Table 4. Parameters of the MfERG second-order kernel response within the central 5° in glaucoma patients compared with that in normal volunteers

	Normal	Superior-dominant	Inferior-dominant	*P* value*			ANOVA *P* value
				Normal	Superior	Inferior	
Amplitude [nV/deg2]							
Nasal hemifield	3.47 ± 1.33	4.62 ± 2.15	4.38 ± 1.85	0.0001	0.1727	0.1533	0.1094
Temporal hemifield	5.39 ± 1.76	5.16 ± 2.32	5.06 ± 2.01				0.8813
Superior hemifield	4.36 ± 1.69	4.18 ± 1.79	4.14 ± 1.80	0.0079	0.5143	0.6411	0.9229
Inferior hemifield	4.89 ± 1.83	4.35 ± 1.37	4.39 ± 1.58				0.5841
Nasal/temporal hemifield	0.64 ± 0.14	0.91 ± 0.14	0.89 ± 0.21				0.0001
Superior/inferior hemifield	0.90 ± 0.21	0.95 ± 0.22	0.95 ± 0.26				0.7718
Peak latency [ms]							
Nasal hemifield	29.1 ± 1.43	29.1 ± 1.25	29.6 ± 1.01	0.0197	0.4184	0.1573	0.5549
Temporal hemifield	29.7 ± 1.39	29.3 ± 1.11	29.9 ± 1.17				0.6507
Superior hemifield	28.9 ± 1.37	28.9 ± 1.38	29.2 ± 1.25				0.6804
Inferior hemifield	29.9 ± 2.01	29.4 ± 1.11	29.7 ± 1.12	0.0162	0.2008	0.0705	0.7403

Values are expressed as mean ± SD.
*Wilcoxon signed-rank test: nasal versus temporal hemifield or superior versus inferior hemifield.

Similarly to the second-order kernel response in both groups, in the first-order kernel response, the summed amplitude in the superior hemisphere was smaller than that in the inferior hemisphere, and the summed amplitudes of the central 5° and 10°, but not that of the central 15°, were smaller in the nasal hemisphere than in the temporal hemisphere. In the peak latencies, there were no hemispherical differences between the superior and inferior hemifields, or between nasal and temporal hemifields, for the three eccentricities in both glaucoma groups.

Comparison of First- and Second-Order Kernels of mfERGs recorded from Concentric Rings in Controls and Glaucoma Patients

Comparison of the first-order kernel of controls and glaucomatous subjects with hemifield defects showed that there was no statistical difference in the amplitude from each hemisphere, or in the S/I or N/T amplitude ratios for the three eccentricities (Table 3; ANOVA). On the other hand, there was a significant prolongation of the trough latency of the central 10° in the nasal, temporal, and superior hemispheres, and in the nasal and superior 15° rings ($P = 0.030$, 0.022, 0.006, 0.019, and 0.027, respectively; ANOVA).

For the second-order kernel, the N/T amplitude ratio of the central 5° was significantly different from that of other eccentricities ($P = 0.0001$; ANOVA; Table 4). Additionally, there was a significant difference in the N/T amplitude ratio between the normal control group and in both the superior and inferior hemifield predominant groups (Fig. 6; $P = 0.0005$, 0.0012, respectively, Scheffé test). There was also a statistically significant prolongation of the trough latency of the response from the central 15° in the hemispheres ($P = 0.014$; ANOVA). The N/T amplitude ratio of the central 5° was the most sensitive parameter that distinguished normal controls from NTG patients.

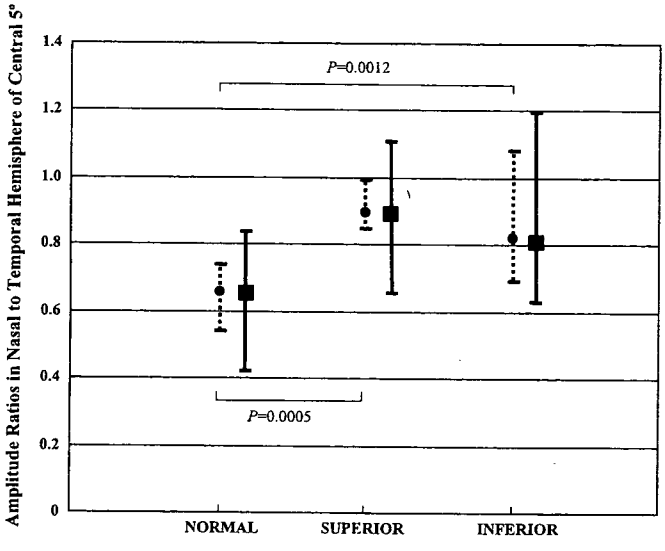

Figure 6. The nasal to temporal amplitude ratios of the central 5° differed significantly between the normal control group and the superior or inferior hemifield-predominant NTG groups. *Solid lines*, 97.5%–2.5%; broken lines, 75.0%–25%.

We calculated the receiver-operating characteristic (ROC) curve, which illustrates the sensitivity and specificity for discrimination of glaucomatous from normal eyes for different cutoff levels for the amplitude of the N/T amplitude ratios of the central 5°. The area under the ROC curve was 0.86. With a cutoff value of 0.83, the sensitivity was 65% and the specificity was 96.7%.

Correlation between the N/T Amplitude Ratio and Static Perimetric Findings

Our calculations showed that the correlations between the N/T amplitude ratio of the first-order kernel with the point

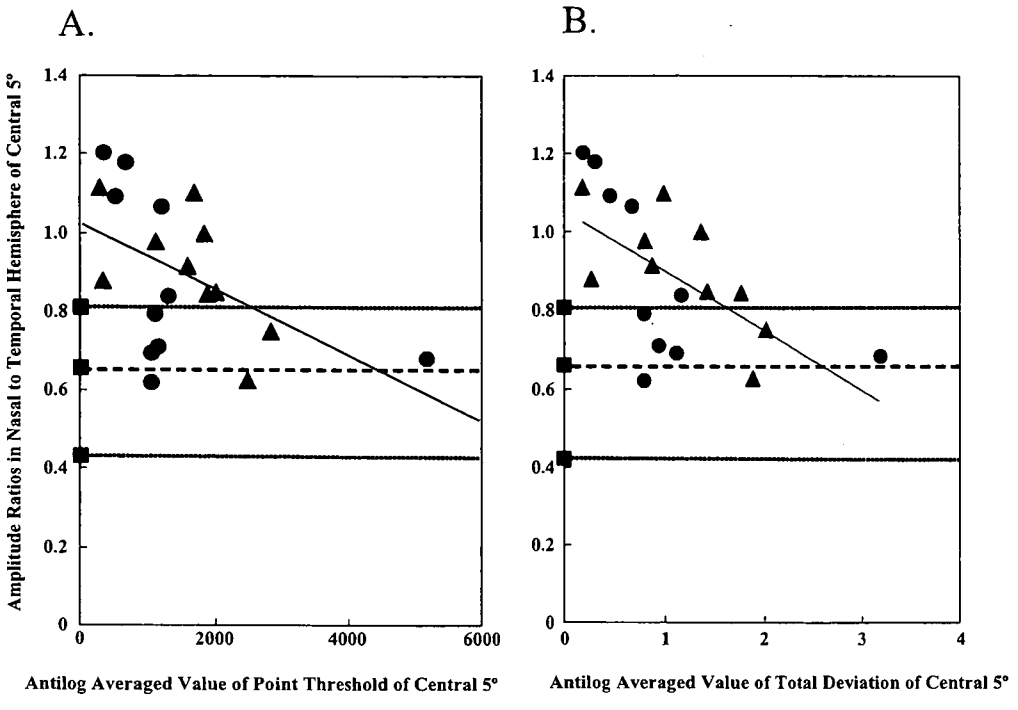

Figure 7. Relationships between nasal to temporal (N/T) amplitude ratio in the second-order kernel and the antilog averaged value of the point threshold (**A**) or of total deviation (**B**) obtained by the Humphrey central 30-2 program in NTG patients. The N/T amplitude ratio of the central 5° was significantly correlated with the antilog averaged value of each parameter of the central 5° (point threshold, r_s = –0.4602, P = 0.0448; total deviation, r_s = –0.6556, P = 0.0042). N/T ratio: ▲, superior; ●, inferior; ■, 10th–90th percentile in normal patients.

threshold or with the total deviation obtained with the Humphrey central 30-2 program were not significant. In addition, although the correlation coefficient between the N/T amplitude ratio of the second-order kernel and the point threshold or total deviation obtained with the Humphrey central 30-2 program increased with larger visual field areas, the correlation was not significant. However, there was a significantly strong correlation between the N/T amplitude ratio in the second-order kernel and the antilog averaged value of each parameter obtained with the Humphrey program central 30-2 (point threshold, r_s = –0.4602, P = 0.045; total deviation, r_s = *0.0020.656, P = 0.004; Fig. 7). A plot of the N/T amplitude ratio in the central 5° showed that 13 of 20 NTG patients were outside the 10th–90th percentile limits of the control group (Fig. 7; mean, 0.65; range of the 10th–90th percentiles, 0.44–0.81). Of these 13 NTG patients, eight had a superior hemisphere-dominant defect.

Discussion

Our results showed that mfERGs can be used to provide useful indices for detecting the presence of glaucomatous optic neuropathy. In particular, the second-order kernel response of the mfERGs within the central 5° can be used as a measure of retinal function in glaucomatous optic neuropathy. The value of this parameter was outside the 10th to 90th percentile range in 65% of NTG patients. The N/T amplitude ratio provided a good index for discriminating between individuals of the NTG and control groups.

