	Superior hemisphere	Inferior hemisphere	P^*
Disc area (mm^2)	1.084 ± 0.243	1.087 ± 0.244	0.049
Cup area (mm^2)	0.310 ± 0.197	0.289 ± 0.185	0.006
Cup/disc area ratio	0.271 ± 0.133	0.251 ± 0.127	0.005
Rim area (mm^2)	0.774 ± 0.158	0.794 ± 0.186	0.003
Height variation contour (mm)	0.368 ± 0.115	0.372 ± 0.113	0.351
Cup volume (mm^3)	0.081 ± 0.095	0.065 ± 0.070	0.001
Rim volume (mm^3)	0.205 ± 0.073	0.211 ± 0.076	0.029
Mean cup depth (mm)	0.237 ± 0.107	0.213 ± 0.088	0.001
Maximum cup depth (mm)	0.634 ± 0.215	0.574 ± 0.191	0.001
Cup shape measure	−0.193 ± 0.090	−0.186 ± 0.108	0.461
Mean RNFL thickness (mm)	0.269 ± 0.086	0.259 ± 0.089	0.037
RNFL cross-sectional area (mm^2)	0.694 ± 0.218	0.674 ± 0.206	0.038

* Wilcoxon signed-rank test.

Table 6. HRT parameter interocular differences (absolute values)

	Disc area	Cup area	C/D ratio	Rim area	HVC	Cup volume	Rim volume	MCD	MXCD	CSM	MRNFLT	RNFLCSA
Mean	0.117	0.164	0.070	0.164	0.064	0.056	0.098	0.045	0.093	0.056	0.051	0.271
SD	0.132	0.146	0.055	0.148	0.055	0.057	0.079	0.039	0.082	0.048	0.045	0.242
Minimum	0.001	0.002	0.000	0.002	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.002
Maximum	1.012	1.046	0.230	1.009	0.304	0.304	0.411	0.208	0.418	0.216	0.227	1.424
95% C.I.	0.375	0.450	0.178	0.454	0.172	0.168	0.253	0.121	0.254	0.145	0.139	0.745

C, cup; D, disc; HVC, height variation contour; MCD, mean cup depth; MXCD, maximum cup depth; CSM, cup shape measure; MRNFLT, mean retinal nerve fiber layer thickness; RNFLCSA, retinal nerve fiber layer cross-sectional area; C.I., confidence interval.

RNFL cross-sectional area in the superior hemisphere were significantly larger than those in the inferior hemisphere. In contrast, the rim area and rim volume in the superior hemisphere were significantly smaller than those in the inferior hemisphere.

Intraocular Differences of HRT Parameters

The intraocular differences in disc areas ranged from 0.001 to 1.012 mm^2, and the 95% confidence interval was 0.375 mm^2. Side differences in other HRT parameters are shown in Table 6.

Discussion

There is a considerable interindividual variability in optic disc morphometry in normal eyes. Many previous studies[1-3,14-26] have attempted to analyze normal optic disc parameters using various methods.

A recent population-based study[2] demonstrated optic disc characteristics using stereoscopic photographs obtained by using a simultaneous stereoscopic fundus camera (TRC-SS2; Topcon Optical, Tokyo, Japan) and IMAGEnet (Topcon) in 5114 subjects who were 55 years of age or older, 98% of whom were white. The population mean (±SD) of the disc area, neural rim area, and cup area were reported as 2.42 ± 0.47 mm^2, 1.85 ± 0.39 mm^2, and 0.57 ± 0.34 mm^2, respectively.

Mean optic disc areas in normal eyes varied among different studies (range, 1.70 mm^2 to 2.89 mm^2)[17,18]. These different results may reflect the inherent great interindividual variability in the appearance of the normal optic disc or differences in the inclusion criteria for normal eyes among the studies, different measurement methods, such as different fundus magnifications, or different definitions of disc and cup borders used by the various investigators.

It should be kept in mind that differences exist between indirect clinical image analysis methods such as the Rodenstock optic nerve head analyzer, computer-aided planimetry, and confocal scanning laser ophthalmoscopy and direct disk measurements,[26] in addition to the variability inherent in the various image analysis devices.[27-29] Dichtl et al.[27] examined the neuroretinal rim area differences between HRT and stereoscopic optic disc photograph measurements (planimetric technique) in 25 normal eyes and 32 glaucomatous eyes. They reported that the neural rim area obtained with HRT was larger, especially in the nasal region, than that obtained with photographs. These differences also increase with increasing glaucomatous optic disc damage. By contrast, another study[3] showed very similar disc measurement values, obtained by two different methods. One study[26] suggested that actual optic disc measurements were larger than those based on clinical imaging methods. Thus, we should always take into account the mea-

Jpn J Ophthalmol
Vol 49: 469–476, 2005

surement method and be aware of the characteristic differences among the various imaging methodologies used in optic disc analysis.

We used a confocal scanning laser ophthalmoscope (HRT) to obtain measurements of various optic disc parameters in the present study. The HRT was recently developed to measure two- and three-dimensional parameters of the optic nerve head with excellent test and retest consistency.[9] A previous study demonstrated that disc measurements obtained with the HRT corresponded to direct optic disc measurements made in phakic eyes.[30] Recently reported mean optic disc areas in normal eyes using HRT ranged from 1.801 mm^2 to 2.67 mm^2.[3,8,9,16] In the present study, the mean (±SD) disc area measured with the HRT was 2.167 ± 0.485 mm^2 with an interindividual variability of 1:4.3. Knowledge of the distribution pattern of each HRT parameter is necessary to determine which statistical methods should be employed. All HRT parameters except cup volume were normally distributed. Cup volume distribution in the normal Japanese in this study was skewed to the right, which is concordant with previous studies in normal white subjects.[16] Compared to recent investigations using HRT, our disc measurement results in Japanese were numerically larger than those in white races[3,8,16] and smaller than those in Hispanics and blacks,[15] although no statistical comparisons between ethnic groups were carried out.

