Laser Scanning Tomography of Optic Discs of the Normal Japanese Population in a Population-based Setting

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Objective: To evaluate the optic disc characteristics using the Heidelberg retina tomograph (HRT) II in a large sample of normal Japanese subjects.

Design: Cross-sectional study.

Participants: A total of 3576 eyes of 2036 normal subjects, with good-quality HRT II images, of 6042 eyes of 3021 subjects aged 40 years or more who participated in the Tajimi Study, a population-based eye study in Japan.

Methods: Optic disc parameters were obtained using HRT II, and the association of gender, age, height, weight, blood pressure, ocular perfusion pressure, refraction, intraocular pressure (IOP), central corneal thickness (CCT), and disc size on HRT parameters was assessed using simple and multiple regression analyses.

Main Outcome Measures: HRT parameters, including disc area, cup area, rim area, cup-to-disc area ratio, cup volume, rim volume, mean cup depth, maximum cup depth, height variation contour, cup shape measure, mean retinal nerve fiber layer (RNFL) thickness, and RNFL cross-sectional area, and the crude and partial correlations of the potential confounders with the HRT parameters.

Results: Disc area, cup-to-disc area ratio, and rim area averaged 2.06 ± 0.41 mm^2 (mean$\pm$standard deviation), 0.23 ± 0.13, and 1.55 ± 0.29 mm^2, respectively. All HRT parameters were strongly or moderately correlated between right and left eyes (Pearson's correlation coefficients = 0.45–0.83, $P<0.001$). Absolute inter-eye differences in several HRT parameters were positively correlated with disc area ($P<0.05$). Multiple regression analyses adjusting for the confounders showed weak but significant correlations of height, refractive error, IOP, and CCT with several HRT parameters (partial correlation coefficient (absolute value) = 0.04–0.16, $P<0.05$), and moderate or weak but significant correlations of disc area with all HRT parameters (partial correlation coefficient [absolute value] = 0.05–0.73, $P<0.05$). Gender, weight, blood pressure, and ocular perfusion pressure did not significantly correlate with HRT parameters.

Conclusions: This report presents reference data of normality for the HRT parameters based on a large sample of normal Japanese subjects. There were small but significant influences of height, refractive error, IOP, and CCT on several HRT parameters. Many HRT parameters were moderately or weakly affected by disc size.

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Because structural changes of the optic disc often precede the development of visual field loss in glaucoma,[1–5] detection of optic disc damage plays a vital role in the diagnosis of glaucoma, especially in its early stages. Although ophthalmoscopy and fundus photography are still widely used for assessing glaucomatous optic disc damage, they are limited by their subjective and qualitative nature.[6–8] With the development of optic nerve imaging instruments, objective and quantitative measurements of the optic disc have become available. A confocal scanning laser ophthalmoscope, such as the Heidelberg retina tomograph (HRT) or HRT II (Heidelberg Engineering, Heidelberg, Germany), allows 3-dimensional topographic analysis of the optic disc and provides a quantitative measure of a variety of optic disc parameters.[9–12]

Understanding of normal optic disc shape and related factors are of critical importance in improving the performance of confocal scanning laser ophthalmoscope to determine glaucomatous changes in the optic disc. Distributions or ranges of the optic disc parameters determined with confocal scanning laser ophthalmoscope in large samples of normal subjects (number of subjects >~500) have been reported by Hermann et al.[13] (1764 eyes of 882 subjects) and Vernon et al.[14] (918 eyes of 459 subjects) in white populations. Because there are racial differences in optic disc characteristics,[15–19] it is worthwhile accumulating such

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information for each of the various ethnicities. For Asian populations, however, to our knowledge, there are only the Turkish hospital-based study by Durukan et al.[20] (1102 eyes of 551 subjects) and 2 Japanese hospital-based studies with relatively small sample sizes by Nakamura et al.[21] (77 eyes of 77 subjects) and Uchida et al.[22] (223 eyes of 223 subjects).

We recently conducted the Tajimi Study, a population-based eye study focusing primarily on estimating the prevalence of glaucoma among Japanese persons aged 40 years or more.[23–27] The purposes of the present report were to evaluate the optic disc characteristics by means of HRT II in a large sample of ophthalmologically normal Japanese subjects who participated in the Tajimi Study and to evaluate associations of possibly related systemic and ocular factors, including gender, age, height, weight, blood pressure, ocular perfusion pressure (OPP), refractive error, intraocular pressure (IOP), central corneal thickness (CCT), and optic disc size with the optic disc characteristics.

Subjects and Methods

Population Sampling

The Tajimi Study, a population-based eye study of Japanese subjects aged 40 years or more was conducted between September of 2000 and October of 2001 in Tajimi City, Japan.[23–27] The details of the Tajimi Study have been published.[23–27] Briefly, of 54,165 inhabitants aged 40 years or more in Tajimi City as of August 1, 2000, 4000 were selected randomly without stratification and were encouraged to participate in the epidemiologic study. The investigation followed the tenets of the World Medical Association's Declaration of Helsinki and the municipal statutes of Tajimi City for protecting personal information; the study protocol was approved by the ethics committee of Tajimi City. Written informed consent was obtained from all participants after the details of the study had been explained fully. Among the selected 4000 participants, 48 died and 82 were not actual residents of or had moved from Tajimi City during the screening period. Of the remaining 3870 persons, 3021 participated in the screening examinations.

Ocular Examinations

Screening and definitive examinations have been reported in detail.[23–27] Briefly, the screening examinations included not only ocular parameters but also parameters such as height, weight, and blood pressure. OPP was calculated as "2/3[diastolic blood pressure + 1/3(systolic blood pressure—diastolic blood pressure)]–IOP." The ocular examinations included measurement of refractive status and corneal curvature using an autorefractometer (KP-8100PA, Topcon, Tokyo, Japan), visual acuity using a Landolt ring chart at a distance of 5 m with refractive correction, and CCT using a specular-type pachymeter (SP-2000P, Topcon), slit-lamp biomicroscopic examination, evaluation of angle width according to the van Herick method, IOP measurement by Goldmann applanation tonometry, fundus examination based on digital color photographs obtained through an undilated pupil using the IMAGEnet digital fundus camera system (TRC-NW6S, Topcon) with angles of 30 and 45 degrees, visual field screening using a frequency doubling technology screener (Humphrey Instruments, San Leandro, CA) with the C-20–1 screening test, and optic disc measurements using HRT II (software version 1.4.1). Participants were referred for definitive examination if ocular disorders or related conditions were suspected and if they met 1 or more of the following criteria: corrected visual acuity <20/30; abnormal findings on slit-lamp examination or on fundus photographs; IOP >19 mmHg (i.e., mean + 2 × standard deviation of the IOP values previously reported in ~12,000 Japanese eyes[28]); angle width grade 2 or less (van Herick method); findings in the optic disc, retina, or both suggestive of glaucoma or other ocular diseases; and at least 1 abnormal test point in the frequency doubling technology visual field test. The definitive examination included slit-lamp examination, gonioscopy, optic disc and posterior pole fundus evaluation with a Goldmann 2-mirror lens (Haag-Streit, Koeniz, Switzerland), applanation tonometry, and visual field testing with the Humphrey Perimeter Central 30–2 Swedish Interactive Threshold Algorithm Standard program (Humphrey Instruments). Unless gonioscopy revealed an occludable angle, the pupil was dilated to obtain stereoscopic disc photographs (3-DX NM; Nidek, Gamagori, Japan) and to observe the ocular fundus in detail by indirect ophthalmoscopy. When the angle was thought to be occludable, the same examinations were carried out with undilated pupils.

Optic Disc Measurements using HRT II

In the screening examination, optic disc parameters were measured using HRT II. HRT II uses a diode laser (670-nm wavelength) to sequentially scan the retinal surface in the horizontal and vertical directions at multiple focal planes. By using confocal scanning principles, a 3-dimensional topographic image is constructed from a series of optical image sections at consecutive focal planes. The topographic image determined from the acquired 3-dimensional image consists of 384×384 (147,456) pixels, each of which is a measurement of retinal height at its corresponding location. For every subject in this study, images were obtained through undilated pupils with a 15-degree field of view. Three topographic images were obtained, combined, and automatically aligned to make a single mean topographic image for analysis. A contour line of the optic disc margin was drawn around the inner margin of the peripapillary scleral ring by one experienced examiner (TT), who was masked to the other clinical information, with viewing non-stereo color fundus photographs. The contour line was reviewed in the topography and reflectance images and the height profile graph included in the instrument by the same examiner. For approximately 500 HRT images randomly chosen, another experienced examiner (GT) double-checked the contour lines and confirmed the correctness of the placement. Twelve HRT parameters obtained with routine analysis were analyzed: disc area, cup area, rim area, cup-to-disc area ratio, cup volume, rim volume, mean cup depth, maximum cup depth, height variation contour, cup shape measure, mean retinal nerve fiber layer (RNFL) thickness, and RNFL cross-sectional area. Magnification errors were corrected using subjects' refractive status and corneal curvature measurements. This instrument and these parameters have been described.[14,17,20,29]

Data Analysis

In the present study, the analysis was restricted to eyes that had valid optic disc measurements with HRT II. Good image quality was defined by appropriate focus, brightness and clarity, minimal eye movement, optic disc centered in the image, and a standard deviation of the mean topographic image $<40\ \mu m$. Eyes in which good-quality images could not be obtained were excluded from the analysis. Eyes of normal subjects based on the screening and definitive examinations were included in the analysis. Normal subjects had a best corrected visual acuity $\geq$20/30, spherical refraction $\leq \pm 5$ diopters (D), cylinder correction $\leq \pm 3$ D, a normal IOP $\leq$21 mmHg, normal appearance of the optic disc and ocular fundus, normal visual field by frequency doubling technology screener or Humphrey perimeter, no previous laser surgery or intraocular surgery, and no significant ocular disease. Patients with glaucoma, suspected glaucoma, IOP >21 mmHg, or exfoliation in at least 1 eye or those with eyes having any inborn aberrations (e.g., tilted disc) were carefully excluded.