Fortune et al.[16] reported that the area under the ROC curve of the amplitude of the oscillatory component in glaucoma patients was 0.88. The area under the ROC curve of the N/T amplitude ratio in our study was 0.86, and thus has approximately the same capability to discriminate between NTG patients and normal subjects.[16]

The mean refractive error in the NTG group was significantly higher than that in the normal group. Kawabata and Adachi-Usami[18] reported that the amplitudes of the first-order kernel of the mfERG were reduced and latencies were delayed in eyes with higher refractive errors. However, as shown in Tables 3 and 4, the amplitudes of the first- and second-order kernels of the NTG group were not significantly smaller than those of the normal group. Using the N/T ratio as the index should decrease the effect of refractive errors.

Hasegawa et al.[10] reported that the peak latencies of P1 and N2 of the first-order kernels in eyes with primary open-angle glaucoma (POAG) were significantly prolonged compared with those in normal eyes, although the differences in the amplitudes of (P1-N1) and (P1-N2) were not significantly different in the two groups. In this study, we demonstrated that there was no hemispherical difference in the amplitudes or the trough latency of the first-order kernel components of mfERGs in either the superior or inferior hemifield-predominant groups. These findings suggest that the first-order kernel components of the mfERG do not provide a good measure of the function of RGCs.

On the other hand, the second-order kernels are mainly attributable to components originating from the inner retinal layer.[19] An algorithm to extract the ONHC has been determined. The latency of this component increases as a function of the distance from the optic nerve head.[6] Bearse et al.[5] reported that the waveform of the second-order kernel had a nasal–temporal symmetry in glaucomatous

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eyes compared with in normal eyes, suggesting that these waveforms might reflect a decrease in surviving RGCs throughout the retina in glaucomatous eyes. In addition, Fortune et al.[16] reported a selective loss of the oscillatory potentials of the first-order kernel from the temporal retina in eyes with POAG. They suggested that this was not only related to abnormalities in the inner plexiform layer in the temporal region but also was partly due to alterations of the ONHC. Kamei and Nagasaka[20] reported that the loss of nasal–temporal asymmetry in the second-order kernel response within the central 5° in eyes with optic disc atrophy might be attributable to RGC dysfunction. However, other investigators[21] reported that components of the second-order kernel were not correlated with glaucomatous visual field changes at early stages of glaucoma, suggesting that these components did not represent RGC function.

In previous analyses using quadrants[14,22] or eccentric groups[8] over the wider visual fields, or all traces over the entire visual field,[9,14] independent components of the mfERGs might have been superimposed on the ONHC, resulting in smaller and more subtle changes in the mfERGs. Even in our study with the averaging of relatively small areas, comparisons between glaucomatous eyes with superior and inferior-dominant hemifield defects showed no statistical difference in the amplitudes, S/I amplitude ratios of the superior to inferior hemispheres, or trough latencies of the second-order kernels.

However, in the comparison of temporal and nasal hemifields within the central 5°, there was a statistical difference in the N/T amplitude ratio between normal volunteers and glaucoma patients, and there was a loss of nasal–temporal asymmetry in glaucoma patients. A loss of the nasal–temporal asymmetry in glaucoma patients has already been reported.[5,6,14–16] Nasal–temporal asymmetry in normal subjects was first described by Sutter and Bearse,[6] who reported it to be elicited in the second-order kernel response of the mfERG under high contrast and fast flicker stimulus conditions. When the number of stimulus elements was 103, the contrast was 98%, and maximum luminance was 600 cd/m^2 with a natural pupil.[6] Thereafter, this phenomenon was also investigated using different stimulus settings such as low-contrast or global flash stimuli.[14–16] We used high initial contrast and fast flicker stimulus conditions, based on the report by Sutter and Bearse,[6] except we used 37 stimulus elements and a maximum luminance of 200 cd/m^2 with a dilated pupil for easy recording and analysis.

Sutter and Bearse[6] also reported that the spatial distribution of the ONHC is higher in the central fields. In the current study, there was a statistically significant difference in the N/T amplitude ratio within the central 5° between NTG patients and normal volunteers, but not in that within the central 10° or 15°. Considering that even within the central 5°, there was no significant difference in the amplitudes between the two groups, the amplitude ratio is useful for decreasing interindividual variations. The amplitudes of the second-order kernel response in the nasal hemisphere within the central 5° in glaucoma patients were larger than those in normal volunteers. We also noticed that in some patients, the N/T amplitude ratios of the second-order kernel were >1.0, and that these values were close to the N/T amplitude ratio of the first-order kernel in normal eyes. Assuming that the second-order kernel of the mfERGs results from contributions of a retinal component and the ONHC,[6] we suggest that in normal subjects these two components had antagonistic effects, whereas in glaucoma patients they did not, because the ONHC is smaller.

We showed that the N/T asymmetry of amplitude of the second-order kernel was inversely correlated with visual field threshold deviation locally and widely. Kato and colleagues[23] showed that in eyes with NTG with hemifield visual defects, a significant correlation existed between Heidelberg retina tomographic parameters and visual field indices in the unaffected hemifields. Similarly, in a frequency-doubling perimetric study,[17] visual field abnormalities, even in the intact hemifield in some NTG eyes with upper or lower hemifield defects, were determined by conventional differential light sensitivity perimetry with a Humphrey field analyzer. Moreover, Thienprasiddhi et al.[24] found that the multifocal visual evoked potential technique might detect functional damage at an earlier stage of glaucoma than traditional automated perimetry. Therefore, the strong correlation between the decrease in N/T asymmetry in glaucomatous eyes and visual field indices might suggest disturbances in the entire visual field even at the earlier stages of glaucoma.

In conclusion, we demonstrated that the second-order kernels of mfERGs largely reflected functions of the inner retinal layer, including those of RGCs. In addition, we showed a high and significant correlation between the N/T amplitude ratio of the second-order kernel and the antilog averaged value of the visual field point threshold and total deviation parameters. Our findings support the use of mfERGs for glaucoma patients. However, the current study was a cross-sectional study, and a prospective longitudinal intensive investigation of mfERGs, including determination of whether progression in glaucoma can affect the mfERG response, or whether loss of nasal–temporal asymmetry appears in early stages of glaucoma or ocular hypertension, is needed. Further study is required before our results can be applied in a clinical setting.

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CLINICAL INVESTIGATION

Long-term Therapeutic Outcome of Acute Primary Angle Closure in Japanese

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Abstract

Purpose: To investigate the long-term clinical course of acute primary angle closure (APAC) and acute primary angle-closure glaucoma (APACG) in Japanese patients.

Methods: We retrospectively reviewed our records of 66 consecutive APAC or APACG eyes observed between February 1992 and December 2003 (mean follow-up, 42.1 months). Immediately after the diagnosis, all patients had received similar medications to halt the acute attack. Subsequently, laser iridotomy or surgical peripheral iridectomy and/or laser iridoplasty were conducted. If intraocular pressure (IOP) control was poor under maximum tolerable ocular hypotensive agents, trabeculectomy with adjunctive mitomycin C (MMC) was undertaken.

Results: After laser therapy, the probability of success, defined as an IOP of <21 mmHg with or without medications, was 81.2% ± 6.2%. In the ten eyes that were trabeculectomized, the probability of success based on the same criterion was 40.0% ± 29.7%. Multivariate analysis revealed that the degree of synechial angle closure ($P = 0.029$) and the preexistence of chronic glaucomatous optic neuropathy ($P = 0.015$) significantly influenced the need for subsequent filtering surgery.

Conclusions: Without the intervention of filtering surgery, 84.6% of eyes with APAC or APACG maintained IOP control with or without antiglaucoma medications. However, APAC and APACG eyes that eventually received trabeculectomy were predisposed to an uncontrollable IOP, even with the intraoperative application of MMC. The severity of APAC or APACG in Japanese may be affected by an underlying creeping angle closure. **Jpn J Ophthalmol** 2007;51:353–359 © Japanese Ophthalmological Society 2007

Key Words: acute primary angle-closure, acute primary angle-closure glaucoma, filtering surgery, Japanese, laser therapy

Introduction

In East Asian countries, primary angle-closure glaucoma or primary angle closure is more common than in Western countries,[1] and often leads to severe bilateral vision impairment.[2,3] The acute forms, acute primary angle closure (APAC) and acute primary angle-closure glaucoma (APACG), can constitute an ophthalmic emergency, requiring early diagnosis followed by appropriate treatment to pull the peripheral iris away from the chamber angle. The classical initial treatment for APAC or APACG includes medication therapy using miotics and carbonic anhydrase inhibitors, laser peripheral iridotomy or surgical peripheral iridectomy, and, in certain cases, filtering surgery.

Recently, it has been reported that primary phacoemulsification and intraocular lens implantation (PPI) for uncontrolled APAC or APACG might safely and effectively reduce intraocular pressure (IOP) and improve visual acuity.[4,5] However, Jacobi and associates[5] reported that five patients (5/43, 11.4%) who underwent PPI required subsequent IOP-lowering surgical intervention for IOP control.[5] Even when the IOP was reduced following the elimination

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of a relative pupillary block, 24%–72% of cases have been reported to show a recurrent IOP rise occurring months to years later, mainly due to extensive synechial angle closure.[6–12] These observations led us to reconsider the value of the classical treatment. In the present study, we investigated the therapeutic outcomes of the classical treatment in a Japanese population in order to reassess the long-term efficacy of this treatment. We also sought to identify the risk factors that indicate a need for surgical procedures to reduce IOP with the goal of identifying new therapeutic approaches for APAC or APACG.