The current study was not designed to be population-based; hence topographic measurements in our study do not represent the normal optic disc of all Japanese. However, this is the first study to describe a large number of normal Japanese optic discs using multiple-center data. Furthermore, all HRT topographic data were analyzed at one institution, and all contour lines were outlined by a single operator in a masked fashion to minimize the operator bias at each institution.

Many previous studies[1–3,17,19,22,24] have suggested that factors such as sex, age, and optic disc size might influence the morphometry of the optic disc. The influence of sex and age on optic disc characteristics remains controversial. Some studies have reported no significant differences in the optic disc area between the sexes,[1,14,20] while others have reported that men have a larger disc area than women.[2,25] The Rotterdam Study[2] demonstrated that the disc area and rim area were 3.2% and 4.3% larger in men than in women, respectively; and the Baltimore Eye Study[1] demonstrated that men had a disc area that was 2%–3% larger than that in women. The present study found that men had numerically larger HRT topographic measurements than did women, although the differences were not statistically significant except for disc area.

Some investigators found no relationship between disc characteristics and age cross-sectionally[1,2,14,16] or longitudinally,[23] whereas others found age-related optic disc changes cross-sectionally.[3,24] An age-related decline in the number of optic nerve axons has previously been shown histologically, with the number of optic nerve fibers lost with age reported to be about 4000–5000/year.[31,32] The present findings suggest that there is an aging effect on several HRT parameters. The rim volume, height variation contour, mean RNFL thickness, and RNFL cross-sectional area declined with age in our HRT analysis. Although mean RNFL thickness and RNFL cross-sectional area by HRT measurement do not represent actual nerve fiber layer (NFL) thickness, our current result is concordant with a recent investigation evaluating the aging effect on nerve fiber thickness using optical coherence tomography (OCT).[33] Additionally, the cup shape measure showed a positive correlation with age. Such stereometric measurements as rim volume, height variation contour, and mean RNFL thickness might represent the number of optic nerve fibers more accurately than conventional two-dimensional parameters, that is, cup area, cup-to-disc area ratio, and rim area. The cup shape measure is a unique HRT parameter that measures the overall three-dimensional slope of the cup. This parameter summarizes in one number the structure of the cup and takes into account its depth variation and the steepness of the cup wall. Its value is typically negative in normal eyes and usually less negative or even positive in steep cups, that is, in the glaucomatous eye. The cup shape measure is also reported to be a sensitive marker of glaucomatous optic disc changes, especially at an early stage.[12,34] This finding suggests that optic discs in elderly subjects may be more susceptible to change and more similar to those seen in glaucoma than is the case in younger subjects. Thus, distinction of age-related deterioration of disc parameters from pathological changes still seems problematic in HRT analysis.

Several studies[17,20,21] concluded that the optic disc size might influence the intrapapillary morphometry. In normal eyes, the larger the optic disc area, the larger the cup area,[20,21] and it may be the case that disc area affects many intrapapillary parameters. Britton et al.[20] demonstrated a linear correlation between disc area and both the neuroretinal rim area ($r = 0.75$) and the cup area ($r = 0.83$). Caprioli et al.[17] reported positive correlations between disc area and cup area and rim area and cup volume using computerized image analysis with the Rodenstock optic nerve head analyzer.

The present study confirms the relationship between the optic disc area and all intrapapillary parameters, except the height variation contour. The height variation contour represents the difference in height between the most elevated point and the most depressed point of the corrected contour line and, theoretically, is independent of the disc area and circumference.

It is important to know the detailed rim shape configuration in normal eyes if we are to make an early detection of a glaucomatous change. In the present study, we compared HRT parameter symmetries between the superior and inferior hemispheres. The HRT rim area and rim volume in the inferior hemispheres were significantly larger than those in the superior hemispheres. This agrees with a previous study that showed the neural rim is broadest in the inferior sector, followed by the superior, nasal, and temporal sectors, in normal eyes, according to a planimetry analysis.[35] Conversely, the NFL parameters of HRT in the inferior hemisphere were significantly smaller than those in the

superior hemisphere. This result also agrees with recent studies that measured NFL thickness with OCT[33] or scanning laser polarimetry (GDx).[36] These findings of NFL characteristics may explain the fact that inferior light sensitivity usually is functionally more predominant than that of the superior hemisphere in normal eyes.[37]

Careful observation of the interocular differences in the optic disc parameters is helpful for early glaucoma detection.[25] The 95% confidence interval of interocular differences of the cup-to-disc area ratio and rim area in this study were 0.178 and 0.454 mm^2, respectively. Our current data are similar to those of a previous study using HRT in a white population.[16] On the other hand, another study[14] showed larger interocular differences in rim area than our data because of the different measurement method employed. The information on side differences in normal eyes seems to have important implications for the early deterioration of the optic nerve head in glaucoma patients.

In conclusion, the present study reported the topographic measurements of the normal Japanese optic disc obtained with HRT. Several HRT parameters seem to be affected by age and disc size. Disc topographic asymmetry between the two hemispheres was present. These topographic characteristics in Japanese are in accordance with the results of previous studies;[3,19,22,24,34] hence, it should be emphasized that several factors can affect the normal individual disc and must be taken into account in evaluating glaucomatous optic neuropathy. Further studies are needed to construct an effective glaucoma classification system based on a normative database considering the above-mentioned, potential influencing factors involved with the use of the confocal scanning laser.