Data were analyzed using SPSS 14.0J for Windows (SPSS Japan, Inc., Tokyo, Japan). Comparisons between groups were analyzed with paired or unpaired *t* test or the chi-square test. Pearson's correlation coefficients were calculated to assess correlations between the 2 variables. Multiple regression analysis was applied to adjust for the effects of potential confounders. All tests were 2-tailed. Because the sample size in the current report was sufficiently large (i.e., >1700 right and 1800 left eyes), parametric tests, including *t* test, Pearson's correlation coefficient, and multiple regression, were used based on the central limit theorem.

Results

Of 6042 eyes of the 3021 participants of the Tajimi Study, reliable HRT II results in ophthalmologically normal eyes were analyzed in 3576 eyes (1769 right eyes and 1807 left eyes) of 2036 participants. Between the included and excluded subjects, the male/female ratio was not statistically different (924/1112 vs. 410/575, $P = 0.051$, χ^2 test), whereas age was significantly younger in the included subjects than in the excluded subjects (56.0±10.0 years vs. 63.4±13.7 years, $P<0.001$, unpaired *t* test). The reasons for exclusion were (1) subjects were screened in their own home (88 eyes); (2) HRT II measurements could not be completed at the screening sites for various reasons, such as subjects' ocular or physical problems (906 eyes); and (3) standard deviation of the HRT II measurements was $\geq 40\ \mu m$ (640 eyes). Eyes of definitive glaucoma, suspected glaucoma, pseudoexfoliation, primary angle closure, ocular hypertension or fellow eyes of these eyes (364 eyes), eyes with other ocular diseases including congenital disc anomalies that could affect the disc shape (84 eyes), pseudophakic eyes (41 eyes), eyes with excessive refractive errors (spherical error $>\pm 5$ D or cylindrical error $>\pm 3$ D) (260 eyes), and eyes with best corrected visual acuity worse than 20/30 (83 eyes) were also excluded.

Inter-eye Difference in HRT Parameters

HRT parameters were compared between right and left eyes in 1540 normal subjects, of whom both eyes were eligible. All HRT parameters were significantly correlated between right and left eyes (Pearson's correlation coefficients $\geq$0.450, $P<0.001$) (Table 1 [available at http://aaojournal.org]). Rim volume and height variation contour showed small but significant inter-eye difference ($P<0.001$, paired *t* test), whereas the other parameters did not. The absolute differences in HRT parameters between right and left eyes are also shown in Table 1 (available at http://aaojournal.org). Among HRT parameters, inter-eye absolute difference was significantly different between male and female subjects only in cup shape measure (0.05±0.04 and 0.06±0.05, respectively, $P = 0.001$), and the difference was still significant ($P = 0.027$) in multiple regression analyses adjusting for age, height, weight, systolic and diastolic blood pressure, OPP, refractive error, IOP, and CCT. Multiple regression analyses adjusting for these confounders and gender showed that disc area (mean value of right and left eyes) was significantly positively correlated with inter-eye absolute difference in cup area, rim area, cup volume, rim volume, and RNFL cross-sectional area ($P<0.05$), suggesting subjects having larger discs tended to show greater inter-eye absolute differences in these HRT parameters, whereas disc area was significantly negatively correlated with the inter-eye absolute difference in cup shape measure ($P<0.001$). Because all HRT parameters were significantly correlated and the results of the analyses were similar between right and left eyes, only the results from the right 1769 eyes (787 male and 982 female subjects) are presented in the following sections.

Association of Gender, Age, Height, Weight, and Blood Pressure with HRT Parameters

A total of 787 male subjects had significantly older age, heavier weight, taller height, higher systolic and diastolic blood pressure, and higher OPP and thicker CCT than 982 female subjects (unpaired *t* test, $P\leq 0.009$), whereas refractive error and IOP were not significantly different ($P\geq 0.126$) (Table 2).

In simple regression analyses, age was negatively correlated with disc area, rim area, rim volume, maximum cup depth, height variation contour, mean RNFL thickness, and RNFL cross-sectional area in both male and female subjects ($P\leq 0.002$) (Table 3 [available at http://aaojournal.org]). These trends are also seen after adjusting for the potential confounders using multiple regression analysis (Tables 4 and 5 [available at http://aaojournal.org]). Cup area and cup-to-disc area ratio were significantly greater in male subjects than female subjects ($P\leq 0.004$). However, after adjusting for the potential confounders, gender-related dif-

Table 2. Comparison of Demographic Data and Heidelberg Retina Tomograph Parameters of Normal Right Eyes between 787 Male and 982 Female Subjects

	All	Male	Female	P*
Age (y)	55.7±9.8 (55.3–56.2)	56.4±9.8 (55.7–57.1)	55.2±9.9 (54.5–55.8)	0.009
Weight (kg)	58.2±10.6 (57.7–58.7)	63.9±10.1 (63.2–64.6)	53.7±8.9 (53.1–54.3)	<0.001
Height (cm)	158.9±8.8 (158.5–159.3)	165.6±6.7 (165.7–166.1)	153.3±6.3 (152.9–153.8)	<0.001
Systolic blood pressure (mmHg)	130.4±22.7 (129.3–131.4)	133.5±22.3 (131.9–135.1)	128.9±22.8 (127.3–130.5)	<0.001
Diastolic blood pressure (mmHg)	78.8±13.2 (78.1–79.4)	80.9±13.2 (80.0–81.8)	77.2±13.1 (76.3–78.2)	<0.001
OPP (mmHg)	49.5±9.8 (49.1–50.0)	51.1±9.6 (50.4–51.7)	48.5±9.8 (47.8,49.2)	<0.001
Refractive error (diopters)[†]	−0.4±1.7 (−0.5 to −0.4)	−0.5±1.8 (−0.6 to −0.3)	−0.4±1.8 (−0.6 to −0.3)	0.612
IOP (mmHg)	14.4±2.5 (14.3–14.6)	14.6±2.6 (14.4–14.8)	14.5±2.4 (14.3–14.6)	0.126
CCT (μm)	520±32 (518–521)	525±33 (523–527)	516±31 (514–518)	<0.001
Disc area (mm²)[‡]	2.06±0.41 (2.04–2.08)	2.08±0.44 (2.04–2.11)	2.05±0.39 (2.02–2.08)	0.085
Cup area (mm²)[‡]	0.51±0.35 (0.49–0.53)	0.54±0.37 (0.51–0.56)	0.50±0.32 (0.47–0.52)	0.002
Rim area (mm²)[‡]	1.55±0.29 (1.54–1.56)	1.54±0.29 (1.52–1.56)	1.55±0.29 (1.53–1.57)	0.181
Cup-to-disc area ratio[‡]	0.23±0.13 (0.23–0.24)	0.24±0.13 (0.23–0.25)	0.23±0.12 (0.22–0.24)	0.004
Cup volume (mm³)[‡]	0.11±0.12 (0.11–0.12)	0.12±0.12 (0.11–0.13)	0.11±0.11 (0.10–0.12)	0.006
Rim volume (mm³)[‡]	0.41±0.14 (0.40–0.42)	0.40±0.14 (0.39–0.41)	0.42±0.14 (0.41–0.43)	0.083
Mean cup depth (mm)[‡]	0.21±0.09 (0.20–0.21)	0.21±0.09 (0.20–0.22)	0.20±0.09 (0.20–0.21)	0.034
Maximum cup depth (mm)[‡]	0.57±0.20 (0.56–0.58)	0.58±0.20 (0.56–0.59)	0.57±0.21 (0.56–0.59)	0.157
Height variation contour (mm)[‡]	0.38±0.09 (0.38–0.39)	0.38±0.10 (0.38–0.39)	0.39±0.10 (0.38–0.39)	0.572
Cup shape measure[‡]	−0.19±0.07 (−0.19 to −0.19)	−0.19±0.07 (−0.19 to −0.18)	−0.19±0.07 (−0.20 to −0.19)	0.033
Mean RNFL thickness (mm)[‡]	0.25±0.07 (0.25–0.26)	0.25±0.07 (0.25–0.25)	0.26±0.07 (0.25–0.26)	0.007
RNFL cross-sectional area (mm²)[‡]	1.29±0.35 (1.27–1.30)	1.27±0.35 (1.24–1.29)	1.31±0.35 (1.28–1.33)	0.028

RNFL = retinal nerve fiber layer; OPP = ocular perfusion pressure; IOP = intraocular pressure; CCT = central corneal thickness.
Data are shown as "mean±standard deviation (95% confidence interval)."
**P* value on comparison between male and female subjects (unpaired *t* test).
[†]Spherical equivalent values.
[‡]Because of multiple comparisons among the 12 Heidelberg Retina Tomograph parameters, Bonferroni correction was applied with a level of significance of 0.0042.

ference in HRT parameters did not reach statistical significance ($P>0.05$) (Tables 4 and 5 [available at http://aaojournal.org]). Height was also weakly correlated with several HRT parameters in simple and multiple regression analyses (Tables 3, 4, and 5 [available at http://aaojournal.org]). Although disc area was not significantly correlated with height in multiple regression analysis, cup-related parameters were positively correlated with height, whereas rim-related parameters were negatively correlated with height (Tables 4 and 5 [available at http://aaojournal.org]). Weight was not correlated significantly with any HRT parameters in multiple regression analyses (Tables 4 and 5 [available at http://aaojournal.org]). Systolic blood pressure and OPP were negatively correlated with some HRT parameters in simple regression analyses, but the significant correlations disappeared after adjusting for the potential confounders (Tables 3, 4, and 5 [available at http://aaojournal.org]).

Association of Refractive Error, IOP, and CCT with HRT Parameters

Multiple regression analysis showed weak but significant positive correlation between refractive error and disc area ($P<0.001$), suggesting the trend that more myopic eyes had smaller discs (Table 4 [available at http://aaojournal.org]). Rim volume, mean RNFL thickness, and RNFL cross-sectional area were negatively correlated with refractive error in both male and female subjects in simple regression analyses ($P<0.001$) and multiple regression analyses ($P<0.001$) (Tables 3 and 4 [available at http://aaojournal.org]), suggesting that more myopic eyes had greater rim volume. Rim volume, mean RNFL thickness, and RNFL cross-sectional area were still negatively correlated with refractive error after adjusting for disc area and the other potential confounders (Table 5 [available at http://aaojournal.org]).