Materials and Methods

We retrospectively reviewed the clinical records of all patients with APAC or APACG who were treated in our department at the Gifu University Graduate School of Medicine between February 1992 and December 2003, and summarized their clinical course after laser and/or surgical intervention. The study was approved by the Institutional Review Board of the Gifu University Graduate School of Medicine. This study included 66 eyes of 57 patients observed for at least 3 months, selected from the 83 consecutive eyes with APAC or APACG treated at our hospital during the above period. Eyes with any other secondary causative factors for developing angle closure, such as aqueous misdirection syndrome, uveitis, and lens-induced glaucoma, were excluded.

The initial ocular diagnostic examinations included visual acuity measurement, slit-lamp examination, measurement of corneal endothelial cell density, IOP measurement with Goldmann applanation tonometry, funduscopy, and the evaluation of angle structure and width by a Goldmann two-mirror gonioscopic lens. In cases of suspected plateau iris or other ocular abnormalities, ultrasound biomicroscopy was also performed.

The diagnosis and definition of APAC or APACG was made based on the criteria of Foster et al.[13] Briefly, APAC was defined as the condition of an eye, in the absence of glaucomatous optic neuropathy (GON), in a patient who had at least two of the following symptoms: ocular or periocular pain, nausea or vomiting, past episodes of intermittent blurring of vision with halos, presenting IOP of more than 21 mmHg, and at least three of the conjunctival hyperemia, corneal epithelial edema, mid-dilated nonreactive pupil, shallow anterior chamber, and the presence of occludable angle with or without peripheral anterior synechiae (PAS). Similarly, APACG was classified as APAC with GON.

Immediately after the diagnosis, all patients underwent the following definitive initial medical management: topical applications of 2% pilocarpine 3–4 times every 5 min and a beta-blocker, and unless contraindicated systemically, intravenous administration of 500 ml of 20% mannitol and 500 mg acetazolamide. In addition, dexamethasone was given topically to inhibit any anterior chamber reaction. After the initial medical therapy, the ocular condition was reexamined. Subsequently, laser peripheral iridotomy (LPI) and/or laser iridoplasty was performed. If severe corneal epithelial edema or a decrease of corneal endothelial cell density was noted, surgical peripheral iridectomy to halt the acute attack was performed. When IOP control was poor under maximum tolerable ocular hypotensive agents (IOP > 30 mmHg), trabeculectomy (TLE) with adjunctive mitomycin C (MMC) was undertaken. Conventional trabeculectomy was performed with a limbal-based flap of the conjunctiva and Tenon's capsule. A half-thickness 4 mm × 4 mm scleral flap was dissected to clear the cornea. Thereafter, 0.04% MMC was instilled intraoperatively, with an exposure time of 5 min, followed by washing with 250 ml of saline solution. After excision of the trabeculum, a peripheral iridectomy was performed. The scleral flap and conjunctiva were sutured firmly with 10-0 nylon.

The IOP data were analyzed by using the Kaplan-Meier life table method to calculate the cumulative probability of successfully controlled IOP, defined as an IOP of <21 mmHg with or without ocular hypotensive agents. Poorly controlled IOP was considered to have reached its end point when the IOP was found to be ≥21 mmHg during three consecutive clinical examinations. When comparing the demographic data between trabeculectomized and nontrabeculectomized eyes, we used both eyes except in cases when the acute attacks affected both eyes simultaneously. Data were analyzed using an unpaired *t* test, Mann-Whitney *U* test, and Fisher's exact probability test. For the multivariate analysis, which was used to evaluate the independence of prognostic factors, we randomly selected one of the eyes in bilateral cases and employed a Cox proportional hazards regression analysis. A *P* value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed with STATA software version 8.2 (Stata, College Station, TX, USA).

Results

Table 1 shows the demographic data for all of the patients. At presentation, mean patient age was 68.4 ± 8.4 years (range, 50–85 years). There were 48 women and nine men. In five patients, the acute attacks affected both eyes simultaneously. APAC had developed in the fellow eye of five patients before the prophylactic LPI. Although two eyes had received previous prophylactic LPI, an acute IOP rise occurred in these eyes as a result of occluded iridotomies. The mean IOP during the attack in the affected eye was 54.2 ± 11.2 mmHg (range, 34 to >80 mmHg). The mean duration of symptoms before the appropriate treatment was 2.6 days (range, 0–23 days). The extent of PAS, which was identified with the aid of an indentation gonioscopic lens after the cessation of the acute attack, varied between 0.0 and 12.0 h. Ten eyes were judged to have signs of preexisting chronic angle-closure glaucoma (APACG) if the cup-to-disc ratio was greater than 0.8. The mean follow-up period was 42.6 ± 31.9 months (range, 4–147 months). Immediately after the initial medical therapy, the IOP

Table 1. Patient background

Sex (male/female)	11 eyes, 9 patients/55 eyes, 48 patients
Age (years)	68.4 ± 8.4 (50–85)
IOP during the attack (mmHg)	54.2 ± 11.2 (34 to >80)
Duration of symptoms (days)	2.6 ± 4.5 (0–23)
APAC/APACG	56 eyes/10 eyes
Extent of PAS (clock hours)	5.3 ± 4.6 (0.0–12.0)
Duration of follow-up (months)	42.0 ± 32.1 (4–147)

Values are means ± SD (range)
IOP, intraocular pressure; PAS, peripheral anterior synechiae; APAC, acute primary angle closure; APACG, acute primary angle-closure glaucoma.

Table 2. Postoperative complications after laser peripheral iridotomy

Complication	No. of cases (%) $n = 62$
Bullous keratopathy[a]	3 (4.8)
Corneal burn	1 (1.6)
Hyphema	1 (1.6)

[a]Two eyes received both laser peripheral iridotomy and trabeculectomy.

decreased to 22.0 ± 13.5 mmHg (range, 3–56 mmHg). During the acute attack, one eye developed anterior ischemic optic neuropathy, while nonischemic central retinal vein occlusion was seen in two eyes.

For further analysis regarding the therapeutic outcome, one eye was excluded because it had no light perception in the initial ocular examinations, and we recommended no further aggressive laser or surgical management in this case. Thereafter, 58 eyes received only LPI, four eyes received LPI and laser gonioplasty, and three eyes received surgical peripheral iridectomy (PI) due to hazy media or decreased corneal endothelial cell density. Laser gonioplasty was employed in three eyes to halt the acute attack, and in one eye with unrecognized plateau iris during an attack. Of the 66 eyes studied, ten eventually required filtering surgery with intraoperative use of MMC for IOP control.

As shown in Table 2, laser peripheral iridotomy caused some complications, such as corneal burn and transient hyphema. In addition, incomplete iridotomy was found in six eyes (9.7%). On the other hand, further postoperative complications after trabeculectomy were noted in some cases. Transient shallow anterior chamber was found in three patients; choroidal detachment in one patient; retinal hemorrhages, presumably caused by drastic IOP reduction, in three patients; transient hyphema in two patients; and leaking bleb several years later in one patient (Table 3). The bullous keratopathy that developed in two eyes was treated by both LPI and TLE. Because of the very short periods between LPI and TLE in these cases, we could not identify whether this complication was attributable to the LPI or TLE, or to acute IOP elevation during the attack. Of the ten trabeculectomized patients, one required additional combined trabeculectomy and cataract surgery, and one required bleb revision for IOP control.

Table 3. Postoperative complications after trabeculectomy

Complication	No. of cases (%) $n = 10$
Shallow anterior chamber	3 (30.0)
Choroidal detachment	1 (10.0)
Hyphema	2 (20.0)
Leaking bleb	2 (20.0)
Retinal hemorrhages	3 (30.0)
Bullous keratopathy[a]	2 (20.0)

[a]Two eyes received both laser peripheral iridotomy and trabeculectomy.

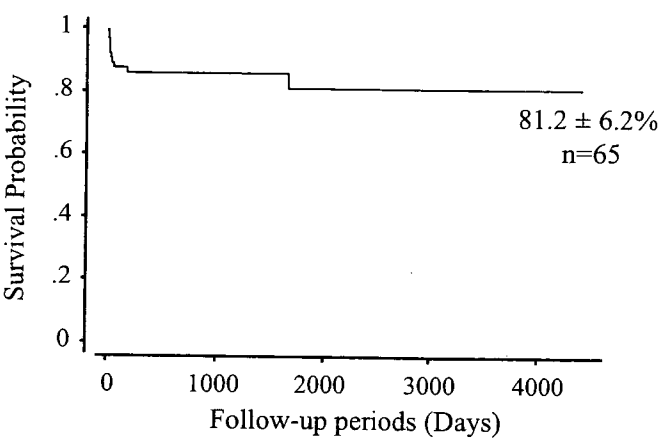

Figure 1. Kaplan-Meier curve showing the probability of success after laser therapy or surgical peripheral iridectomy. After laser therapy or surgical peripheral iridectomy, the probability of success, defined as an intraocular pressure of <21 mmHg with or without medication, was 81.2 ± 6.2%.