Appendix: Members of the HRT Study Group

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LABORATORY INVESTIGATION

Correlation Between Individual Differences in Intraocular Pressure Reduction and Outflow Facility Due to Latanoprost in Normal-Tension Glaucoma Patients

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Abstract

Purpose: The amount of intraocular pressure (IOP) reduction achieved by the use of latanoprost eyedrops varies among patients, and there are even nonresponders. This report examines whether there is any correlation between the amount of individual variability in IOP reduction and the uveoscleral outflow facility after latanoprost eyedrop instillation in normal-tension glaucoma patients.

Methods: Sixteen normal-tension glaucoma patients (mean age, 56.4 years) were enrolled in the study to investigate the relationship between the amount of IOP reduction and outflow facility. Before treatment, subjects underwent circadian IOP measurement and then tonography, and the outflow facility was calculated. Subsequently, patients began treatment once daily with latanoprost instillation in one eye. After 4 weeks of daily latanoprost treatment, circadian IOP was measured again.

Results: Mean pretreatment outflow facility was 0.23 ± 0.05 μl/min per mmHg. On average, latanoprost instillation decreased IOP by 2.8 mmHg, but the reduction varied among individuals from –0.3 mmHg to 5.8 mmHg. No significant correlation was noted between the outflow facility and the IOP decline associated with latanoprost.

Conclusion: Because there was no significant correlation between individual IOP reduction by latanoprost and outflow facility, the differences in substantial change in uveoscleral outflow after latanoprost administration may be one explanation for the individual variation in IOP reduction after treatment with this drug. **Jpn J Ophthalmol** 2006;50:20–24 © Japanese Ophthalmological Society 2006

Key Words: intraocular pressure reduction, latanoprost, normal-tension glaucoma, uveoscleral outflow facility

Introduction

Generally, intraocular pressure (IOP) is determined by aqueous humor flow volume through the ciliary epithelium, trabecular outflow, uveoscleral outflow, and episcleral venous pressure. These factors are summarized in the Goldmann formula $Fin = C(IOP - Pv) + Fu$, where Fin is aqueous humor production, C is outflow facility, Pv is episcleral venous pressure, and Fu is uveoscleral outflow.[1] The ocular hypotensive mechanism of latanoprost is thought to result mainly from increased uveoscleral outflow, reflecting degradation of the extracellular matrix (ECM) after matrix metalloproteinase (MMP) activation by the drug.[2–5]

Although a subgroup of glaucoma patients is known to be unresponsive to latanoprost administration, the mechanism is unknown. Despite some differences between reports in the definition of latanoprost nonresponders, 5% to 25% of patients fall into this group.[6–9] IOP reduction by

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latanoprost therapy is difficult to predict, as a poor response to latanoprost is not related to baseline IOP or patient age.[9] Therefore, we first studied whether an individual difference in latanoprost IOP reduction amount exists in normal-tension glaucoma patients. Then, we measured IOP and outflow facility in the subjects to investigate whether individual differences in IOP reduction and individual differences in outflow facility were correlated.

Patients and Methods

The subjects included six men and ten women in whom normal-tension glaucoma was diagnosed between January 2002 and March 2003 by the glaucoma clinic at Gifu University School of Medicine. Diagnosis was based on reproducible visual field defects of the retinal nerve fiber layer type, corresponding optic disc excavation, normal open angles, and IOP readings within the normal range. Subjects had no previous intraocular surgery and had never received any ocular hypotensive medications. All were Japanese. The study was performed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients after provision of detailed information about the study.

Before treatment, subjects underwent IOP measurement in a sitting position every 2 h for 24 h using a Goldmann applanation tonometer, and they also underwent tonography (STX; Inami, Tokyo, Japan). Measurements were obtained at room temperature. Tonography was performed in a quiet environment with subjects supine, arms at their sides, after topical application of oxybuprocaine (Benoxil; Santen, Osaka, Japan). All tonography was carried out between 3 to 5 P.M. by a single experienced examiner. After these measurements, patients began treatment once daily with latanoprost instillation (Xalatan; Pfizer, Tokyo, Japan) in the eye showing the worse mean deviation in the central 30-2 program for the Humphrey Field Analyzer. After 4 weeks of daily latanoprost treatment, IOP was measured by Goldmann applanation tonometry to construct a diurnal curve including findings at 10 A.M., 12 noon, 2 P.M., and 4 P.M.. The diurnal IOP and circadian IOP were the mean of intraocular pressure readings measured for 6 h, from 10 A.M. to 4 P.M., and for 24 h, respectively.

Demographic and clinical data for the patients are summarized as follows. Their mean age ± SD was 56.4 ± 14.5 years (range, 32–77). The mean refractive index was −2.3 ± 3.0 D (range, −8.5 to +1.4). The mean deviation (MD) and corrected pattern standard deviation (CPSD) for the central 30-2 program of the Humphrey Field Analyzer before latanoprost eyedrop instillation were −10.92 ± 8.32 dB (range, −30.54 to −1.09) and 8.3 ± 3.8 dB (range, 0.0–12.9), respectively.

Statistical analysis was carried out by a paired t test, an unpaired t test, or regression analysis, as appropriate for the items evaluated. The significance level adopted was $P < 0.05$ (two-tailed test).