IOP was positively correlated with some cup-related parameters in multiple regression analyses ($P<0.05$) (Table 5 [available at http://aaojournal.org]), suggesting the trend that eyes with higher IOP had greater cup. CCT showed weak but significant negative correlations with cup volume in multiple regression analyses ($P<0.05$) (Tables 4 and 5 [available at http://aaojournal.org]).

Association of Disc Area with the Other HRT Parameters

Disc area was correlated with all HRT parameters except height variation contour with P values of ≤ 0.001 (Table 6 [available at http://aaojournal.org]). Cup area and cup volume were relatively strongly correlated with disc area (Pearson's correlation coefficients ≥ 0.61). In multiple regression analyses after adjusting for the potential confounders, disc area was also correlated with all HRT parameters except height variation contour with P values <0.001 (Table 5).

Discussion

A total of 3576 eyes of 2036 ophthalmologically normal Japanese subjects who participated in the Tajimi Study[23–27] were included in the present analyses. The age distribution of the Tajimi Study participants was similar to that of the Japanese population.[23,30] In the Tajimi Study, although the distribution of IOP was widely overlapped between normal and glaucoma eyes,[23] the criteria for diagnosing glaucoma were not based on IOP, but on findings in the visual field and optic disc in accordance with the criteria of the International Society for Geographical and Epidemiological Ophthalmology.[31] Moreover, ophthalmologically normal eyes in the current analyses were selected according to more strict criteria as described previously. Thus, these criteria should achieve reasonably high specificity of normal eyes in the present report.

In the present report, descriptive statistics of the HRT parameters in the population were presented. All HRT parameters were strongly or moderately correlated between right and left eyes. Absolute inter-eye differences in several HRT parameters were positively correlated with disc area. Multiple regression analyses adjusting for the potential confounders showed weak but significant correlations of height, refractive error, IOP, and CCT with several HRT parameters, and moderate or weak but significant correlations of disc area with many HRT parameters. Gender, weight, blood pressure, and OPP did not significantly correlate with HRT parameters.

Several investigators have reported racial differences in optic disc characteristics.[15–19] In normal subjects of various races, Tsai et al.,[15] using HRT, found that disc area, cup area, cup-to-disc area ratio, cup volume, and maximum cup depth were significantly greater in 43 African-Americans than in 44 whites, with intermediate values for 45 Asians and 48 Hispanics. In another study of normal subjects, Girkin et al.,[17] using HRT II, found significantly greater disc area, cup area, rim area, cup volume, mean cup depth, and mean RNFL thickness in 144 normal eyes (84 subjects) of African-Americans than in 109 normal eyes of 68 white subjects. In normal white subjects, Hermann et al.,[13] using HRT, reported that the mean disc area was 1.82 mm^2 (882 subjects), and Vernon et al.[14] (459 subjects), using HRT II, reported that the mean and median disc areas were 1.98 and 1.93 mm^2, respectively. Girkin et al.,[17] using HRT II, reported that the mean disc areas were 2.26 mm^2 for normal African-American subjects and 1.98 mm^2 for normal white subjects. In the present report on 2036 normal Japanese subjects using HRT II, the mean disc area was 2.06 mm^2 (Table 2). The normal range of disc area was between 1.36 and 3.00 mm^2 in the current population if the normal range is defined between the 2.5 and 97.5 percentiles. The mean value of the disc area in the present report tended to be greater than that in normal white subjects[13,14] but smaller than that in normal black subjects.[17]

The characteristics of optic discs are usually well correlated between right and left eyes in each subject. One of the established criteria for diagnosing glaucoma in population-based studies, such as "difference of the vertical cup-to-disc ratio is 0.2 or more between both eyes,"[23,31–34] is based on the inter-eye similarity in optic disc shape in normal eyes. In previous studies, one study of 551 normal Turkish subjects found no significant inter-eye differences in HRT parameters,[20] whereas other studies on normal white subjects reported significant inter-eye differences in some HRT parameters, although the differences were small.[13,35,36] In the present report, all HRT parameters were strongly or moderately correlated between right and left eyes and no apparently significant inter-eye difference was found as a whole in all parameters except rim volume and height variation contour (Table 1 [available at http://aaojournal.org]). However, the absolute inter-eye differences in some parameters were not as small as clinically ignorable. For example, absolute inter-eye difference in cup-to-disc area ratio (0.07) was equivalent to 30% of the bilateral mean (0.23) of the parameter. Thus, the current results indicate that inter-eye difference in HRT parameters is not always small enough in each individual and that it cannot be adopted as a useful diagnostic tool in detecting disc pathology, especially among subjects with large optic discs because the absolute inter-eye difference was positively correlated with the optic disc size.

Several studies have reported significant gender-related differences in HRT parameters.[13–15,20,22] In normal subjects of various races, Tsai et al.,[15] using analysis of variance, found that women had a significantly greater rim volume and that men had significantly greater cup area, cup-to-disc area ratio, cup volume, and cup-to-disc ratio. In normal Turkish subjects, Durukan et al.,[20] using the *t* test, found that women had significantly greater height variation contour, mean RNFL thickness, and RNFL cross-sectional area. In normal white subjects, Hermann et al.[13] and Vernon et al.,[14] using the Mann-Whitney test, found that the women had significantly greater rim volume, mean RNFL thickness, and RNFL cross-sectional area. In Japan, Uchida et al.,[22] using the Mann-Whitney test, found that men had significantly greater disc area. However, none of these investigators adjusted for other important potential confounders such as age, height, and refraction using multiple regression analysis. In the present report, some HRT parameters were significantly different between male and female subjects using unpaired *t* test (Table 2), but the significant differences diminished after adjusting for the potential confounders using multiple regression analysis (Tables 4 and 5 [available at http://aaojournal.org]). Thus, gender itself is not thought to influence HRT parameters.

Between age and optic disc characteristics, several investigators observed significant association,[20–22,37–39] whereas others did not.[13,14,16,40,41] In normal white subjects, Hermann et al.,[13] using HRT, reported that although the disc area and mean RNFL thickness were smaller in older subjects (age, 52–70 years) than in younger subjects (35–40 years), no significant differences were noted. Vernon et al.[14] found no significant age-related differences in HRT parameters in normal white subjects, although rim and RNFL-related parameters tended to decrease with age. In contrast, although they were hospital-based studies and the numbers of subjects were not sufficiently large, one study of normal Japanese subjects found that mean RNFL thickness and RNFL cross-sectional area significantly decreased with increasing age,[21] and another study found that rim volume, height variation contour, mean RNFL thickness, and RNFL cross-sectional area significantly decreased with increasing age and that cup shape measure significantly increased with increasing age.[22] In the present report, several HRT parameters, including disc area, correlated with age in both crude and partial correlation analyses. Approximately one third of the study participants had to be excluded from the analysis of HRT data, and because there was significant difference in age between the included and excluded subjects, the association of age with HRT parameters in the included subjects should be interpreted with caution. For example, the association between older age and smaller disc area may be attributable to the cohort effect than to the longitudinal effect because disc size is supposed to be unchanged throughout lifetime. However, this significant correlation between age and some HRT parameters indicates the importance of adjusting for age as a possible confounder in multiple regression analyses in the current subjects. After adjusting for disc area and the other potential confounders, rim area, rim volume, height variation contour, mean RNFL thickness, and RNFL cross-sectional area significantly decreased with increasing age, whereas cup area, cup-to-disc area ratio, and cup shape measure significantly increased with increasing age (Table 5 [available at http://aaojournal.org]). Our findings are consistent with those of the above previous studies of normal Japanese subjects. If age-related decrease in nerve fibers exists,[42–45] it is possible that HRT parameters that reflect the amount of nerve fibers may slightly decrease with increasing age.

In the present report, partial correlation analyses showed that disc area was not correlated with height, whereas some of the other HRT parameters were significantly correlated with height (Tables 4 and 5 [available at http://aaojournal.org]). After adjusting for the potential confounders, with increasing height, cup-related parameters weakly but significantly increased, whereas rim-related parameters weakly but significantly decreased. In contrast with our findings, the investigators of the Rotterdam Study, using image analysis of stereoscopic optic disc photographs, found no significant height-related differences in cup area and cup-to-disc area ratio.[41] Although the reasons for the discrepancy are unclear, racial differences and differences in methods of evaluating optic disc morphology are at least partially responsible.

In the present report of normal subjects (spherical refraction $\leq \pm 5$D and cylinder correction $\leq \pm 3$ D), both crude and partial correlation analyses showed that several HRT parameters weakly correlated with refractive error (Tables 3, 4, and 5 [available at http://aaojournal.org]). After adjusting for the potential confounders, disc area significantly decreased with an increase in myopia (Table 4 [available at http://aaojournal.org]). After adjusting for disc area and the other potential confounders, rim volume, height variation contour, mean RNFL thickness, and RNFL cross-sectional area significantly increased with an increase in myopia (Table 5 [available at http://aaojournal.org]). Some studies showed a significant influence of refractive errors on HRT parameters.[15,21] Tsai et al.[15] found that rim volume significantly increased with an increase in myopia in normal subjects of various races (refractive error between -6 and $+3$ D). Nakamura et al.[21] found that mean cup depth and maximum cup depth significantly increased with an increase in myopia in a relatively small sample of normal Japanese subjects (77 subjects, refractive error between -5 and $+4.13$ D). In contrast, Bowd et al.[38] and Durukan et al.[20] found no significant association between refractive error and HRT parameters in normal white subjects (refractive error $\leq \pm 5$ D) and normal Turkish subjects (refractive error between -4.75 and $+4.25$ D), respectively. Although the reasons for the differences among these studies and our study, are unclear, differences in sample sizes, subject characteristics, including age, refractive errors, and races, or methods of analyses might have affected the results.

Many studies have reported a significant effect of optic disc size on optic disc characteristics.[13–16,20–22,37,38,40,41] However, in normal Turkish subjects, Durukan et al.[20] found cup shape measure and height variation contour to be independent of disc area. In normal white subjects, Vernon et al.[14] found height variation contour to be the only parameter independent of disc area. Two previous studies of normal Japanese subjects using HRT also found height variation contour to be independent of disc area.[21,22] In the present report, all HRT parameters except height variation contour moderately or weakly correlated with disc area with P values of ≤ 0.001 in both crude and partial correlation analyses (Tables 5 and 6 [available at http://aaojournal.org]). Our findings are consistent with those of previous studies in that height variation contour, which is the height difference between the most elevated and most depressed points of the contour line, is independent of or minimally affected by optic disc size.[14,20–22] On the other hand, as in previous studies,[13–15,20–22,37,38,40] many cup, rim, or RNFL-related HRT parameters were closely influenced by optic disc size, suggesting that optic disc size should be considered in evaluating these parameters.