After laser therapy or surgical peripheral iridectomy, the probability of success, defined as an IOP of <21 mmHg with or without medications, was 81.2 ± 6.2% (Fig. 1). No further medical or surgical treatment was needed in 31 eyes (31/65, 47.7%), and only medication treatment was required in 24 eyes (24/65, 36.9%). Of the 24 eyes that received only further medical treatment, 17 received pilocarpine, 14 beta-blockers, 9 prostaglandin analogs, and 4 oral or topical carbonic anhydrase inhibitors. In the ten eyes (10/65, 15.4%) trabeculectomized owing to inadequate IOP control, the

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Table 4. Comparison of patient backgrounds between trabeculectomized and nontrabeculectomized eyes

	Nontrabeculectomized	Trabeculectomized	*P* value
Sex (male/female)	8 eyes / 43 eyes	2 eyes / 8 eyes	0.6626
Age (years)	68.1 ± 8.4 (50–85)	69.8 ± 9.1 (52–82)	0.5726
IOP during the attack (mmHg)	54.4 ± 11.8 (34 to >80)	55.5 ± 7.1 (46–70)	0.7337
Duration of symptoms (days)	2.1 ± 3.7 (0–21)	4.4 ± 6.9 (0–23)	0.1435
APAC/APACG	47 eyes / 4 eyes	5 eyes / 5 eyes	0.0039
Extent of PAS (clock hours)	5.3 ± 4.6 (0.0–12.0)	10.1 ± 2.1 (8.0–12.0)	0.0007
Duration of follow-up (months)	41.8 ± 31.0 (4–147)	53.8 ± 41.2 (5–108)	0.4188

Values are means ± SD (range).
IOP, intraocular pressure; PAS, peripheral anterior synechiae; APAC, acute primary angle closure; APACG, acute primary angle-closure glaucoma.

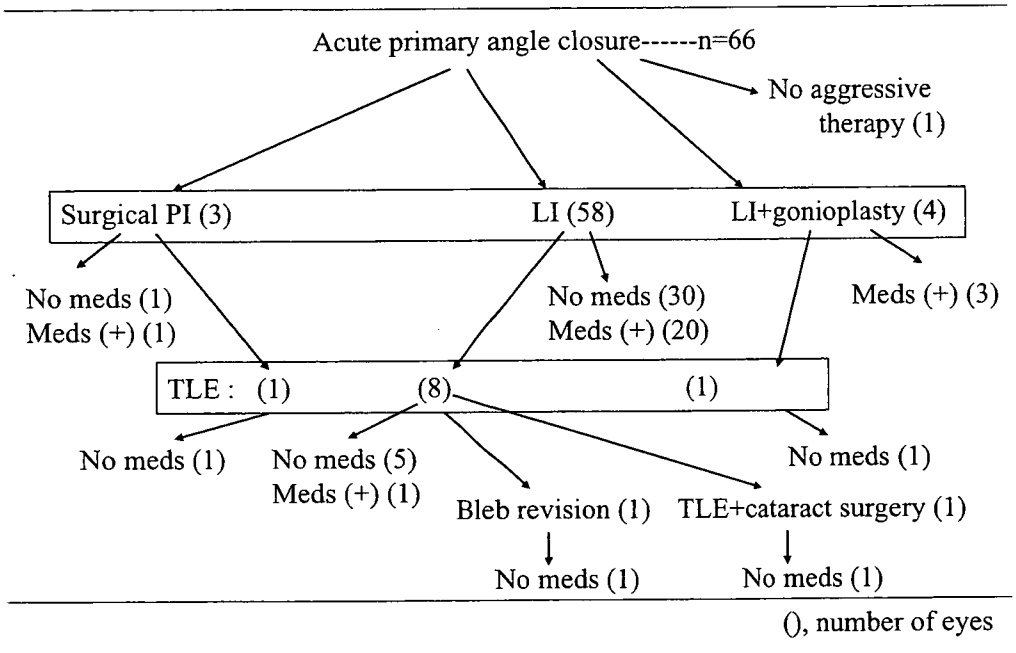

Figure 2. Flow chart of therapeutic outcome in eyes with acute primary angle closure. After laser intervention, no further medical or surgical treatment was needed in 31 eyes (31/65; 47.7%), and only topical treatment was required in 24 eyes (24/65; 36.9%). Ten eyes (10/65; 15.4%) were inevitably trabeculectomized due to inadequate control of intraocular pressure (IOP). Of these, one required additional combined trabeculectomy and cataract surgery, and one required bleb revision for IOP control. Number of eyes is shown in parentheses. *PI*, peripheral iridectomy; *LI*, laser iridotomy; *TLE*, trabeculectomy.

probability of success based on the same criterion was only 40.0 ± 29.7% (Figs. 2 and 3).

Differences in the extent of PAS and glaucoma type between the trabeculectomized and nontrabeculectomized eyes were statistically significant (Table 4). The Cox proportional hazards model revealed that the extent of PAS showed a significant hazard ratio with regard to the required trabeculectomy after LPI or surgical PI (hazard ratio: 1.366, $P = 0.029$; Table 5) and preexisting chronic glaucomatous optic neuropathy (hazard ratio: 6.474, $P = 0.015$; Table 5).

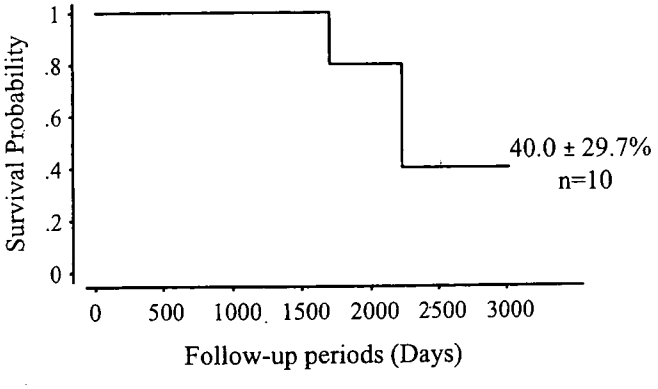

Figure 3. Kaplan-Meier curve showing the probability of success after trabeculectomy with mitomycin C. In the ten eyes trabeculectomized owing to uncontrolled IOP, the probability of success, defined as an IOP of <21 mmHg with or without medication, was only 40.0 ± 29.7%.

Discussion

The present findings demonstrated that, with the classical therapeutic modality, 84.8% of all APAC or APACG eyes could maintain good IOP control without a need for trabeculectomy, a finding apparently compatible with the reported results of the newly developed PPI procedure[4,5]

Table 5. Hazard ratios of potential risk factors for required filtering surgery after laser therapy

Risk factor	Hazard ratio	95% confidence interval	*P* value
Sex (male)	2.173	0.053–3.980	0.481
Age	1.018	0.932–1.112	0.695
IOP during the attack	1.007	0.925–1.096	0.878
Duration of symptoms	1.008	0.891–1.140	0.902
APAC/APACG (APACG)	6.474	0.035–0.691	0.015
Extent of PAS	1.366	1.033–1.806	0.029

Values are means ± SD (range).
IOP, intraocular pressure; PAS, peripheral anterior synechiae; APAC, acute primary angle closure; APACG, acute primary angle-closure glaucoma.

with respect to its IOP-reducing effect. We also found that the extent of PAS and preexisting chronic glaucomatous optic neuropathy were indicators of a risk of developing subsequent uncontrolled IOP after the elimination of the relative pupillary block.

Until recently, the nomenclature of primary angle closure was not uniform, and the literature contained little information about glaucomatous optic nerve damage in the many articles concerning primary angle closure. Recently, a new definition of angle closure has been proposed,[13,14] and is gradually being recognized worldwide. According to this definition, the term "glaucoma" is used only for cases with glaucomatous optic neuropathy and its corresponding visual field loss. In the present study, we retrospectively classified the eyes into two groups: those with APAC and those with APACG, on the basis of clinical records. However, in some cases we had difficulty determining whether a patient had preexisting glaucomatous optic nerve head or visual field abnormalities. The visual field following the acute attack usually shows a nonspecific change,[15,16] and often returns to normal after the attack ceases.[16] Additionally, hazy media or a swollen optic disc during the attack often leads to a misdiagnosis, especially when there are early glaucomatous optic disc changes such as localized optic nerve head excavation (notching) or slight generalized optic nerve head expansion.

In this series of Japanese subjects, we demonstrated that laser therapy alone could prevent a recurrent IOP rise in approximately 50% of APAC eyes. The remainder received further ocular hypotensive therapy to maintain an IOP of 21 mmHg or less, although a drainage procedure was required in 15.4% of eyes. Playfair and Watson[6] and Krupin et al.[7] reported that controlled IOP was achieved with surgical PI or LPI alone in 72% and 76% of eyes, respectively, and with antiglaucoma agents in 84% and 96% of eyes, respectively. In 137 APAC patients who underwent LPI or surgical PI as a primary treatment, Buckley et al.[17] showed that good IOP was maintained in 80 eyes (58.4%) that required no further medications, while 21 eyes (15.3%) ultimately required trabeculectomy. A recent study from the United Kingdom[18] found that no additional treatment after LPI was required in 44% of cases, and that further medical or surgical intervention was required in 21% and 35% of cases, respectively. On the other hand, Aung and associates[19] reported from Singapore that 58.1% of eyes with APAC developed an IOP rise after resolution of the acute attack, and that 32.7% eventually underwent filtering surgery because of poor IOP control. They suggested that the relatively high proportion of required trabeculectomy reflected racial differences in the outcome of LPI after APAC in Asian populations. The proportion of eyes requiring no further medical therapy after laser therapy was similar in our study, while the number requiring filtering surgery was much smaller in our study.