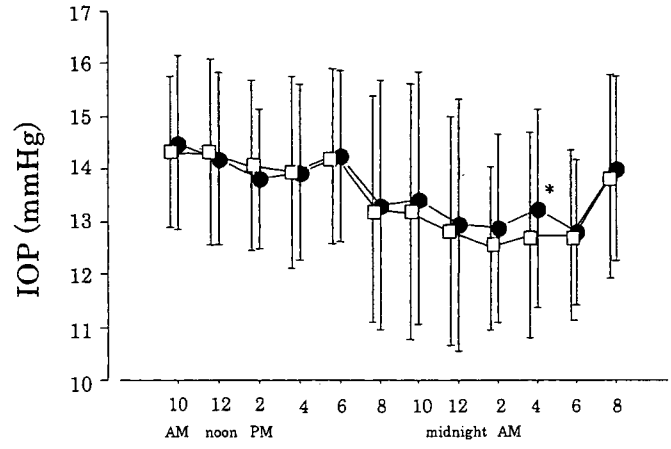

Figure 1. Pretreatment 24-h intraocular pressure (IOP) measurements. IOP did not differ significantly between the eye later to be treated with latanoprost and the fellow eye except at 4 A.M. (●, untreated eyes; □, eyes to be treated with latanoprost; *paired t test, $P = 0.0152$).

Results

The tonographically measured outflow facility was 0.23 ± 0.05 μl/min per mmHg (range, 0.14–0.31). Mean diurnal IOP, mean circadian variation, maximum and minimum circadian variation, and the circadian variation range of the pretreatment 24-h IOP were 14.1 ± 1.3 mmHg (10.8–17.0), 13.6 ± 1.3 mmHg (10.9–16.1), 15.6 ± 1.5 mmHg (12–19), 11.4 ± 1.3 mmHg (10–14), and 4.2 ± 1.3 mmHg (2–8), respectively.

IOP measured before treatment was higher in the daytime than at night. IOP in the eye assigned to subsequent latanoprost treatment did not differ significantly from that in the fellow eye at any time point except at 4 A.M. (paired t test, $P = 0.0152$; Fig. 1).

After 4 weeks of latanoprost administration, IOP was reduced significantly in the treated eye regardless of the time of measurement; IOP was approximately 2.8 mmHg less than in the fellow eye (unpaired t test, $P < 0.0001$). This also was true for diurnal IOP, compared with pretreatment measurements, again by approximately 2.8 mmHg (paired t test, $P < 0.0001$; Figs. 2, 3).

The average IOP reduction differed among individuals from −0.3 to 5.8 mmHg. The relationship between the IOP reduction and the pretreatment outflow facility is shown in Fig. 4. The r^2 value was 0.083, and the slope of the regression line was small, indicating no statistical significance ($P = 0.2780$). On the other hand, the change in uveoscleral outflow (ΔFu) and the mean IOP reduction resulting from latanoprost were significantly correlated (Fig. 5).

Discussion

In the current study of normal-tension glaucoma patients, 4 weeks of latanoprost instillation resulted in an IOP reduction of approximately 2.8 mmHg, compared with baseline

Jpn J Ophthalmol
Vol 50: 20–24, 2006

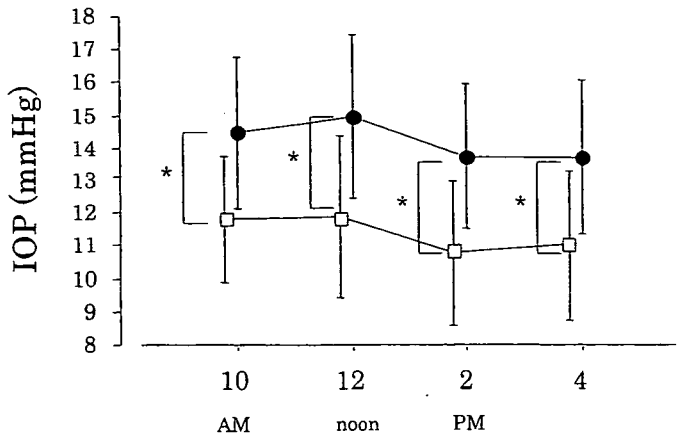

Figure 2. Diurnal IOP in the treated eyes after 4 weeks of daily latanoprost instillation was significantly lower than in the fellow eyes (●, untreated eyes; □, latanoprost-treated eyes; *unpaired t test, $P < 0.0001$).

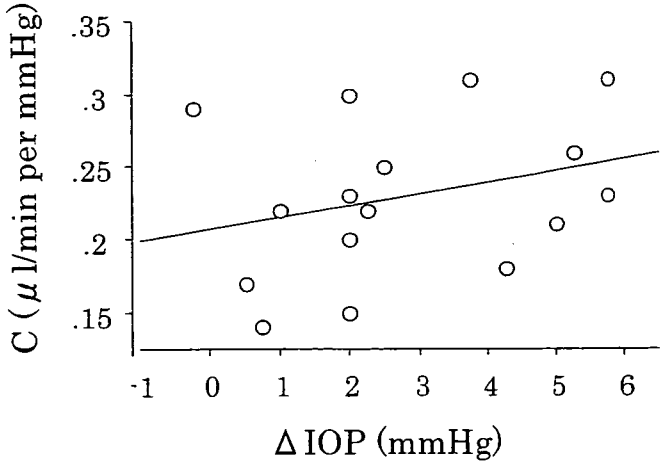

Figure 4. No correlation was seen between outflow facility (C) and the mean IOP decrease associated with latanoprost ($n = 16$; $r^2 = 0.083$, $P = 0.2780$).