A recent study reported a significant association between systemic blood pressure and some of the HRT parameters in 232 Greek patients without glaucoma.[46] Topouzis et al[46] found a significant association of lower diastolic blood pressure with increased cup area and decreased rim area in multiple regression analysis. However, Jonas and Gründler[47] analyzed stereo optic disc photographs of 167 normal white subjects and found no significant influence of systemic hypertension on optic disc structure, including disc area and rim area. The present report on normal Japanese subjects did not find a significant association of systemic blood pressure with HRT parameters after adjusting for the possible confounders (Tables 4 and 5 [available at http://aaojournal.org]). Although the true reasons for these discrepancies are hard to be determined, differences in races and blood pressure itself between the studies may be possible explanations.

In the present report, weak but significant correlations between higher IOP and greater cup-related parameters were found in multiple regression analyses including disc area as an independent variable (Table 5). A similar relationship was found in the Blue Mountains Eye Study using optic disc photographs.[48] Investigators of the Beijing Eye Study also reported that rim area evaluated with optic disc photographs was significantly smaller in eyes with IOP >21 mmHg than those with IOP ≤ 21 mmHg, although, for the eyes with elevated IOP, neither the optic disc appearance nor the perimetric results were taken into account.[49] These findings, including ours using HRT II, suggest that eyes with higher IOP tend to have greater cup even in normal eyes.

In the present report, after adjusting for the potential confounders, CCT showed weak but significant negative correlations with a few cup-related parameters, suggesting that eyes with a thinner cornea tended to have a greater cup (Tables 4 and 5 [available at http://aaojournal.org]). This may have some clinical implication, if one considers the recently reported findings that thinner cornea is a risk factor for developing glaucoma from ocular hypertensive eyes in the Ocular Hypertension Treatment Study[50] and the European Glaucoma Prevention Study.[51]

One limitation of the present report is the exclusion of a significant proportion of eyes that did not undergo HRT II measurements or in which HRT II images could not be obtained, or those without good-quality optic disc images. Because the excluded subjects were significantly older than the included subjects and age was significantly related to many HRT parameters, the exclusion may have influenced the current results, and the interpretation of age-related changes in HRT parameters in the current subjects should be done with caution. Another limitation of the present report is that only normal subjects with good central vision, no high refractive error, and clear ocular media were included in the analyses. Our definitions of normality may have excluded some potentially normal subjects from the analyses. Despite these limitations, our data provide a reference range of normality for HRT parameters based on a large sample of normal Japanese subjects. The reference range for normality provided in this report becomes a basis for comparison of optic disc characteristics between normal and glaucomatous eyes. Whether the reference range can improve the ability of glaucoma diagnosis in Japanese subjects requires further research.

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Table 1. Heidelberg Retina Tomograph Parameters in Right and Left Eyes in 1540 Normal Subjects of Whom Both Right and Left Eyes Were Eligible

	Right Eyes	Left Eyes	P Value*	Correlation Coefficient†	Absolute Difference
Disc area (mm^2)	2.06±0.41 (2.04–2.08)	2.07±0.41 (2.05–2.09)	0.087	0.830 (<0.001)	0.18±0.15 (0.17–0.19)
Cup area (mm^2)	0.51±0.34 (0.49–0.52)	0.50±0.35 (0.48–0.52)	0.327	0.821 (<0.001)	0.16±0.14 (0.15–0.16)
Rim area (mm^2)	1.55±0.29 (1.54–1.57)	1.57±0.29 (1.55–1.58)	0.012	0.647 (<0.001)	0.19±0.16 (0.18–0.19)
Cup-to-disc area ratio	0.23±0.13 (0.23–0.24)	0.23±0.13 (0.22–0.24)	0.063	0.769 (<0.001)	0.07±0.06 (0.06–0.07)
Cup volume (mm^3)	0.11±0.12 (0.11–0.12)	0.11±0.12 (0.10–0.11)	0.030	0.802 (<0.001)	0.05±0.06 (0.05–0.05)
Rim volume (mm^3)	0.41±0.14 (0.40–0.42)	0.43±0.15 (0.42–0.43)	<0.001	0.529 (<0.001)	0.11±0.09 (0.10–0.11)
Mean cup depth (mm)	0.21±0.09 (0.20–0.21)	0.20±0.09 (0.20–0.21)	0.246	0.776 (<0.001)	0.04±0.04 (0.04–0.05)
Maximum cup depth (mm)	0.57±0.20 (0.56–0.58)	0.58±0.21 (0.56–0.58)	0.596	0.726 (<0.001)	0.12±0.10 (0.11–0.12)
Height variation contour (mm)	0.39±0.09 (0.38–0.39)	0.40±0.10 (0.39–0.40)	<0.001	0.450 (<0.001)	0.08±0.07 (0.08–0.08)
Cup shape measure	−0.19±0.07 (−0.19–0.19)	−0.19±0.07 (−0.20–0.19)	0.478	0.493 (<0.001)	0.05±0.04 (0.05–0.06)
Mean RNFL thickness (mm)	0.26±0.07 (0.25–0.26)	0.26±0.08 (0.26–0.27)	0.013	0.534 (<0.001)	0.05±0.04 (0.05–0.06)
RNFL cross-sectional area (mm^2)	1.30±0.34 (1.28–1.31)	1.32±0.37 (1.30–1.34)	0.011	0.511 (<0.001)	0.28±0.23 (0.27–0.29)

RNFL = retinal nerve fiber layer.
Data are shown as "mean±standard deviation (95% confidence interval)."
*P value on comparison between right and left eyes (paired t test).
†Pearson's correlation coefficients with P values in the parentheses. Because of multiple comparisons among the 12 Heidelberg Retina Tomograph parameters, Bonferroni correction was applied with a level of significance of 0.0042.

Table 3. Correlation Coefficients of Simple Linear Regression Analyses

	Age		Height		Weight		Systolic Blood Pressure	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
Disc area	−0.13 (<0.001)	−0.11 (0.001)	NS	0.09 (0.008)	NS	NS	NS	NS
Cup area	NS	NS	NS	0.07 (0.034)	NS	NS	NS	NS
Rim area	−0.11 (0.002)	−0.15 (<0.001)	NS	NS	NS	NS	NS	NS
Cup-to-disc area ratio	NS	NS	NS	NS	NS	NS	NS	NS
Cup volume	−0.10 (0.007)	NS	NS	0.11 (<0.001)	NS	NS	NS	NS
Rim volume	−0.18 (<0.001)	−0.21 (<0.001)	NS	0.07 (0.035)	NS	NS	−0.08 (0.031)	−0.08 (0.012)
Mean cup depth	−0.15 (<0.001)	−0.07 (0.025)	0.13 (<0.001)	0.12 (<0.001)	0.08 (0.033)	NS	NS	NS
Maximum cup depth	−0.20 (<0.001)	−0.10 (0.002)	0.15 (<0.001)	0.13 (<0.001)	0.09 (0.015)	NS	NS	NS
Height variation contour	−0.17 (<0.001)	−0.17 (<0.001)	0.10 (0.008)	0.07 (0.025)	0.07 (0.044)	NS	−0.10 (0.008)	−0.08 (0.011)
Cup shape measure	0.08 (0.034)	0.14 (<0.001)	NS	−0.07 (0.039)	NS	NS	NS	NS
Mean RNFL thickness	−0.29 (<0.001)	−0.27 (<0.001)	0.18 (<0.001)	0.12 (<0.001)	0.14 (<0.001)	NS	−0.13 (0.001)	−0.12 (<0.001)
RNFL cross-sectional area	−0.33 (<0.001)	−0.3 (<0.001)	0.17 (<0.001)	0.14 (<0.001)	0.13 (<0.001)	NS	−0.13 (0.001)	−0.13 (<0.001)

NS = not significant (P>0.05); RNFL = retinal nerve fiber layer.
Pearson's correlation coefficients are shown with P values in the parentheses.
*Spherical equivalent values.

in 1769 Normal Right Eyes of 787 Male and 982 Female Subjects

Diastolic Blood Pressure		Ocular Perfusion Pressure		Refractive Error*		Intraocular Pressure		Central Corneal Thickness	
Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
NS	NS	NS	NS	NS	NS	−0.08 (0.04)	NS	NS	NS
NS	NS	NS	NS	NS	0.07 (0.25)	NS	NS	NS	NS
NS	NS	NS	NS	NS	NS	−0.09 (0.016)	NS	NS	NS
NS	NS	NS	NS	NS	0.08 (0.013)	NS	NS	NS	NS
NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
NS	NS	NS	NS	−0.20 (<0.001)	−0.18 (<0.001)	NS	NS	0.07 (0.043)	NS
NS	NS	NS	NS	−0.13 (<0.001)	NS	NS	NS	NS	NS
NS	NS	NS	NS	−0.16 (<0.001)	NS	NS	NS	NS	NS
NS	NS	−0.08 (0.020)	NS	−0.27 (<0.001)	−0.18 (<0.001)	NS	NS	NS	NS
NS	NS	NS	NS	NS	0.08 (0.010)	NS	NS	NS	NS
NS	NS	−0.80 (0.024)	−0.08 (0.016)	−0.32 (<0.001)	−0.25 (<0.001)	NS	NS	NS	NS
NS	NS	−0.07 (0.046)	−0.08 (0.014)	−0.31 (<0.001)	−0.21 (<0.001)	NS	NS	NS	NS

Table 4. Partial Correlation Coefficients in Multiple Regression Analysis on Each of the Heidelberg Retina Tomograph Parameters in 1769 Normal Eyes of 787 Male and 982 Female Subjects