We speculate that the comparatively lower proportion of APAC eyes requiring trabeculectomy in the present study might reflect the use of a therapeutic approach including latanoprost and dorzolamide during the last decade in Japan. Indeed, two clinical trials have been reported regarding the efficacy of latanoprost in patients with chronic PACG.[20,21] Although the use of latanoprost may aggravate the inflammatory response in the anterior chamber,[22] it might be a therapeutic option for APAC, especially after complete cessation of an acute attack. In our consecutive series, of 24 eyes that had only further medication treatment following laser therapy or surgical PI, 13 eyes received latanoprost and/or dorzolamide.

Generally, APAC is recognized to be more severe in Asians than in Western populations,[23] possibly owing to the longer duration of symptoms,[24] the thickness and rigidity of the irides, or genetic and anatomic predisposition to angle closure.[24,25] In eyes with dark irides, so-called creeping angle closure is thought to be the most common type of angle closure.[26–28] Accordingly, the disease usually progresses asymptomatically, eventually resulting in circumferential permanent angle closure and persistent intraocular pressure elevation. However, in a previous biomicroscopy study of the fellow eyes of acute primary angle-closure patients in a Japanese series,[29] we showed that appositional angle closure beginning in the vicinity of Schwalbe's line is the exclusive predominant type rather than creeping angle closure. Multivariate analysis of the association of each factor with subsequent medically uncontrolled IOP after laser therapy identified the extent of organic angle closure and putative preexisting chronic glaucomatous optic neuropathy as potential risk factors. Therefore, one plausible

reason for the lower incidence of cases that ultimately required filtering surgery in the present study might be the comparatively low appositional angle closure starting at the bottom of the chamber angle in Japanese subjects.

It is well recognized that performing surgery on a congestive eye is far more hazardous than surgery on a quiet eye. In addition, there is a high risk of failure associated with any ocular surgery on inflamed eyes with increased IOP. Success in IOP control with or without ocular hypotensive agents after trabeculectomy was reported in 21 patients (65.6%) with medically failed APAC.[30] This result is consistent with the present findings, although fewer of our patients required filtering surgery. However, of the ten trabeculectomized eyes, two (20%) developed corneal decompensation several years postoperatively. Furthermore, unilateral cataract progression presumably due to the LPI or drainage procedure occurred in five cases, with one of these requiring cataract extraction. On the other hand, the recently introduced PPI procedure for APAC have been reported to result in some intraoperative or early postoperative complications, including iris prolapse, vitreous loss, and IOP elevation to >25 mmHg.[5] Additionally, in one study, of 43 APAC eyes that underwent PPI, five (11.5%) required subsequent surgical intervention to lower IOP.[5] In the present study, we showed that the degree of PAS and the putative preexistence of chronic glaucomatous optic neuropathy were significant indicators of poor IOP control. Therefore, it may be crucial for clinicians to differentiate, prior to surgical intervention, between eyes predisposed to recurrent IOP increase and those that are not.

Our present study has many limitations, including small sample size, a retrospective study design, and the variability of follow-up periods. The initial treatment was performed in a definitive manner; however, in several cases a beta-blocker and hyperosmotic agents had not been used because of the patient's systemic condition. The meaning of the term "maximum tolerable ocular hypotensive agents" has been changing yearly as new drugs have become available in Japan. Additionally, during follow-up after the cessation of acute attack, patients had received various topical ocular hypotensive medications. Moreover, although we conducted ultrasound biomicroscopy in cases of suspected plateau iris based on conventional gonioscopy, we did not use ultrasound biomicroscopy in all PAC cases. Regrettably, the follow-up period varied (range, 4–147 months) because of the tendency for APAC patients to be older and the retrospective nature of this study.

Nevertheless, with the classical treatment for APAC or APACG eyes in a Japanese population, 84.6% of eyes could maintain good IOP control with antiglaucoma drugs or no medications, and without the intervention of filtering surgery. Additionally, we showed that the outcome in these cases could be predicted on the basis of putative preexisting chronic glaucomatous optic neuropathy and the extent of permanent angle closure. A prospective large-scale intensive investigation is required to identify a treatment that will improve the prognosis and reduce post- and intraoperative complications in cases of acute APAC.

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A Pilot Study to Detect Glaucoma With Confocal Scanning Laser Ophthalmoscopy Compared With Nonmydriatic Stereoscopic Photography in a Community Health Screening

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Purpose: To assess the efficacy and practical usefulness of the Heidelberg Retina Tomograph II (HRT II) compared with nonmydriatic stereoscopic photography in a public glaucoma screening.

Methods: We examined 1173 local residents, aged 40 years or older, who visited a community health screening in Komatsu City. Initial glaucoma screening consisted of noncontact pneumotonometry, nonmydriatic stereoscopic fundus photography, and HRT II. When glaucoma was suspected, the subjects were referred for a definitive examination, in which slit-lamp biomicroscopic examination, Goldmann applanation tonometry, Humphrey 30-2 test, gonioscopy, and optic nerve head evaluation were performed.

Results: A total of 97.2% (2279/2345) of the nonmydriatic stereoscopic optic disc photographs could be interpreted and 93.4% (2189/2345) were good images. HRT II measurements were successful in 99.0% (2322/2345) of eyes, and acceptable images were obtained in 91.9% (2154/2345) of eyes. On the basis of clinical diagnoses, 94 eyes of 60 participants were diagnosed with glaucoma. The sensitivity of nonmydriatic stereoscopic photographs for personal-level analysis and eye-level analysis was 95.8% and 95.5%, respectively. Using Moorfield's regression analysis, HRT sensitivity and specificity were 72.3% to 91.5% and 84.0% to 93.1%, respectively, for personal-level analysis, and 60.3% to 72.6% and 89.7% to 95.6%, respectively, for eye-level analysis.

Conclusion: Although HRT II did not detect glaucoma as well as optic nerve stereophotographs in this Japanese population, it may play a role in community health screening.

Key Words: Heidelberg Retina Tomograph II, nonmydriatic stereoscopic photography, public glaucoma screening

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More than 50% of glaucoma patients remain undiagnosed in the United States[1] and Europe.[2] Recently, a Japanese population screening study[3] revealed that the prevalence of primary open-angle glaucoma (POAG) in the Japanese population older than 40 years was estimated to be 3.9%, of which 93.3% of POAG patients were previously undiagnosed. Therefore, a mass screening method for glaucoma is urgently needed. Three-dimensional evaluation of the optic disc by glaucoma specialists is thought to be the ideal method but subjective techniques are routinely used to evaluate the optic disc and retinal nerve fiber layer, and test results clearly depend on the examiner's experience. Consequently, it would be useful to introduce objective quantitative measurements. Recently, a number of new devices have been developed for this purpose,[4–7] including the Heidelberg Retina Tomograph II (HRT II; Heidelberg Instruments, Heidelberg, Germany), a confocal scanning laser ophthalmoscope that allows a rapid 3-dimensional topographic analysis of the optic disc and retina without pupillary dilatation.

The purpose of this study was to investigate the efficacy and practical usefulness of the HRT II compared with nonmydriatic stereoscopic photography in a public glaucoma screening.

SUBJECTS AND METHODS

Study Population

This study was approved by the Ethical Committee of Kanazawa University Graduate School of Medical Science. Subjects were recruited at an annual community health screening project in Komatsu City, Japan, conducted from June 2003 to July 2003. To be eligible to participate in the health checkup, a citizen must be older than 40 years and without an opportunity to receive a health checkup at an office. At the checkup, we posted a bill about glaucoma screening at the building entrance and arranged to use a venue nearby. Three thousand subjects participated in the community health checkup, of which 1173 subjects participated in the glaucoma screening. Written informed consent was obtained from all participants in the study.

Initial Screening Examination

The screening methods used in this study were implemented in 2 stages. After obtaining informed consent, an initial screening was performed, which included recording of personal data (sex, age, personal and family histories of glaucoma, systemic and local disease, and subjective ocular symptoms), autorefractometry, tonometry, digital nonmydriatic stereoscopic photography, and HRT II.

Intraocular pressure (IOP) was measured using noncontact pneumotonometry (NCT) (Canon, TX-F, Tokyo, Japan). Refractive status was measured using an autorefractometer (Nidek, ARK-730A, Gamagori, Japan). Nonsimultaneous 30-degree-field stereoscopic digital color images of optic nerve heads were obtained without pupillary dilatation using the IMAGEnet digital fundus camera system (Topcon, NSW6S, Tokyo, Japan). Two sequential photographs of each eye were taken with a lateral shift in camera position to obtain a stereo effect. All participants underwent imaging (scanning field, 15×15 degrees) with an HRT II. All images were obtained by 1 of 2 trained technicians. Magnification errors were corrected using patients' corneal curvature measurements. The contour line of the optic disc edge was drawn by consensus between 2 of the authors (S.O., H.T.) while viewing stereoscopic photographs of the optic disc.