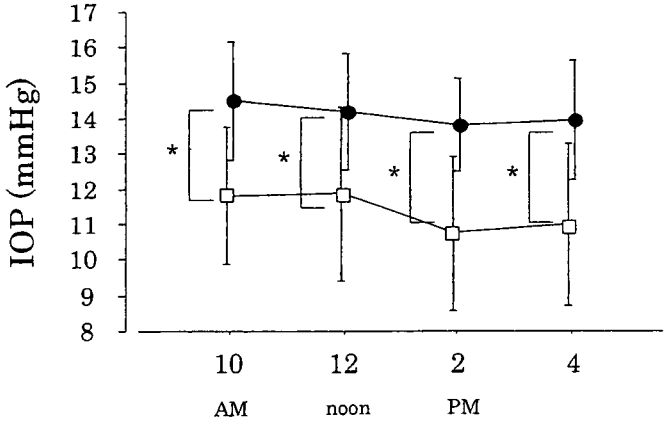

Figure 3. Diurnal IOP before and after 4 weeks of daily latanoprost instillation. Latanoprost administration significantly reduced IOP (●, before treatment; □, after treatment; *paired t test, $P < 0.0001$).

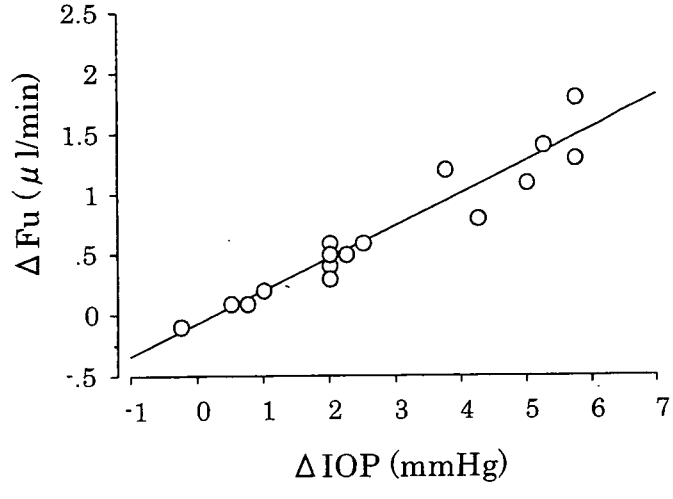

Figure 5. Correlation between and mean latanoprost-induced IOP reduction was significant ($n = 16$; $y = 0.269x - 0.072$; $r^2 = 0.917$, $P < 0.0001$).

measurements or with measurements in untreated contralateral eyes. Furthermore, the value of ΔFu correlated strongly with IOP reduction, suggesting that latanoprost-induced IOP reduction may depend chiefly on uveoscleral outflow. However, we could not predict the amount of IOP reduction by latanoprost prior to its administration.

Latanoprost (13,14-dihydro-17-phenyl-18,19,20-trinor-prostaglandin F_2 -isopropyl- ester), a prostaglandin F_2 derivative and selective FP receptor agonist, activates MMP. This promotes metabolic turnover and remodeling of the ECM adjacent to ciliary muscle cells, increasing uveoscleral outflow and thus reducing intraocular pressure.[2,3] Using tonography and fluorophotometry, most investigators have found no significant change in outflow facility or aqueous humor flow volume related to the instillation of latanoprost.[1,4,5,10] To our knowledge, only one study tonographically demonstrated the improvement of outflow by latanoprost.[10] The analysis performed in the current study was based on the first point of view, since most animal and human studies have indicated that IOP reduction with latanoprost monotherapy results almost exclusively from increased uveoscleral outflow.

Latanoprost instilled once daily causes a 25% to 35% IOP reduction in normal volunteers and in patients with ocular hypertension and primary open-angle glaucoma.[1,6–9,11–14] The drug continues to exert its ocular hypotensive effects throughout a 24-h period.[15–17] Our results were in agreement with such findings. Even eyes with

Table 1. Goldmann equation of aqueous humor dynamics and derived equations

Derivation steps	Equations
Goldmann equation	$Fin = C(IOP - Pv) + Fu$
Step 1, solve for IOP	$IOP = (Fin - Fu)/C + Pv$
Step 2, substitute changed values	$IOP¢ = (Fin - Fu¢)/C + Pv$
Step 3, calculate the difference and simplify	$DIOP = DFu/C$

It is assumed that the uveoscleral outflow, *Fu*, changes to *Fu¢* when *IOP* changes to *IOP¢* and that other parameters remain constant.

Fin, aqueous humor production; *C*, outflow facility; *IOP*, intraocular pressure before latanoprost; *IOP¢*, intraocular pressure after latanoprost; *Pv*, episcleral venous pressure; *DIOP*, *IOP¢ – IOP*; *Fu*, uveoscleral outflow before latanoprost; *Fu¢*, uveoscleral outflow after latanoprost; *DFu*, *Fu¢ – Fu*.

normal-tension glaucoma showed a significant mean reduction in IOP of approximately 2.8 mmHg (19.9%) after 4 weeks of latanoprost therapy, compared with the untreated eyes and the fellow eyes. In previous reports, latanoprost reduced IOP in normal-tension glaucoma patients by up to 3.6 mmHg (21% to 24%).[18,19] One might expect that future therapy with a combination of agents could reduce IOP more than 30% from baseline values even in normal-tension glaucoma patients.

Aqueous humor dynamics in the steady state are defined by the Goldmann equation,[1] $Fin = C(IOP - Pv) + Fu$. If it is assumed that *Pv*, *Fin*, and *C* do not change between before and after latanoprost instillation and that uveoscleral outflow (*Fu*) changes to *Fu¢* when *IOP* changes to *IOP¢*, then $\Delta IOP = \Delta Fu/C$, where $\Delta IOP = IOP¢ - IOP$ and $\Delta Fu = Fu¢ - Fu$ (Table 1). Thus, a change in the outflow facility causes changes in IOP variation, even if ΔFu is constant.