	Age	Height	Weight	Systolic Blood Pressure	Ocular Perfusion Pressure	Refractive Error	Intraocular Pressure	Central Corneal Thickness	Gender
Disc area	−0.14 (<0.001)	NS	NS	NS	NS	0.09 (<0.001)	NS	NS	NS
Cup area	NS	0.04 (0.049)	NS	NS	NS	0.07 (0.005)	NS	NS	NS
Rim area	−0.15 (<0.001)	−0.07 (0.003)	NS	NS	NS	0.05 (0.035)	NS	NS	NS
Cup-to-disc area ratio	NS	0.07 (0.002)	NS	NS	NS	0.06 (0.020)	NS	NS	NS
Cup volume	−0.06 (0.008)	0.06 (0.008)	NS	NS	NS	0.07 (0.002)	NS	−0.05 (0.037)	NS
Rim volume	−0.12 (<0.001)	−0.05 (0.024)	NS	NS	NS	−0.12 (<0.001)	NS	NS	NS
Mean cup depth	−0.05 (0.037)	0.09 (<0.001)	NS	NS	NS	NS	NS	NS	NS
Maximum cup depth	−0.07 (0.002)	0.08 (<0.001)	NS	NS	NS	NS	NS	−0.05 (0.049)	NS
Height variation contour	−0.06 (0.015)	NS	NS	NS	NS	−0.16 (<0.001)	NS	NS	NS
Cup shape measure	0.08 (0.001)	NS	NS	NS	NS	NS	NS	NS	NS
Mean RNFL thickness	−0.14 (<0.001)	NS	NS	NS	NS	−0.16 (<0.001)	NS	NS	NS
RNFL cross-sectional area	−0.19 (<0.001)	NS	NS	NS	NS	−0.12 (<0.001)	NS	NS	NS

NS = not significant ($P>0.05$); RNFL = retinal nerve fiber layer.
Multiple regression analysis with each Heidelberg retina tomograph parameter as the dependent variable and age, height, weight, systolic and diastolic blood pressure, ocular perfusion pressure, refractive error (spherical equivalent), intraocular pressure, central corneal thickness, and gender as the independent variables. Partial correlation coefficients are shown with P values in the parentheses. Diastolic blood pressure was excluded from the model because of strong correlation between systolic and diastolic pressure.

Table 5. Partial Correlation Coefficients in Multiple Regression Analysis Including Disc Area as an Independent Variable on Each of the Heidelberg Retina Tomograph Parameters in 1769 Normal Eyes of 787 Male and 982 Female Subjects

	Age	Height	Weight	Systolic Blood Pressure	Ocular Perfusion Pressure	Refractive Error	Intraocular Pressure	Central Corneal Thickness	Gender	Disc Area
Cup area	0.09 (<0.001)	0.08 (0.001)	NS	NS	NS	NS	NS	NS	NS	0.73 (<0.001)
Rim area	−0.09 (<0.001)	−0.08 (0.001)	NS	NS	NS	NS	NS	NS	NS	0.56 (<0.001)
Cup-to-disc area ratio	0.09 (<0.001)	0.09 (<0.001)	NS	NS	NS	NS	NS	NS	NS	0.53 (<0.001)
Cup volume	NS	0.09 (<0.001)	NS	NS	NS	NS	0.05 (0.037)	−0.05 (0.040)	NS	0.60 (<0.001)
Rim volume	−0.11 (<0.001)	−0.05 (0.026)	NS	NS	NS	−0.13 (<0.001)	NS	NS	NS	0.13 (<0.001)
Mean cup depth	NS	0.10 (<0.001)	NS	NS	NS	NS	0.05 (0.041)	NS	NS	0.44 (<0.001)
Maximum cup depth	NS	0.09 (<0.001)	NS	NS	NS	NS	0.05 (0.026)	NS	NS	0.33 (<0.001)
Height variation contour	−0.07 (0.007)	NS	NS	NS	NS	−0.16 (<0.001)	NS	NS	NS	−0.05 (0.027)
Cup shape measure	0.14 (<0.001)	NS	NS	NS	NS	NS	NS	NS	NS	0.39 (<0.001)
Mean RNFL thickness	−0.17 (<0.001)	NS	NS	NS	NS	−0.15 (<0.001)	NS	NS	NS	−0.18 (<0.001)
RNFL cross-sectional area	−0.17 (<0.001)	NS	NS	NS	NS	−0.14 (<0.001)	NS	NS	NS	0.19 (<0.001)

NS = not significant ($P>0.05$); RNFL = retinal nerve fiber layer.
Multiple regression analysis with each Heidelberg retina tomograph parameter as the dependent variable and age, height, weight, systolic and diastolic blood pressure, ocular perfusion pressure, refractive error (spherical equivalent), intraocular pressure, central corneal thickness, gender, and disc area as the independent variables. Partial correlation coefficients are shown with P values in the parentheses. Diastolic blood pressure was excluded from the model because of strong correlation between systolic and diastolic pressure.

Table 6. Correlation Coefficients of Each Pair of the Heidelberg Retina Tomograph Parameters in 1769 Normal Eyes

	Disc Area	Cup Area	Rim Area	Cup-to-Disc Area Ratio	Cup Volume	Rim Volume	Mean Cup Depth	Maximum Cup Depth	Height Variation Contour	Cup Shape Measure	Mean RNFL Thickness
Cup area	0.72										
Rim area	0.56	−0.17									
Cup-to-disc area ratio	0.52	0.95	−0.39								
Cup volume	0.61	0.90	−0.21	0.85							
Rim volume	0.13	−0.38	0.64	−0.51	−0.34						
Mean cup depth	0.44	0.79	−0.33	0.84	0.86	−0.20					
Maximum cup depth	0.34	0.65	−0.29	0.71	0.73	−0.13	0.92				
Height variation contour	−0.05*	−0.14	0.10	−0.16	−0.11	0.68	0.16	0.24			
Cup shape measure	0.37	0.58	−0.17	0.57	0.48	−0.23	0.46	0.12	−0.09		
Mean RNFL thickness	−0.15	−0.29	0.13	−0.30	−0.23	0.75	0.07*	0.16	0.83	−0.20	
RNFL cross-sectional area	0.20	−0.05*	0.34	−0.12	−0.03*	0.80	0.22	0.28	0.80	−0.07	0.93

RNFL = retinal nerve fiber layer.
Pearson's correlation coefficients are shown. All correlation coefficients except those with asterisks (*) show *P* values of ≤0.001.

Optic Disc Topography and Peripapillary Retinal Nerve Fiber Layer Thickness in Nonarteritic Ischemic Optic Neuropathy and Open-Angle Glaucoma

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Objective: To evaluate the results of scanning laser tomography and scanning laser polarimetry (SLP) and the correlations with visual field damage (VFD) in eyes with nonarteritic ischemic optic neuropathy (n-AION) compared with eyes with open-angle glaucoma (OAG).

Design: Cross-sectional study.

Participants: Thirty-three eyes of 33 patients with n-AION and 33 eyes with OAG whose age and VFD evaluated with the Humphrey field analyzer were matched to those of the n-AION eyes.

Main Outcome Measures: The parameters of optic disc topography obtained with the Heidelberg Retina Tomograph II (HRT II) and retinal nerve fiber layer (RNFL) thickness with GDx with variable corneal compensation and the correlation to VFD.

Results: The cup area, cup-to-disc area ratio, and mean cup depth were significantly smaller, and the cup shape measure more negative, in the n-AION eyes than in the OAG eyes ($P<0.001$), whereas rim area was significantly greater ($P<0.001$). Multivariate analyses showed that none of disc area, rim area, and mean cup depth in the n-AION eyes and only rim area ($P = 0.029$) in the OAG eyes was significantly associated with mean deviation (MD). Ellipse average of RNFL thickness significantly correlated with MD in the n-AION eyes ($P = 0.045$) and in the OAG eyes ($P = 0.022$).

Conclusions: Disc topography of eyes with n-AION was quantitatively characterized by small and shallow cupping and a relatively large rim area compared to eyes with OAG matched for age and VFD. In eyes with n-AION, significant correlation with VFD was found only for the RNFL thickness evaluated with SLP but not for the HRT II parameters. *Ophthalmology 2006;113:1340–1344 © 2006 by the American Academy of Ophthalmology.*

Nonarteritic anterior ischemic optic neuropathy (n-AION) is thought to result from acute perfusion insufficiency around the optic nerve head (ONH). Although the exact etiology of ischemia in n-AION is unknown, decreased circulation to the posterior ciliary arteries is thought to be the main cause of the disease.[1,2] Unlike arteritic AION, complete occlusion of posterior ciliary arteries is not mandatory and circulation resumes after the acute phase.[1] Systemic diseases such as ischemic heart disease,[3] hypercholesterolemia,[3] diabetes mellitus,[3–5] hypotension,[6,7] and possibly hypertension[4] are thought to be risk factors for n-AION.

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In patients who develop n-AION, the ONHs have anatomic characteristics such as small disc area, no to minimal physiologic cupping, and an increased number of branches of the central retinal vessels within the disc; they are often referred to as the "disc at risk."[8] In addition to empirical and qualitative knowledge, some quantitative studies using fundus photographs have reported small discs, small cup-to-disc ratios, or both.[9–12] Three-dimensional and quantitative methods of evaluation of the ONH morphology and retinal nerve fiber layer (RNFL) thickness using confocal scanning laser ophthalmoscopy, the Heidelberg Retina Tomograph II (HRT II, Heidelberg Engineering, Dossenheim, Germany), and scanning laser polarimetry (SLP), the GDx Nerve Fiber Analyzer with Variable Corneal Compensation (GDx VCC, Laser Diagnostic Technologies, Inc., San Diego, CA), have been developed recently but have not been used to study n-AION eyes, with the exception of a few studies.[13–15] Moreover, the relationship between the morphologic changes and visual field damage (VFD) in n-AION eyes has never been investigated.

The aims of this cross-sectional study were to (1) evaluate the OHN topography and the RNFL thickness in

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n-AION eyes and (2) assess the correlation of these parameters with VFD and compare with eyes with OAG matched by age and VFD.