Evaluation of Optic Nerve Head

The optic nerve was evaluated from nonsimultaneous stereoscopic digital photographs of the optic disc using a 3-dimensioanl Viewer System (Topcon, 3D Viewer and Stereo Viewer System, Tokyo, Japan), which consisted of electronic shutter glasses (StereoGraphics Corp, Crystal Eyes 3, San Rafael, CA), an emitter (StereoGraphics Corp, E-2), and a 19-inch flat screen monitor (Nanao, T766, Matto, Japan). The photographic quality was classified as "good quality," "poor quality," or "not available." Poor quality was when obtaining a stereo view failed or was poor, but still assessable. The subjects with poor quality stereoscopic photographs were referred for a definitive examination except those were judged to be obviously normal by monoscopic fundus photography.

HRT II Confocal Scanning Laser Ophthalmoscopy

For every participant, 3 topographic images were obtained, combined, and automatically aligned to generate one mean topographic image for analysis.. Moorfield's regression analysis (MRA),[5] incorporated in the HRT II software (version 1.6), was applied for this screening. The imaging quality of HRT II was classified as "acceptable (topographic standard deviation $\leq 50\,\mu m$)," "unacceptable (topographic standard deviation $> 50\,\mu m$)," or "not available."

Definitive Examination

A definitive examination was performed, masked to the initial screening results, when the subject was suspected to have glaucoma. The criteria for definitive examination eligibility are summarized in Table 1. When at least one finding suggested the presence of glaucoma, the subjects were recruited for definitive examination.

In the definitive examination, slit-lamp biomicroscopic examination, Goldmann applanation tonometry, visual field test with a Humphrey Field Analyzer II 30-2 SITA Standard program (Carl Zeiss Meditec Inc, Dublin, CA) and gonioscopy using a 4-mirror gonioscope (Menicon, PG-410, Nagoya, Japan) were performed. The pupil was dilated with 0.5% tropicamide and 0.5% phenylephrine hydrochloride and fundus examination was carried out with a slit-lamp and super field NC lens (Volk Optical Inc, Mentor, OH) or a 4-mirror gonioscope. Patients with occludable angles (20 subjects), or with driving responsibilities after the examination (3 subjects), were not dilated for this examination.

Evaluation of Visual Field

Two examiners evaluated the test results from the Humphrey Field Analyzer. We initially set the reliability criteria at fixation loss, $\leq 33\%$ and false-positive and false-negative, $\leq 20\%$. However, only 73.7% (370 eyes) of the visual field data collected in the definitive examinations (502 eyes of 251 subjects) passed these criteria, so we applied the criteria in accordance with a recent Japanese population study (fixation loss, $> 50\%$; false-positive and false-negative, $> 50\%$).[3] Fifty-seven eyes (11.4%) failed these criteria. The criteria for abnormal visual fields were based on a recent Japanese population study.[3] Briefly, abnormal visual field data were defined by the presence of at least one abnormal hemifield, which was determined by the criteria proposed by Anderson and Patella.[8] A hemifield was judged to be abnormal when the pattern deviation probability plot showed a cluster of 3 or more nonedge contiguous points, having sensitivity with a probability of less than 5% in the upper or lower hemifield, and in one of these, a probability of less than 1%.

Diagnosis of Glaucoma

A glaucoma specialist (K.S.) determined the final diagnosis on the basis of optic disc appearance, including

TABLE 1. The Criteria for Definitive Examination Eligibility

(1) IOP of 21 mm Hg or higher in either eye
(2) Any findings regarding the presence of abnormality including glaucomatous change [one or more of the following existed: the vertical cup/disc ratio of the optic nerve head was more than or equal to 0.6, the rim width at the superior portion (11-1 h), or inferior portion (5-7 h) was less than or equal to 0.2 of disc diameter, the difference in the vertical cup/disc ratio was more than or equal to 0.2 between both eyes, or a nerve fiber layer defect or splinter disc hemorrhage was found] as seen in stereoscopic fundus photographs
(3) A "borderline" or "outside normal limits" classification as detected by HRT II
(4) Failure to take stereoscopic fundus photographs or obtain HRT II images

nerve fiber layer defects, results of Humphrey Field Analyzer examinations, and clinical findings that were obtained through initial screening and definitive examinations. The criteria for glaucoma diagnosis were based on previous population studies.[3,9] Category 1 glaucoma was diagnosed when the vertical cup/disc ratio of the optic nerve head was more than or equal to 0.7, or the rim width at the superior portion (11 to 1 h) or inferior portion (5 to 7 h) was less than or equal to 0.1 of disc diameter, or the difference in vertical cup/disc ratio was more than or equal to 0.2 between both eyes, or a nerve fiber layer defect was found, and the hemifield-based visual field abnormality was compatible with optic disc appearance or nerve fiber layer defect. When the visual field test result was not reliable or available, category 2 glaucoma was diagnosed. This was where the vertical cup/disc ratio of the optic nerve head was more than or equal to 0.9, or the rim width at the superior portion (11 to 1 h) or inferior portion (5 to 7 h) was less than or equal to 0.05, or the difference in vertical cup/disc ratio was more than or equal to 0.3 between both eyes. Suspect glaucoma was diagnosed when the cup/disc ratio of the eye was 0.7 or more but less than 0.9, or the rim width at the superior portion (11 to 1 h) or inferior portion (5 to 7 h) was 0.1 or less but more than 0.05 of the disc diameter, or the difference in vertical cup/disc ratio was 0.2 or more but less than 0.3 between both eyes, or a nerve fiber layer defect was found, and the visual field test was not reliable or available or did not show a compatible hemifield-based defect. In definitive diagnosis, anomalous discs, including tilted discs and superior segmental optic hypoplasia, were carefully excluded. The glaucoma status of each person was classified on the basis of the more affected eye.

Main Outcome Measures

To evaluate the practical usefulness of HRT II and nonmydriatic stereoscopic photography for mass screening, the imaging status of each instrument for each diagnostic category and by age were calculated. The grouping was performed for the HRT II examination results based on the MRA. "Borderline" outcomes were treated as test positive (only normal was test negative, MRA 1) and borderline outcomes were treated as test negative (normal, borderline results were considered test negative, MRA 2). After these groupings, sensitivities, specificities, positive predictive value and negative predictive value for participants (person-level analysis) and for individual eyes (eye-level analysis), were calculated between the MRA diagnosis of HRT II and clinical diagnosis gold standards. Sensitivities of stereoscopic photographs for participants and for individual eyes were also calculated. Data from unacceptable topographic images, unacceptable photographs, and subjects who did not undergo definitive examinations were excluded from this data analysis.

Data Analysis

The privacy of personal medical information was protected at the data analysis center of Kanazawa University Graduate School of Medical Science. Statistical analysis was performed using StatMate III software (ATMS, Tokyo, Japan). Differences between groups were evaluated using Student t test. The χ^2 test was used to compare proportions.

RESULTS

The average age of all participants (435 male, 738 female) was 61.6 ± 10.5 years (mean ± standard deviation). Of the 1173 subjects (2345 eyes) examined in the initial screening, 296 (25.2%) were referred for definitive examination, but 45 declined or were unable to participate. As a result, 251 subjects (84.8%) underwent definitive examination. On the basis of the clinical diagnosis, 94 eyes of 60 participants were diagnosed with definite glaucoma and 41 eyes of 29 participants were diagnosed with suspect glaucoma. After the definitive examination, diagnoses of 6 subjects were changed. One subject diagnosed with glaucoma was changed to superior segmental optic hypoplasia and 1 subject diagnosed with glaucoma was converted to suspect glaucoma. In addition, 4 subjects with suspect glaucoma were subsequently diagnosed as normal.

The rate of previously undiagnosed glaucoma was 90.0% (54/60). The number of POAG subjects was 58. Of these, 55 subjects were diagnosed with category 1 criteria, and 3 were diagnosed with category 2 criteria. Of the 58 POAG subjects, 50 (86.2%) had an IOP of 21 mm Hg or less without medication (both in initial screening and definitive examination in both eyes) and 8 had an IOP of more than 21 mm Hg. No subjects were found to have primary angle-closure glaucoma. There were 2 secondary glaucoma subjects who were diagnosed with category 1 and exfoliation glaucoma. The average age of all

TABLE 2. Prevalence Rate of Definitive Glaucoma in the Screened Population

	Glaucoma (%; 95% Confidence Interval)		
Age Groups (y)	Male	Female	All
40-49	0/46 (0%, 0-0)	3/113 (2.7%, −0.3-5.7)	3/159 (1.9%, −0.2-4.0)
50-59	2/91 (2.2%, −0.8-5.2)	5/201 (2.5%, 0.3-4.7)	7/292 (2.4%, 0.6-4.2)
60-69	8/174 (4.6%, 1.5-7.7)	10/236 (4.2%, 1.6-6.8)	18/410 (4.4%, 2.4-6.4)
70 and older	13/103 (12.6%, 6.2-19.0)	19/164 (11.6%, 6.7-16.5)	32/267 (12.0%, 8.1-15.9)
All subjects	23/414 (5.6%, 3.4-7.8)	37/714 (5.2%, 3.6-6.8)	60/1128 (5.3%, 4.0-6.6)