A significant correlation was evident between ΔFu and mean IOP reduction resulting from latanoprost ($y = 0.269x - 0.072$; $r^2 = 0.917$, $P < 0.0001$) (Fig. 5). Therefore, the more latanoprost reduced the IOP, the more uveoscleral outflow increased. Values of ΔFu showed a considerable range, (–0.1 to 1.8).

The correlation coefficient (r^2) between the amount of latanoprost intraocular pressure reduction (ΔIOP) and the amount of uveoscleral outflow increase (ΔFu) indicates that the two are closely related. On the other hand, outflow facility, *C*, was not significantly correlated with the reduction of intraocular pressure induced by latanoprost (ΔIOP). These results indicate that the IOP reduction by latanoprost in each subject depended essentially on uveoscleral outflow. Furthermore, the relative increase in uveoscleral outflow after latanoprost instillation (ΔFu) varied considerably, from –0.1 to 1.8. This may be one explanation for the variation in the amount of IOP reduction achieved by this drug.

Of the 16 patients, 1 (6.25%) had approximate ΔFu values of 0 or less, suggesting that in some individuals latanoprost fails to enhance uveoscleral outflow. Linden and Alm[20] proposed in 1998 that variation in the increase in uveoscleral outflow might reflect variation in sensitivity of the FP receptor. Alternatively, Gandolfi and Cimino[21] hypothesized that some latanoprost nonresponders might have limited ability to activate the drug by de-esterification. Finally, Tsubai et al.[22] suggested that even with pharmacologic MMP activation, metabolic turnover and remodeling of the ECM adjacent to ciliary muscle cells may differ among individuals, possibly contributing to variation in IOP reduction.

In conclusion, individual differences in increased uveoscleral outflow seemed to be responsible for individual differences in the amount of IOP reduction by latanoprost. The mechanism, however, remains unclear, and further investigation is required to address this issue.

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Incidence of Disc Hemorrhages in Open-angle Glaucoma Before and After Trabeculectomy

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Purpose: To investigate the effects of reduction of intraocular pressure (IOP) by surgical intervention on the frequency of disc hemorrhages in eyes with primary open-angle glaucoma (POAG) and normal-tension glaucoma (NTG).

Design: Retrospective study.

Methods: We studied 99 eyes of 99 patients with POAG and 50 eyes of 50 patients with NTG, who underwent trabeculectomy with adjunctive mitomycin C (MMC) and were followed regularly at 1 to 3-month intervals at the Glaucoma Service of Gifu University Hospital. We applied Kaplan-Meier life-table analysis for the detection of disc hemorrhages before and after trabeculectomy.

Results: Trabeculectomy significantly reduced IOP (in POAG: 19.6 ± 4.4 down to 11.1 ± 4.2 mm Hg; in NTG: 15.3 ± 1.5 down to 11.3 ± 4.5 mm Hg; mean ± SD). Life-table analysis revealed that the final cumulative probability of detecting a disc hemorrhage after surgery in POAG was 5.5 ± 2.2% (calculated probability ± SE) and was significantly lower than that (33.4 ± 7.8%) before surgery ($P < 0.0001$, log-rank test). Likewise, the final probability after surgery in NTG was 23.1 ± 6.3% and was significantly lower than that (42.1 ± 8.8%) before surgery ($P = 0.0063$, log-rank test).

Conclusions: IOP reduction via surgical intervention significantly decreases the frequency of disc hemorrhages in open-angle glaucoma patients.

Key Words: trabeculectomy, disc hemorrhage, POAG, NTG

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Disc hemorrhages were first reported by Bjerrum[1] in 1889. Since a rediscovering report by Drance[2] in 1970, a close association has been well recognized between disc hemorrhages and retinal nerve fiber layer defects in glaucomatous optic neruropathy,[3] and with the deterioration of the glaucomatous visual field changes associated with them.[4–13]

Although some investigators[14–16] had some suggestions on the mechanisms underlying disc hemorrhages in glaucomatous eyes, there are still no established theories on the subject. Begg et al[14] found similarities between disc hemorrhage and a small infarction within the optic nerve head. In an experimental study in primates, Sugiyama et al[15] showed that disc hemorrhage was a venous hemorrhage of the retina surface, and they also speculated that it originated in a retinal circulation disorder. Conversely, Quigley et al[16] suggested that it might occur secondary to stretching of the anterior capillaries with posterior bowing of the lamina cribrosa.

Many researchers believe that disc hemorrhage is a prognostic factor of glaucomatous optic neuropathy. Our research group[11,17] previously demonstrated that disc hemorrhage in normal-tension glaucoma (NTG) is the most significant factor that leads to the progression of visual field disorder. Moreover, Drance et al[18] pointed out disc hemorrhage as a factor likely to cause the progression of visual field changes alongside women and migraine in a study of 160 NTG patients.

Ocular hypotensive therapy is well known to reduce the risks of visual field progression toward glaucoma.[19,20] Therefore, if disc hemorrhage is highly implicated in the deterioration of glaucomatous visual fields, it is conceivable that the incidence of hemorrhage may change after intraocular pressure (IOP) reduction via surgical intervention. Hendrickx et al[21] studied alterations in the incidence of disc hemorrhages with antiglaucoma treatment. They found that no alterations in the incidence of disc hemorrhages were seen before and after treatment in NTG patients, as opposed to significant decreases observed in primary open-angle glaucoma (POAG) patients and glaucoma suspects.

In the present longitudinal study, we explored whether the incidences of disc hemorrhages in POAG and NTG eyes decrease as a result of IOP reduction via trabeculectomy with the intraoperative adjunctive use of MMC.