Materials and Methods

Thirty-three consecutive patients (33 eyes) with n-AION who met the inclusion criteria between January 2002 and December 2003 at the Inouye Eye Hospital or the outpatient clinic of the Department of Ophthalmology, University of Tokyo Graduate School of Medicine, were included after providing informed consent. The study was approved by the Institutional Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Inclusion criteria were as follows: (1) eyes with a history of acute onset of n-AION ≥4 months before enrollment in the study, (2) eyes in which reliable assessments of visual field, HRT II, and GDx VCC were available, and (3) eyes without ocular diseases, except n-AION and slight cataract, that could affect the results of visual field testing, GDx VCC, and HRT II.

n-AION was diagnosed based on a history of an acute event of optic disc swelling, superficial hemorrhage at the optic disc border and adjacent retina, or both as the cause of an acute, painless, and incomplete visual loss. Because most of the patients in the current study were referred from other hospitals or clinics, the objective symptoms of the acute phase of n-AION were confirmed by ourselves in 11 of the 33 eyes studied. In the other 22 eyes, we reconfirmed the existence of objective symptoms in the acute phase by asking the referring ophthalmologists. We also conducted detailed interviews of the patients to confirm the sudden visual loss or other symptoms at the onset of the disease. No patient had findings suggestive of arteritic-AION described by Beck et al[12] that includes systemic symptoms of giant cell arteritis, sudden marked visual loss to the level of hand motions or less, a chalky-white swollen optic disc, occlusion of 1 or the other posterior ciliary artery observed on fluorescein fundus angiography, and a high erythrocyte sedimentation rate (>50 mm/hour). Fluorescein angiography had been performed in 25 of the 33 patients, excluding those with a history of drug allergy or renal or hepatic dysfunctions. Erythrocyte sedimentation rate testing was performed in 15 patients in whom possibility of inflammatory vascular diseases or temporal arteritis could not be excluded. No patients underwent biopsy of the temporal artery. Because ≥4 months had passed after the acute onset, the swelling and hemorrhages of the disc had subsided, and the disc borders were clearly delineated at the time of this study.

The 3-dimensional features of the ONH were determined using the HRT II. For each patient, 3 topographic images were obtained, combined, and automatically aligned to create a single mean topographic image used for analysis. Magnification errors were corrected using the patients' corneal curvature measurements. An experienced examiner outlined the optic disc margin on the mean topographic image while viewing color photographs of the optic disc. Good-quality images required focused reflectance with a standard deviation ≤50 μm. The topographic parameters studied were disc area, cup area, rim area, cup-to-disc area ratio, cup volume, rim volume, mean cup depth, and cup shape measure for the comparison between the n-AION and OAG eyes, and disc area, rim area, and mean cup depth for the multivariate analysis of the correlation with VFD.

The thickness of the peripapillary RNFL was evaluated by an experienced examiner with GDx VCC, which is a modified SLP system with a variable corneal compensator. A SLP macular image first was obtained to determine the eye-specific corneal polarization axis and magnitude. A polarimetry image around the optic disc then was obtained by compensating for the eye-specific corneal polarization. The quality of the polarimetry image was evaluated with the Q-score provided by the GDx VCC standard software, and images with a Q-score of ≤7 were not used in this study. The GDx VCC parameters investigated in this study were ellipse average (TSNIT average), superior average, and inferior average.

Visual field testing was performed with the 30-2 program of the Swedish Interactive Threshold Algorithm standard strategy of the Humphrey Visual Field Analyzer (HFA; Carl Zeiss Meditec, Oberkochen, Germany). Only reliable results (fixation loss <20%, false-positive error <33%, or false-negative error <33%) were used. For each patient with n-AION or OAG, the visual field examination and ocular imaging with the HRT II and GDx VCC were completed within 1 month of each other. The HFA parameters investigated were mean deviation (MD), average of total deviation in the superior hemifield (TD_{sup}), and average of total deviation in the inferior hemifield (TD_{inf}).

From the stored data of patients with OAG from whom reliable HFA, GDx VCC, and HRT II measurements had been obtained in the same 2 clinics and during the same time period, 33 OAG eyes were randomly chosen with age and MDs that matched to those of the AION eyes. For each pair of eyes, the differences in the age and MD did not differ by >3 years and >2 dB, respectively. However, the location of VFD and the degree of damage in each superior or inferior hemifield was not matched between the 2 groups.

OAG was diagnosed based on normal open angles, typical glaucomatous optic disc appearances corresponding to VFD, the absence of apparent pale color of the optic disc, and the absence of any contributing ocular or specific systemic disorders. The typical glaucomatous optic disc appearance included enlargement of the vertical cup-to-disc ratio, apparent difference of the vertical cup-to-disc ratio between both eyes, local narrowing of the neural rim, splinter hemorrhage, and/or visible nerve fiber layer defect.

Statistical Analysis

Means of the data were compared between the n-AION eyes and the OAG eyes using Student's *t* test. According to the Bonferroni's method, $P<0.05$/the number of the comparisons was considered statistically significant with consideration for the multiple comparisons. The prevalence of dominant superior or inferior hemifield damage in the HFA results was compared between the 2 groups using the Fisher exact test. Because disc area, rim area, and mean cup depth were correlated with each other, their correlation with MD was calculated using the multiple regression analysis in which the dependent variable was MD and independent variables were disc area, rim area, and mean cup depth. The multiple regression analyses in which dependent variable was MD, TD_{sup}, or TD_{inf} and the independent variables disc area and the corresponding RNFL thickness (TSNIT average, inferior average, or superior average, respectively) were performed. Statistical analyses were performed using a statistical software package, SPSS 13.0J for Windows (SPSS Japan Inc., Tokyo, Japan).

Results

There were no statistically significant differences between the n-AION eyes and the OAG eyes in gender, refractive error, or VFD ($P>0.05/6$ with Bonferroni's correction) except visual acuity, which was significantly worse in the n-AION eyes ($P = 0.003<0.05/6$) (Table 1).

Beside the 33 eyes with n-AION included in the current study, 16, 8, and 5 eyes were excluded because of unreliable results on the HRT II, GDx VCC, or both, respectively. There was no significant difference in age (61.8±10.4 vs. 63.8±11.7 years, $P =$

Table 1. Patient Demographic Data

	n-AION	OAG	P Value*
Men/women	17/16	18/15	0.6
Age (y)	61.8±10.4	61.8±10.3	—
Best-corrected visual acuity (log MAR)	0.31±0.54	0.04±0.38	0.003†
Refractive error (diopters)	−1.1±3.4	−3.1±3.5	0.022
Mean deviation (dB)	−12.3±8.3	−12.3±8.2	—
Pattern standard deviation (dB)	10.6±5.8	10.8±4.6	0.9
TD_{sup} (dB)	−8.20±9.22	−14.5±10.4	0.011
TD_{inf} (dB)	−13.9±10.4	−9.6±8.6	0.077

log MAR = logarithm of the minimal angle of resolution; dB = decibels; n-AION = nonarteritic anterior ischemic optic neuropathy; OAG = open-angle glaucoma; TD_{inf} = average of total deviation in the inferior hemifield; TD_{sup} = average of total deviation in the superior hemifield. Values are expressed as the mean ± standard deviation.

*Unpaired *t* test except for men/women, for which the chi-square test was used.

†Statistically significant with consideration for the multiple comparisons ($P<0.01$).

0.5, unpaired *t* test), visual acuity (0.31±0.54 vs. 0.81±1.58 in logarithm of the minimal angle of resolution, $P = 0.1$), and VFD (−12.3±8.3 vs. −11.8±9.9 dB in MD, $P = 0.4$) between the 33 included eyes and 29 excluded eyes.

TD_{inf} was significantly worse than TD_{sup} ($P<0.05$, unpaired *t* test) in 16 of 33 eyes with n-AION and in 7 of 33 eyes with OAG, respectively. TD_{sup} was significantly worse than TD_{inf} ($P<0.05$) in 7 of 33 eyes with n-AION and in 16 of 33 eyes with OAG, respectively. These figures were significantly different between n-AION and OAG ($P = 0.009$, Fisher exact test).

The cup area, cup-to-disc area ratio, cup volume, and mean cup depth were significantly smaller, and the cup shape measure more negative in the n-AION eyes than in the OAG eyes, whereas the rim area was significantly greater in the n-AION eyes (all $P<0.001$). The superior average of RNFL thickness obtained with GDx VCC was smaller in the n-AION eyes ($P = 0.001$), whereas

Table 2. HRT II and GDx VCC Parameters

Parameter	n-AION	OAG	P Value*
HRT II			
Disc area (mm^2)	1.94±0.38	2.20±0.56	0.031
Cup area (mm^2)	0.41±0.45	1.09±0.67	<0.001†
Rim area (mm^2)	1.49±0.55	1.04±0.32	<0.001†
Cup-to-disc area ratio	0.21±0.20	0.48±0.19	<0.001†
Cup volume (mm^3)	0.07±0.13	0.30±0.29	<0.001†
Rim volume (mm^3)	0.37±0.20	0.28±0.17	0.053
Mean cup depth (mm)	0.13±0.07	0.29±0.10	<0.001†
Cup shape measure	−0.18±0.07	−0.07±0.06	<0.001†
GDx VCC			
TSNIT average (μm)	40.7±11.0	44.9±10.1	0.1
Superior average (μm)	42.6±12.7	53.0±12.0	0.001†
Inferior average (μm)	46.7±16.2	45.4±12.3	0.7

GDx VCC = GDx Nerve Fiber Analyzer with Variable Corneal Compensation; HRT II = Heidelberg Retina Tomograph II; n-AION = nonarteritic anterior ischemic optic neuropathy; OAG = open-angle glaucoma; TSNIT average = ellipse average.

Values are expressed as mean ± standard deviation.

*Unpaired *t* test.

†Statistically significant with consideration for multiple comparisons.

Table 3. Results of the Multiple Regression Analyses for the HRT Parameters Associated with Mean Deviation

	n-AION		OAG	
HRT II Parameter	*Standardized β*	*P Value*	*Standardized β*	*P Value*
Disc area	−0.042	0.871	0.012	0.949
Rim area	−0.016	0.967	0.433	0.029
Mean cup depth	0.389	0.277	0.384	0.061

HRT II = Heidelberg Retina Tomograph II; n-AION = nonarteritic anterior ischemic optic neuropathy; OAG = open-angle glaucoma.

no significant difference was seen in the TSNIT average and inferior average of RNFL thickness between the 2 groups ($P = 0.1$ and 0.7, respectively) (Table 2). The superior average was significantly smaller than the inferior average in the n-AION eyes ($P = 0.001$, paired *t* test), whereas the superior average was significantly greater in the OAG eyes ($P = 0.002$). But the absolute differences between the superior and inferior averages were not significantly different between the n-AION and OAG eyes ($P = 0.090$).