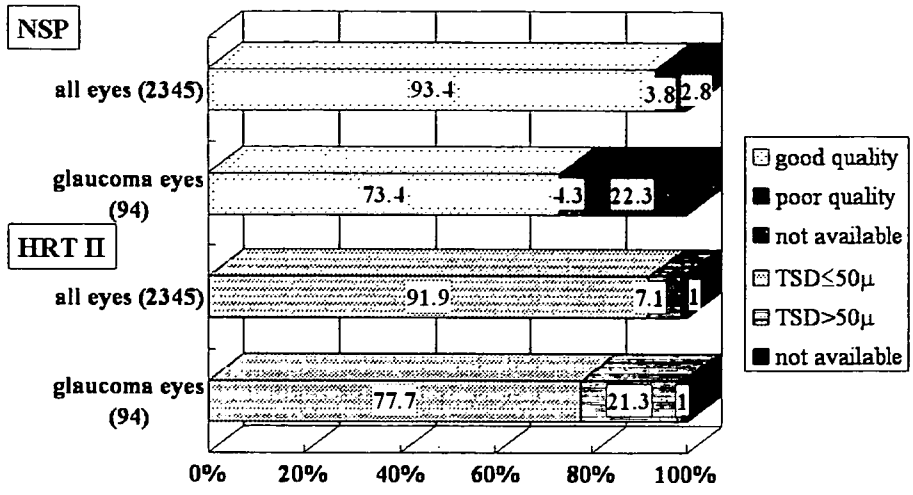

FIGURE 1. Comparison of images acquired by nonmydriatic stereoscopic photography and HRT II for diagnosis. NSP indicates nonmydriatic stereoscopic photography; TSD, topographic standard deviation.

glaucoma patients was 69.1 ± 10.2 years (mean ± standard deviation). For the 45 subjects who did not undergo definitive examination, diagnosis was based on the initial screening and 10 subjects met the criteria of category 2. However, these 45 subjects were excluded from the data analysis. Table 2 shows the age-specific prevalence of glaucoma in this screened population. The estimated prevalence of POAG and exfoliation glaucoma was 5.1% (58/1128) (95% confidence interval, 3.8%-6.4%) and 0.2% (2/1128) (95% confidence interval, −0.1%-0.5%), respectively.

The imaging status of each instrument for each diagnostic category and by age is shown in Figure 1 and Table 3, respectively. The distribution of the quality of HRT II images obtained is shown in Figure 2. Figure 3 is a Venn diagram that summarizes the number of eyes that could not be interpreted by stereoscopic photography, those eyes that could not be scanned by HRT II, and both. Of the 66 eyes that could not be interpreted by stereoscopic optic disc photography, glaucoma was diagnosed in 21 eyes (31.8%). In the 23 eyes that could not be scanned by HRT II, glaucoma was diagnosed in 1 eye (4.3%). Figure 4 is a Venn diagram to show which eyes had poor quality stereoscopic photography, or unacceptable quality (above 50 μm) HRT II, and both.

We reviewed the methods for detecting definitive glaucoma. When subjects with not available HRT II scans and not available stereoscopic photographs were considered along with subjects defined as test positive, glaucoma was detected in 58 subjects (58/60, 96.7%) by nonmydriatic stereoscopic photography, in 52 subjects (52/60, 86.7%) by HRT II imaging and in 2 subjects (2/60, 3.3%) by elevated IOPs. When the subjects with not available HRT II scans and not available nonsimultaneous stereoscopic photographs were excluded, glaucoma was detected in 46 subjects (46/48, 95.8%) by nonmydriatic stereoscopic photography and in 52 subjects (52/60, 86.7%) by HRT II imaging. When the subjects with poor quality nonsimultaneous stereoscopic photographs and unacceptable HRT II scans were excluded, glaucoma was detected in 46 subjects (46/48, 95.8%) by nonmydriatic stereoscopic photography and in 43 subjects (43/47, 91.5%) by HRT II imaging.

The sensitivity, specificity, positive predictive value, and negative predictive value of HRT II are shown in Table 4. The sensitivity of nonmydriatic stereoscopic photography for personal-level analysis was 95.8% and that for eye-level analysis was 95.5%. Although the sensitivity for eye-level analysis of nonmydriatic stereoscopic fundus photography was significantly higher than that of HRT II (both MRA 1 and MRA 2, $P < 0.001$), the sensitivity for personal-level analysis was not significantly higher than that of HRT II when borderline outcomes were treated as test positive ($P = 0.654$).

TABLE 3. The Image Status of Each Instrument by Age

	NSP			HRT II		
Age Groups (y)	Good Image Eyes	Poor Image Eyes	Not Available Eyes	TSD ≤ 50 μm	TSD ≥ 50 μm	Not Available Eyes
40-49	321 (99.7%)	0 (0%)	1 (0.3%)	310 (96.3%)	11 (3.4%)	1 (0.3%)
50-59	577 (95.2%)	20 (3.3%)	9 (1.5%)	585 (96.5%)	16 (2.7%)	5 (0.8%)
60-69	785 (92.4%)	46 (5.4%)	19 (2.2%)	785 (92.4%)	62 (7.2%)	3 (0.4%)
70 and older	506 (89.3%)	24 (4.2%)	37 (6.5%)	474 (83.6%)	79 (13.9%)	14 (2.5%)
All subjects	2189 (93.4%)	903 (3.8%)	66 (2.8%)	2154 (91.9%)	168 (7.2%)	23 (0.9%)

NSP indicates nonmydriatic stereoscopic photography; TSD, topographic standard deviation.

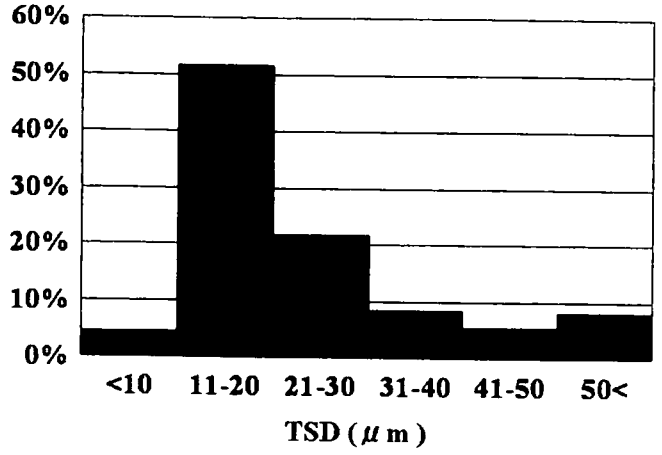

FIGURE 2. Distribution of topographic standard deviation (TSD) of HRT II in both eyes of all the subjects who participated.

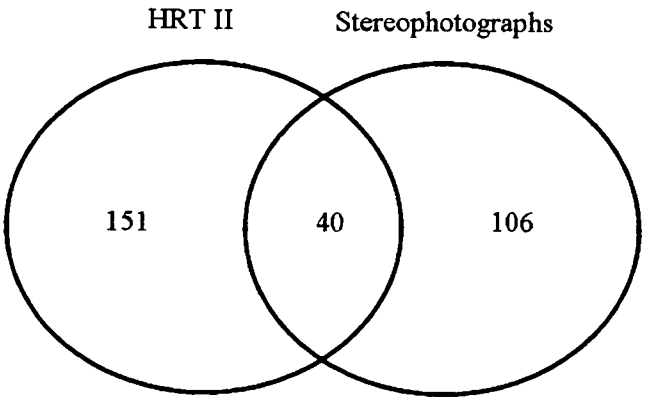

FIGURE 4. Venn diagram showing the number of eyes which had poor quality stereoscopic photography, or unacceptable quality (above 50 μm) HRT II, or both.

DISCUSSION

The fact that most glaucoma is undiagnosed[1–3] may partly be attributed to the lack of an ideal screening method. A mass glaucoma screening method that is safe, specific, sensitive, and acceptable to participants is needed. Recently, frequency-doubling technology (FDT) perimetry was shown to be an effective method for glaucoma screening,[10,11] but evaluating the optic disc or nerve fiber layer directly may be a preferable method to eliminate variability due to subjective judgment. Several novel digital imaging technologies[4–7] have been developed for the structural investigation of the optic nerve head. Scanning laser tomography, optical coherence tomography, and scanning laser polarimetry discriminated between glaucomatous and normal eyes with clinically useful sensitivities and specificities in hospital-based studies.[4–7] In addition, Harasymowycz et al[12] reported that HRT II using MRA or cup shape measurements may be a valid screening tool to detect clinically diagnosed glaucomatous optic nerve damage in high-risk populations. It was reported that the measurement of optic disc parameters on stereoscopic fundus photographs was limited by difficulties in obtaining high-quality photographs on all subjects, even if the pupils are dilated.[13] Recently, the digital nonmydriatic fundus camera was improved, and Detry-Morel et al[14] reported that a total of 98.1% of optic disc photographs taken by the nonmydriatic fundus camera could be interpreted and therefore could be a useful and quick method to screen for glaucomatous damage in a community. Furthermore, recent improvement in the digital nonmydriatic fundus camera enables stereophotographs of the optic disc to be taken without pupillary dilatation. In the present study, we evaluated the efficacy of HRT II scanning using MRA compared with nonmydriatic stereoscopic fundus photography in a population-based glaucoma screening.

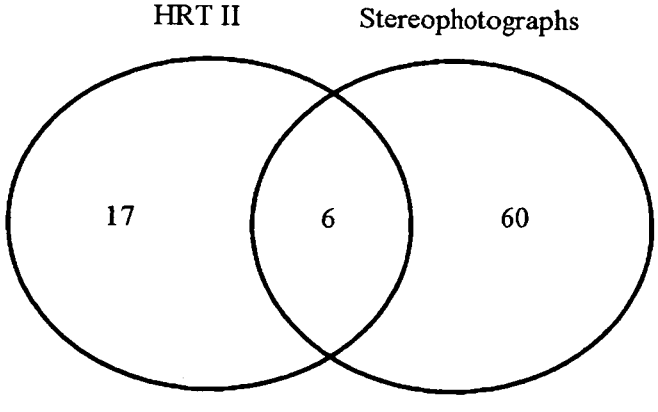

FIGURE 3. Venn diagram showing the number of eyes which could not be interpreted by stereoscopic photography, or which could not be scanned by HRT II, or both.