PATIENTS AND METHODS

Of a total of 404 eyes from 265 patients with POAG, and 164 eyes from 115 patients with NTG who underwent

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trabeculectomy at Gifu University Hospital between April 1990 and August 1997, patients had to meet the following criteria to be eligible for the present study: (1) preoperative follow-up period of at least 6 months, (2) postoperative period of at least 12 months, (3) reliable preoperative and postoperative perimetric test results, meaning less than 20% fixation loss and less than 33% false-positive or false-negative answers, using a Humphrey Field Analyzer (Program 30-2, Zeiss-Humphrey Instruments, Inc, San Leandro, CA), (4) abnormal Glaucoma Hemifield Test result with a mean deviation (MD) better than −20.00 dB at the time of surgery, and (5) best-corrected visual acuity better than or equal to 20/40. When both eyes of a patient fulfilled the above criteria, only the right eye was subjected to the study. This study was approved by the Institutional Review Board of Gifu University School of Medicine, and verbal informed consent was obtained from all patients.

The diagnosis of NTG was carried out based on the following criteria: (1) IOP measured with Goldmann applanation tonometry including the 24-hour diurnal curve had a peak equal to or less than 21 mm Hg in both eyes without any medication for glaucoma; (2) both eyes demonstrated a gonioscopically normal open angle; (3) at least 1 eye showed the presence of typical visual field defects corresponding to glaucomatous disc changes; and (4) neuroradiologic, rhinologic, and general medical examinations did not disclose any pathology responsible for optic nerve damage other than glaucoma. Diagnostic criteria for POAG were the same as those for NTG except for preoperative IOP, where an IOP equal to or greater than 22 mm Hg should have been recorded in at least 1 eye in our clinic or in other medical institutions.

Antiproliferative surgery was adopted when an eye was judged to have a progressive visual field defect with the maximum of tolerable medical treatments. All surgeries were performed according to a modification of Cairns technique.[22] In short, a limbal-based conjunctival incision and a 4 × 4 mm half-layer scleral flap were made; mitomycin C was then applied as described in detail elsewhere.[22] After 5 minutes, the wound was irrigated with copious amounts of balanced salt solution. Thereafter, an approximately 0.5 × 3 mm limbal block was dissected and a peripheral iridectomy was performed. The scleral flap was closed with interrupted 10-0 nylon sutures, and the anterior chamber was reformed by injecting balanced salt solution. The conjunctival wound was closed tightly with a continuous 10-0 nylon shoelace suture.

The patients were followed up regularly at the Department of Ophthalmology, Gifu University Hospital, Japan at 1 to 3-month intervals (mean 1.5 mo). At each visit, patients had ocular examinations including visual acuity, IOP measurements with a Goldmann applanation tonometer, and direct ophthalmoscopy. Visual field examinations were conducted at intervals of 3 to 12 months (mean 5.5 mo).

A disc hemorrhage was defined as an isolated hemorrhage seen on the optic disc tissue or in the peripapillary retina extending to the disc rim. Alternative causes of the hemorrhage were excluded by diagnostic testing for ischemic optic neuropathy, papillitis, central retinal vein occlusion, diabetic retinopathy, and posterior vitreous detachment. The incidence rate of disc hemorrhages was calculated from the number of all detected disc hemorrhages per patient per year, in time periods before or after trabeculectomy.

We classified the subjects into high and low postoperative IOP groups according to their postoperative IOP, to investigate the relationships between postoperative IOP and incidence of disc hemorrhages in open-angle glaucoma. Postoperative IOP was defined as an average value obtained from 5 consecutive recordings at the latest visits. High postoperative IOP in POAG patients was defined when their postoperative IOP was 15 mm Hg or above, whereas in NTG patients it was defined as a postoperative IOP exceeding 9 mm Hg. The low postoperative IOP group in POAG patients consisted of subjects whose postoperative IOP was 14 mm Hg or below, whereas that in NTG patients consisted of subjects whose postoperative IOP was below 10 mm Hg. A study by Quigley and Maumenee[23] and other reports[24,25] documented that POAG patients whose IOPs after ocular hypotensive therapy were 15 mm Hg or less had comparatively stable visual field defects. The American Academy of Ophthalmology guidelines suggest that in NTG patients the initial target IOP should be reduction from a baseline of at least 30%.[26] We set here a borderline IOP between the high and the low postoperative IOP groups in the NTG patients as 10 mm Hg, because in the present study a 30% decrease of IOP from baseline (preoperative averaged IOP in NTG patients was 15.3 mm Hg as described in the results) was calculated to be 10.71 mm Hg. In addition, we compared the detection of disc hemorrhages at postoperative stages between eyes with disc hemorrhages before surgery and those without hemorrhages.

Statistical analysis was performed using the χ^2 test, Fisher exact probability test, Mann-Whitney U test, or unpaired t test to compare the patients' demographic data in NTG and POAG cases, or in each case with and without disc hemorrhage. IOP alteration before and after surgery was analyzed by using a paired t test. The comparison in the incidence rate or prevalence of disc hemorrhages before and after surgery was analyzed by Wilcoxon signed-rank test or Fisher exact probability test. The data were also analyzed using the Kaplan-Meier life-table method using a PC-SAS (Statview for Windows version 5.0, SAS Institute Inc, Cary, NC) to calculate the cumulative probabilities of detection of disc hemorrhages per eye before and after trabeculectomy. When a disc hemorrhage was noticed, the eye was defined to have reached the end point. The survival curves were compared using a log-rank test. We calculated the probability of nondetection of the disc hemorrhages, and converted it to the probability of detecting disc hemorrhages. The cumulative incidence of patients with disc hemorrhages was based on the first disc hemorrhage observed within

the follow-up period of the study. A P value less than 0.05 was considered to be significant.