The multiple regression analyses showed that disc area, rim area, and mean cup depth in the n-AION eyes were not associated with MD ($P>0.2$); only rim area ($P = 0.029$) in the OAG eyes were significantly associated with MD (Table 3). TSNIT average and MD were correlated in both the n-AION ($P = 0.045$) and OAG ($P = 0.022$) eyes, respectively. Superior ($P<0.001$) and inferior ($P = 0.003$) averages in the n-AION eyes and superior ($P = 0.039$) average in the OAG eyes were significantly correlated with the corresponding VFD (Table 4).

Discussion

In the typical clinical course of n-AION, disc swelling and hemorrhages on the disc or at the margins are seen at the time of onset. The disc swelling tends to resolve within 2 months; pallor appears earlier, frequently by 1 month.[16] Colen et al[14] report a case of n-AION in which the RNFL thickness obtained by SLP with fixed corneal compensation (FCC) decreased from 62 to 49 μm within the first month after onset and then remained unchanged. Considering these factors, in the current study we included only eyes with follow-up periods of ≥4 months after the onset of n-AION.

The ONHs in n-AION eyes are characterized by a small disc area, no or minimal cupping, and an increased number of branches of the central retinal vessels within the disc.[8] Studies using quantitative measures on fundus photographs revealed a smaller disc size of 2.74±0.45 mm^2 in n-AION eyes (vs. 3.34±0.73 mm^2 in normal eyes),[9] 2.31±0.26 mm^2 (vs. 2.71±0.68 mm^2 in normal eyes),[10] and smaller cup-to-disc ratios of 0.154±0.117[11] and 0.16±0.15 (vs. 0.31±0.19 in normal eyes).[12] We could not demonstrate this finding, but our study was not sufficiently powered to do so. Moreover, in the current study, small and shallow cupping in eyes with n-AION, compared to eyes with OAG matched for age and MD, was demonstrated quantitatively. The cup area, mean cup depth, and cup-to-disc area ratio were approximately half and the cup volume one fourth of the values in the OAG eyes.

Table 4. Results of the Multiple Regression Analyses for the GDx VCC Parameters Associated with the Corresponding Visual Filed Damage

Parameter	n-AION		OAG	
	Standardized β	*P Value*	*Standardized β*	*P Value*
TSNIT average for MD	0.41	0.045	0.42	0.022
Inferior average for TD_{sup}	0.67	<0.001	0.31	0.102
Superior average for TD_{inf}	0.59	0.003	0.38	0.039

GDx VCC = GDx Nerve Fiber Analyzer with Variable Corneal Compensation; MD = mean deviation; n-AION = nonarteritic anterior ischemic optic neuropathy; OAG = open-angle glaucoma; TSNIT average = ellipse average; TD_{sup} = average of total deviation in the superior hemifield; TD_{inf} = average of total deviation in the inferior hemifield.

The current study is also the first documentation of RNFL thickness measured using SLP with VCC in eyes after n-AION. Banks et al[13] measured the RNFL thickness in eyes with n-AION or AION using SLP with FCC.[13] Those authors reported the average thicknesses as 59±7 and 51±9 μm in the acute (n = 18 eyes) and chronic (n = 20 eyes) phases, respectively. Colen et al.[14] reported the follow-up of 1 case of n-AION using SLP with FCC, in which the RNFL thickness (the "superior average") decreased from 62 μm 10 days after onset to 48 μm 9 months later. Compared to those reports, the TSNIT averages in 33 n-AION eyes of the current study (40.7±11.0 μm) were relatively smaller. Because anterior segment birefringence varies widely in human eyes, SLP with FCC often provides inappropriate data on RNFL thickness.[17,18] Moreover, the RNFL thickness values tend to be higher with FCC than with VCC,[18] possibly explaining the discrepancy in RNFL thickness in n-AION eyes between the current and previous studies.[13,14]

In the n-AION eyes of this study, the superior average of RNFL thickness was significantly smaller than the inferior average. This is contrary to the results in normal[19,20] or OAG[19] eyes and the current results on OAG, and suggested that the superior region of the ONH was more commonly affected in n-AION. Although the HRT parameters did not significantly correlate with VFD, the results of GDx VCC were significantly associated with the corresponding VFD with regression coefficients of 0.41 to 0.67 (Table 3).

Eyes with slight cataract were included in the current study. Even slight cataract can possibly affect the results of visual field testing. However, Carrillo et al[21] recently reported that the average change in MD after extraction of cataract in OAG patients whose preoperative log MAR visual acuity averaged 0.24 (between 20/30 and 20/40) was <0.1 dB and not statistically significant, suggesting that at least slight or mild cataract should not have apparent effects on the average of MD in a group of patients. Moreover, in the current study, because age of the n-AION patients and that of the OAG patients were matched (61.8±10.4 vs. 61.8±10.3 years), the total amount of the influence of (slight) cataract should be similar between the 2 groups, if it existed.

Most of the patients with n-AION had no experience with visual field testing using the HFA prior to this study, whereas the patients with OAG had several experiences. According to Heijl et al,[22] improvement of MD between the initial and second tests of the HFA in newly diagnosed glaucoma patients averaged 2.81 dB, which corresponded to 23% of the average of MD of the current n-AION eyes (−12.3 dB). Therefore, differences in the HRT parameters between the n-AION eyes and the OAG eyes, which ranged 30% to 320% (Table 2), cannot be explained completely by the influence of learning effects in the HFA testing.

In conclusion, the ONH topography in n-AION eyes was quantitatively characterized by small and shallow cupping and a relatively larger rim area compared to the age- and MD-matched OAG eyes. In n-AION eyes, the RNFL thickness evaluated with GDx VCC showed a good correlation with VFD, whereas the HRT results did not significantly correlate with VFD.

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Optic Disc and Peripapillary Morphology in Unilateral Nonarteritic Anterior Ischemic Optic Neuropathy and Age- and Refraction-Matched Normals

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Purpose: To compare optic disc morphologic features and peripapillary retinal nerve fiber layer (RNFL) thickness between the unaffected eyes of patients with unilateral nonarteritic anterior ischemic optic neuropathy (NAION) and their affected eyes and the eyes of age- and refraction-matched normal control subjects.

Design: Cross-sectional comparative study.

Participants: Thirty-one patients with unilateral NAION and 62 age- and refraction-matched normal control subjects.

Methods: Optic disc morphologic features and peripapillary RNFL thickness were evaluated in both eyes of patients with unilateral NAION and in one randomly chosen eye of the normal control subjects.

Main Outcome Measures: Optic disc and cup parameters were measured using the Heidelberg Retina Tomograph II (Heidelberg Engineering GmbH, Dossenheim, Germany), and RNFL thickness was measured by scanning laser polarimetry with variable corneal compensation (GDx VCC; Carl Zeiss Meditec, Dublin, CA).

Results: There was no significant difference in the disc area between the NAION affected eyes and the unaffected fellow eyes. The cup area, cup-to-disc area ratio, cup volume, and cup shape measure were greater, whereas the peripapillary RNFL thickness was smaller in the former than the latter ($P = 0.001$ to approximately 0.043). When the unaffected eyes of patients with NAION and the age- and refraction-matched normal control eyes were compared, the disc area, cup area, cup-to-disc area ratio, cup volume, mean cup depth, and cup shape measure were smaller in the former ($P = 0.0006$ to approximately 0.03); there was no significant difference in the RNFL thickness between the two ($P>0.06$).

Conclusions: A comparison of the eyes with NAION and the fellow eyes indicated that the cup was slightly larger in the former than in the latter, suggesting the acquired enlargement of the cupping after NAION develops. A comparison of the unaffected fellow eyes in patients with NAION and the age- and refraction-matched normal control eyes suggested that a smaller disc area and smaller cupping were predisposing risk factors for the development of NAION.

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Nonarteritic anterior ischemic optic neuropathy (NAION) is an acute optic disc disorder characterized by a sudden painless visual loss, visual field defects, optic disc edema, and peripapillary hemorrhages.[1,2] Although the detailed cause of NAION is unclear, ischemia of the optic disc may be the pathogenesis.[2-4] Characteristic appearances of the optic discs before and after the onset of NAION should be important when considering the course of the disease, and optic disc morphologic features related to NAION have been investigated from many aspects. However, the morphologic alterations that occur after NAION and whether there are predisposing characteristics of the optic disc before the onset of NAION are still debated. It is difficult to study the optic disc appearance before the onset of NAION because of the uncommon nature of the disease.

Previous studies have compared eyes after NAION develops and control eyes of ophthalmologically healthy subjects to investigate the acquired changes after the development of NAION.[5-7] However, such comparisons do not always reflect the true changes resulting from NAION because the disc appearance in premorbid eyes differs from that of normal eyes.[8-10] Investigating the unaffected fellow eyes of patients with unilateral NAION can be a surrogate method based on the assumption of the bilateral similarity of optic disc morphologic features that has been confirmed in at least a normal population.[11] Although two previous studies compared the optic disc morphologic features between eyes in which NAION developed and the unaffected fellow eyes, the studies reported somewhat conflicting results, that is, that there were no substantial changes in the cup-to-disc ratio evaluated on stereoscopic fundus photo-

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graphs[12] and that there was slight but significant enlargement in the cup-to-disc area ratio but no changes in cup area or cup volume measured by scanning laser tomography.[13] More recently, it was reported that optic disc shape parameters determined with optical coherence tomography (OCT), including cup-to-disc area ratio, were not significantly different between eyes after the onset of NAION and the fellow eyes.[14]

A comparison of the optic discs between the unaffected fellow eyes of patients with unilateral NAION and normal control subjects should be useful to investigate the premorbid risk factors for NAION. Previous studies[8–10] have reported a smaller optic disc area and smaller cup-to-disc area ratio based on stereoscopic photographs of the unaffected fellow eyes of patients with unilateral NAION compared with normal controls. A recent study using OCT found a significant difference in cup-to-disc area ratio but not in optic disc area between the unaffected fellow eyes of NAION patients and those of normal controls.[14] However, age, gender ratio, refractive error (which may affect the optic disc area and cup-to-disc area ratio), or a combination thereof,[15–20] were not or were only partially matched between the patients with unilateral NAION and normal subjects in those studies.[8–10,14] Moreover, no study has applied scanning laser tomography or scanning laser polarimetry to the investigation on the comparison of the unaffected fellow eyes with normal control eyes.