RESULTS

A total of 99 eyes from 99 patients with POAG, and 50 eyes from 50 patients with NTG met the criteria for inclusion in the present study. Patients' characteristics are listed in Table 1. Patients with and without an observed disc hemorrhage are shown in Tables 2 and 3. There were 34 eyes with disc hemorrhages and 115 without. The age at the time of surgery averaged 56.9 years (mean ± SD, range: 27 to 83 y). The preoperative follow-up period averaged 3.6 years and ranged from 0.6 to 14.5 years. The postoperative follow-up period averaged 6.8 years and ranged from 1.3 to 11.8 years.

Trabeculectomy significantly reduced IOP from 19.6 ± 4.4 to 11.1 ± 4.2 mm Hg (mean ± SD) in POAG eyes, and from 15.3 ± 1.5 to 11.3 ± 4.5 mm Hg in NTG eyes ($P < 0.001$, $P < 0.001$, respectively; paired t test). In POAG, the disc hemorrhages before and after surgical intervention were found in 18 (18.2%) and 4 eyes (4.0%), respectively ($P = 0.0026$, Fisher exact probability test). On the other hand, in NTG, disc hemorrhages before and after surgical intervention were found in 16 (32.0%) and 9 eyes (18.0%), respectively ($P = 0.1659$, χ^2 test). In POAG, there were 2 eyes with disc hemorrhages and 79 eyes without disc hemorrhages, in both preoperative and postoperative periods ($P = 0.1501$, Fisher exact probability test, Tables 3 and 4). In NTG, there were 6 eyes with disc hemorrhages and 31 eyes without disc hemorrhages, in both preoperative and postoperative periods ($P = 0.0219$, Fisher exact probability test, Tables 2 and 5).

The life-table analysis revealed that the cumulative probability of detecting disc hemorrhages before surgery in NTG was significantly higher than that in POAG ($P = 0.0341$, log-rank test, Fig. 1). The final cumulative probability of detecting a disc hemorrhage after surgery in POAG was calculated to be 5.5 ± 2.2% (calculated probability ± SE) and was significantly lower than that (33.4 ± 7.8%) before surgery ($P < 0.0001$, log-rank test). Likewise, the final probability after surgery in NTG was 23.1 ± 6.3% and was significantly lower than that (42.1 ± 8.8%) before surgery ($P = 0.0063$, log-rank test). The cumulative probability of detecting disc hemorrhages after surgery in NTG was significantly higher than that in POAG ($P = 0.0059$, log-rank test, Fig. 2).

The incidence rate of disc hemorrhages before and after surgery in POAG was 0.08 ± 0.24 (range: 0.00 to 1.95) and 0.01 ± 0.06 (range: 0.00 to 0.47) times per year, respectively (mean ± SD). There was a significant difference between them ($P = 0.0014$, Wilcoxon signed-rank test). Similarly, the incidence rate in NTG was 0.26 ± 0.50 (range: 0.00 to 1.91) and 0.04 ± 0.10 (range: 0.00 to 0.53) times per year, respectively. There was a significant difference between them ($P = 0.0029$, Wilcoxon signed-rank test). The mean interval for the appearance of disc hemorrhages was 1.04 ± 1.33 (range: 0.00 to 3.30) years for patients with NTG (16 eyes) and 2.08 ± 2.19 (range: 0.00 to 7.12) years for POAG eyes (18 eyes).

The high postoperative IOP group included 27 NTG subjects and 26 POAG subjects, and the low postoperative IOP group included 23 NTG subjects and 73 POAG subjects. Comparing the incidence of disc hemorrhages after filtering surgery between the high and

TABLE 1. Patients' Demographic Data

	NTG (50 Patients)	POAG (99 Patients)	P
Age (y)	58.3 ± 9.8 (34-75)	56.3 ± 14.6 (27-83)	0.5707
Sex (male/female)	18/32	53/46	0.0642
Follow-up periods (y)			
Preoperative	3.4 ± 2.7 (0.6-11.9)	3.7 ± 3.1 (0.6-14.5)	0.5736
Postoperative	7.7 ± 2.6 (1.3-11.3)	6.3 ± 3.0 (1.3-11.8)	0.0059
Visual acuity			
Preoperative	0.9 ± 0.4 (0.2-1.5)	0.9 ± 0.4 (0.3-1.5)	0.7612
At the last visit	0.5 ± 0.5 (HM-1.5)	0.5 ± 0.5 (LS-1.5)	0.6731
IOP (mm Hg)			
Preoperative	15.3 ± 1.5 (12-18)	19.6 ± 4.4 (13-41)	< 0.0001
Postoperative	11.3 ± 4.5 (2-20)	11.1 ± 4.2 (1-23)	0.7613
HFA program central 30-2 MD (dB)			
Preoperative	− 11.7 ± 4.4 (− 19.9 ~ − 1.5)	− 12.1 ± 5.0 (− 19.6 ~ − 0.1)	0.4344
Postoperative	− 16.5 ± 7.8 (− 32.8 ~ − 3.0)	− 18.1 ± 8.1 (− 32.0 ~ − 0.1)	0.1950
DH (positive/negative)			
Preoperative	16/34	18/81	0.0905
Postoperative	9/41	4/95	0.0104
Past history (positive/negative)			
DM	3/47	11/88	0.3857
HT	12/38	25/74	> 0.9999

DH indicates disc hemorrhage; DM, diabetes mellitus; HFA, Humphrey Field Analyzer; HM, hand motion; HT, hypertension; LS, light sense.

Values indicate means ± SD (range).