The aims of the current study were to compare quantitatively and three dimensionally the optic disc morphologic features and peripapillary retinal nerve fiber layer (RNFL) thickness using scanning laser tomography and laser scanning laser polarimetry (1) between the affected eyes and the unaffected fellow eyes of patients with unilateral NAION to determine the changes that develop after the onset of NAION and (2) between the unaffected fellow eyes of NAION patients and the eyes of age- and refraction-matched normal subjects, with a gender ratio similar to that in the patients with NAION, to determine the premorbid risk factors for the development of NAION.

Patients and Methods

Thirty-one consecutive patients with unilateral NAION who met the inclusion criteria between January 2002 and June 2006 at the Inouye Eye Hospital or the outpatient clinic of the Department of Ophthalmology, University of Tokyo Graduate School of Medicine, were included after providing informed consent. The study was approved by the institutional ethics committee and adhered to the tenets of the Declaration of Helsinki.

Inclusion criteria for this cross-sectional study of unilateral NAION were: (1) an eye with a history of acute-onset NAION 4 months or longer before enrollment in the study and a ophthalmologically healthy fellow eye; (2) reliable assessments of visual field tests, scanning laser tomography, Heidelberg Retina Tomograph II (HRT II; Heidelberg Engineering GmbH, Dossenheim, Germany), and scanning laser polarimetry with variable corneal compensation (GDx VCC; Carl Zeiss Meditec, Dublin, CA) results available for both eyes; and (3) no ocular diseases that might affect the results of visual field testing, HRT II, or GDx VCC in both eyes, except NAION in one eye and slight cataract in either eye. Standard automated perimetry (SAP) was performed using the Humphrey Visual Field Analyzer with Swedish interactive threshold algorithm standard strategy (Carl Zeiss Meditec).

An ophthalmologically healthy eye was defined as an eye without abnormal findings on complete ophthalmologic assessments, including slit-lamp and fundus examinations, best-corrected visual acuity exceeding 20/25, intraocular pressure of less than 21 mmHg, a deep anterior chamber, normal optic disc appearance based on clinical stereoscopic examination, and normal SAP results. The SAP results were judged as reliable when fixation loss was less than 20% and false-positive or false-negative error was less than 33% and as normal when it showed neither glaucomatous abnormalities according to the criteria described by Anderson and Patella[21] nor other pathologic findings.

The diagnosis of NAION was based on a history of an acute event with optic disc swelling; superficial hemorrhages at the optic disc border or adjacent retina; and acute, painless, and incomplete visual loss. Because most patients in the current study were referred from other hospitals or clinics, the authors confirmed the objective symptoms of the acute phase of NAION in 13 of the 32 eyes studied. In the other 19 eyes, the authors reconfirmed the objective symptoms in the acute phase by contacting the referring physician. The authors also conducted detailed interviews with the patients to confirm the sudden visual loss or other subjective symptoms at the onset of the disease. Neurologic and neuroradiologic examinations showed no other reason for an acute optic neuropathy, including autoimmune optic neuropathy.[22] No patient had findings suggestive of arteritic AION described by Beck et al[10] that includes systemic symptoms of giant cell arteritis, sudden marked visual loss to the level of hand movements or less, a chalky-white swollen optic disc, occlusion of one or the other posterior ciliary artery observed on fluorescein fundus angiography, and a high erythrocyte sedimentation rate (>50 mm/hour). Fluorescein angiography had been performed in 24 of the 31 patients; fluorescein angiography was not performed in patients with renal or hepatic dysfunctions or in those who had history of drug allergy. The erythrocyte sedimentation rate was measured in 15 patients in whom the possibility of inflammatory vascular diseases or temporal arteritis could not be excluded completely. All 15 patients had an erythrocyte sedimentation rate within the normal limits. No patients underwent temporal artery biopsy. Because at least 4 months had passed after the acute onset of the disease, the swelling and hemorrhages of the optic disc had subsided and the disc borders were delineated clearly at the time of the study.

Sixty-two randomly chosen subjects with no ocular pathologic features also were studied to compare the background data and the optic disc morphologic features with the 31 patients with unilateral NAION. To match the ages and refractions with patients with unilateral NAION, the 62 ophthalmologically healthy subjects were within ±3 years of age and their spherical equivalence was within ±2 diopters of those of each patient with NAION. Both eyes of the normal subjects satisfied the inclusion criteria for an ophthalmologically healthy eye as described previously. Data for the age- and refraction-matched normal controls were selected from the authors' hospital-based database of normal eyes. All ophthalmologic examinations were conducted by the same examiners with the same methods as in the patients with NAION. The ratio of male to female subjects in the control group (25:37) was similar to that of the patients with NAION (14:17).

The best-corrected visual acuity was measured using a retroilluminated Landolt visual acuity chart at 5 m and was converted into logarithm of the minimum angle of resolution scores for statistical analysis. The intraocular pressure was measured by Goldmann applanation tonometry.

The three-dimensional features of the optic nerve head were determined using the HRT II. For each patient, 3 topographic

Table 1. Demographic Data from Patients with Unilateral Nonarteritic Anterior Ischemic Optic Neuropathy and Age- and Refraction-Matched Normal Subjects

	Unilateral Nonarteritic Anterior Ischemic Optic Neuropathy				
	Affected Eyes	Unaffected Eyes	P Value*	Normal†	P Value‡
No. of patients	31			62	
Male/female	14/17			25/37	0.8
Age (yrs)	60.7±11.9			59.1±10.3	0.6
Visual acuity (logMAR)	0.54±0.71	−0.05±0.06	<0.001	−0.06±0.05	0.4
Refractive error (D)	−0.6±3.4	−0.5±3.4	0.5	−0.3±1.8	0.6
Mean deviation (dB)§	−8.7±0.4	−0.52±1.7	<0.001	−0.31±0.9	0.8

D = diopters; logMAR = logarithm of minimum angle of resolution.
The values are expressed as the mean±standard deviation.
*Comparison between affected eyes and unaffected eyes (Wilcoxon signed-rank test).
†Normal control subjects age- and refraction-matched with those of patients with unilateral nonarteritic anterior ischemic optic neuropathy.
‡Comparison between unaffected fellow eyes of patients with nonarteritic anterior ischemic optic neuropathy and age- and refraction-matched normal control eyes (Mann–Whitney *U* test).
§Mean deviation of the Humphrey Field Analyzer results.

images were obtained, combined, and automatically aligned to create one mean topographic image used for analysis. Magnification errors were corrected using the patient's refraction and corneal curvature measurements. One experienced examiner (HS) outlined the optic disc margin on the mean topographic image while viewing color photographs of the optic disc for all NAION, fellow, and normal eyes. Good-quality images required focused reflectance with a standard deviation not exceeding 50 μm. The topographic parameters studied were the disc area, cup area, rim area, cup-to-disc area ratio, cup volume, rim volume, mean cup depth, and cup shape measure.

The peripapillary RNFL thickness was obtained by experienced examiners using the GDx VCC. A polarimetry macular image first was obtained to determine the eye-specific corneal polarization axis and magnitude. Subsequently, a polarimetry image around the optic disc was obtained by compensating for the eye-specific corneal polarization. The quality of the polarimetry images was evaluated with the Q-score provided by the GDx VCC standard software, and images with a Q-score of 7 or less were not used in this study. The GDx VCC parameters studied were the ellipse average (temporal-superior-nasal-inferior-temporal average), superior average, and inferior average.

Statistical Analysis

The Wilcoxon signed-rank test was used to compare data between the eyes in which NAION had developed and the fellow eyes. The Mann–Whitney *U* test was used to compare the unaffected fellow eyes of patients with NAION and the normal control eyes. A *P* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using a statistical software package, JMP 6.0.3 for Windows (SAS Japan, Inc., Tokyo, Japan).

Results

Thirty-one patients with unilateral NAION were included from among 58 patients with NAION examined during the study period. Twenty-seven patients were excluded because of bilateral NAION (5 patients) or unreliable results from HRT II, GDx VCC, or visual field examinations, or a combination thereof (22 patients). The demographic data from both eyes of patients with unilateral NAION and the eyes of normal control subjects did not differ significantly except for the corrected visual acuity and the mean deviation from the Humphrey Field Analyzer (Table 1).

Between the affected and unaffected fellow eyes of the patients with unilateral NAION, the optic disc areas were well correlated with each other (Spearman rank correlation coefficient, R_s = 0.6843; $P<0.0001$) and were not significantly different (P = 0.079, Wilcoxon signed-rank test; Table 2). Most cup parameters, including the cup area, cup-to-disc area ratio, cup volume, and cup shape measurements, were greater in the affected eyes than in the unaffected fellow eyes (P = 0.004 to approximately 0.043, Wil-

Table 2. Comparison of Parameters of the Heidelberg Retina Tomograph II and the GDx with Variable Corneal Compensation between Affected and Unaffected Eyes of 31 Patients with Unilateral Nonarteritic Ischemic Optic Neuropathy

	Affected Eyes	Fellow Eyes	P Value*
HRT II parameters			
Disc area (mm²)	1.87±0.48	1.75±0.44	0.079
Cup area (mm²)	0.56±0.56	0.36±0.42	0.006
Rim area (mm²)	1.31±0.33	1.38±0.27	0.2
Cup-to-disc area ratio	0.26±0.22	0.18±0.17	0.004
Cup volume (mm³)	0.11±0.17	0.07±0.09	0.043
Rim volume (mm³)	0.33±0.15	0.41±0.15	0.002
Mean cup depth (mm)	0.17±0.10	0.16±0.09	0.4
Cup shape measure	−0.16±0.08	−0.21±0.08	0.001
GDx VCC parameters			
TSNIT average (μm)	37.9±8.3	55.6±9.3	<0.0001
Superior average (μm)	39.1±9.0	66.1±10.4	<0.0001
Inferior average (μm)	43.4±13.5	63.4±10.4	<0.0001

HRT II = Heidelberg Retina Tomograph II; GDx VCC = GDx with variable corneal compensation; TSNIT = temporal-superior-nasal-inferior-temporal.
Values are expressed as the mean±standard deviation.
*Comparison between affected and unaffected eyes (Wilcoxon signed-rank test).