Nonmydriatic stereoscopic photographs and HRT II scans were successfully obtained in the large majority of eyes (97.2% and 99.0%, respectively). Good quality photographs (enabling good stereopsis) were obtained in 93.4% of eyes by a nonmydriatic stereoscopic camera. Acceptable images (topographic standard deviation no greater than 50 μm) were obtained in 91.9% of eyes by HRT II. These results were equal to HRT II in a population-based glaucoma screening for high-risk population (acceptable quality, 88%).[12] Therefore, both instruments were deemed acceptable for mass glaucoma screening.

HRT sensitivity and specificity were 72.6% and 89.7%, respectively, when borderline outcomes were treated as test positives (MRA 1) and 60.3% and 95.6%, respectively, when borderline outcomes were treated as test negatives (MRA 2) for eye-level analysis. These results were similar to those reported by Ford et al,[15] although the MRA of HRT II was based on the data from white subjects while our study population was Japanese. As Vitale et al[16] showed previously, at the

TABLE 4. Agreement Between HRT II-MRA and Clinical Diagnosis

	Sensitivity (95% Confidence Interval)	Specificity (95% Confidence Interval)	Positive Predictive Value (95% Confidence Interval)	Negative Predictive Value (95% Confidence Interval)
Person-level analysis (n = 977)				
MRA 1	43/47 (91.5%, 84.6-88.8)	781/930 (84.0%, 77.2-82.2)	43/192 (22.4%, 19.8-25.0)	781/785 (99.5%, 99.1-99.9)
MRA 2	34/47 (72.3%, 63.8-69.6)	866/930 (93.1%, 88.1-91.9)	34/98 (34.7%, 31.7-37.7)	866/879 (98.5%, 97.8-99.2)
Eye-level analysis (Right eye and left eye, n = 2053)				
MRA 1	53/73 (72.6%, 70.7-74.5)	1777/1980 (89.7%, 88.4-91.0)	53/256 (20.7%, 18.9-22.5)	1777/1980 (98.9%, 98.4-99.4)
MRA 2	44/73 (60.3%, 58.2-62.4)	1896/1980 (95.6%, 94.7-96.5)	44/128 (34.4%, 32.3-36.5)	1896/1980 (98.5%, 98.0-99.0)
Right eye (n = 1029)				
MRA 1	25/36 (69.4%, 66.6-72.2)	900/993 (90.6%, 88.4-92.4)	25/118 (21.2%, 18.7-23.7)	900/911 (98.8%, 98.1-99.5)
MRA 2	20/36 (55.6%, 52.6-58.6)	955/993 (96.2%, 95.0-97.4)	20/58 (34.5%, 31.6-37.4)	955/971 (98.4%, 97.6-99.2)
Left eye (n = 1024)				
MRA 1	28/37 (75.7%, 73.1-78.3)	877/987 (88.9%, 88.4-91.0)	28/138 (20.3%, 17.7-22.9)	877/886 (99.0%, 98.4-99.6)
MRA 2	24/37 (64.9%, 62.0-67.8)	941/987 (95.3%, 94.7-96.5)	24/70 (34.3%, 31.4-37.2)	941/954 (98.6%, 97.9-99.3)

MRA 1: "borderline" outcomes were treated as test positive; MRA 2: "borderline" outcomes were treated as test negative.

personal-level sensitivity increased and specificity decreased, relative to eye-level analysis. Indeed, in this study, HRT sensitivity increased without much impact on specificity when borderline outcomes were treated as test positives (MRA 1) at personal-level analysis. Although HRT was not sensitive enough for eye-level analysis, HRT might be useful for glaucoma screening for personal-level analysis.

Although the ratio of a good image obtained with nonmydriatic stereoscopy was 93.4% that was obtained for glaucoma was only 73.4%. By the same token, definite glaucoma was detected in 31.8% (21/66) of eyes in which stereoscopic photographs could not be interpreted. In other words, those eyes in which stereoscopic photographs could not be interpreted seemed to be a high-risk group for glaucoma. Conversely, of the 23 eyes for which HRT II imaging data could not be obtained, definite glaucoma was diagnosed in only one eye (4.3%). In addition, of the 199 eyes for which acceptable images could not be obtained, definite glaucoma was diagnosed in 21 eyes (21/199, 10.6%). Therefore, detection number by HRT II (52/60) exceeded the detection number by stereoscopic photography (46/48) as long as interpretable photographs or images were obtained.

Most subjects with POAG (92.3%) had an IOP below 21 mm Hg in the Tajimi study.[3] In our study, 86.2% (50/58) of all patients with POAG had an IOP below 21 mm Hg and a single measurement of IOP detected only 3.3% of all glaucoma. A recent Japanese population study[3] reported the mean IOP of a Japanese population to be 14.6 ± 2.7 mm Hg (standard deviation) in the right eye and 14.5 ± 2.7 mm Hg in the left eye. Therefore, our cut-off IOP value in this study might be not appropriate. If the cut-off IOP value was 17 or 19 mm Hg, the glaucoma detection rate using IOP was 18.3% (11/60) or 11.6% (7/60), respectively. Thus, our results are consistent with the conclusion of past reports that measurement of IOP alone is a poor tool to detect glaucoma.[14,17,18]

The estimated prevalence of POAG (5.1%) in this study appeared to be higher than that of a recent Japanese population-based glaucoma survey (3.9%).[3] This difference could be partly because our study population may have been biased by the use of volunteers, probable overrepresentation of subjects interested in glaucoma, and the older age of our subjects [61.6 ± 10.5 y (mean ± standard deviation)] compared with the participants in the Japanese survey [58.4 ± 11.8 y (mean ± standard deviation)].[3] Since the efficiency of screening methods was the main interest of our study, rather than estimation of the prevalence of glaucoma, a random sample of eligible participants was not requested.

In this study, there were several limitations owing to the population-based and large-scale study. First, we did not perform definitive examinations of participants whose eyes appeared normal in the initial screening examinations. Subjects with glaucoma may therefore have been overlooked. In a recent Japanese population study,[3] 4 out of 119 glaucoma patients were detected by FDT alone, suggesting that 3.4% (4/119) of glaucoma patients were overlooked by monoscopic fundus photography. In this study, we evaluated stereoscopic fundus photographs of optic discs to estimate vertical cup-to-disc ratio, which is reported to be more reliable than monoscopic evaluation.[19] However, we still cannot deny the possibility that we too overlooked a few glaucoma patients. Moreover, it is likely that obtaining a pair of images that enable a stereo view would fail, particularly in more elderly subjects.[13] In fact, in this study a total of 6.6% of the photographs did not enable a good stereo view, 10.7% of which were from subjects aged 70 years or older. Of 126 subjects where good quality photographs in at least one eye could not obtained, 71 subjects were judged to be normal by monoscopic fundus photography. The remaining 55 subjects were referred for a definitive examination and 14 were diagnosed as definite glaucoma. Therefore, it is unlikely that we overlooked considerable number of glaucoma.

Second, we could not perform definitive examinations on all subjects recruited for definitive examinations. However, there was no significant difference between the average age of subjects who had definitive examinations [61.4 ± 10.4 y (mean ± standard deviation)] and those who did not [66.1 ± 11.1 y (mean ± standard deviation)] ($P = 0.083$, Student t test). Also, the proportion of glaucoma patients in the group undergoing a definitive examination (23.9%, 60/251) was similar to that of the group that failed to attend the definitive examination (22.2%, 10/45) ($P = 0.807$, χ^2 test), in whom glaucoma was identified in the initial screening. Therefore, we think that this second limitation did not greatly influence the efficiency of HRT II in this screening.

Third, we performed visual field tests once and almost all the subjects were inexperienced in these tests. It was reported in an Ocular Hypertension Treatment Study[20] that most visual field abnormalities were not verifiedon retest so the reliability of the visual field test is limited. However, in definitive examinations we determined the final glaucoma diagnosis not only on visual field tests but also on disc appearance judged by a glaucoma specialist. Of the subjects classified as category 1, all fulfilled the rather conservative criteria of at least one abnormal hemifield and a compatible optic disc appearance, a nerve fiber layer defect, or both. Glaucoma subjects in category 2 may also include some preperimetric or suspected glaucoma patients even though more strict diagnostic criteria were applied to optic disc appearance.

This study showed that the use of nonmydriatic stereoscopic fundus photography and HRT II is a suitable approach for an initial glaucoma mass screening because images of both eyes can be rapidly acquired without the need for pupillary dilatation. This screening could conceivably be performed in the absence of a trained ophthalmologist and without pupillary dilatation. The evaluation of stereophotographs is subjective and test results clearly depend on the examiner's experience. In addition, good photographs were harder to obtain on glaucoma eyes than normal eyes, results that are similar to a Baltimore Eye Survey.[13] Compared with optic disc stereophotographs, HRT II provided objective and quantitative data and measurements were successful in almost all glaucomatous eyes. In this study, we defined regions of interest (ROIs) by drawing contour lines on stereoscopic photographs. However, if HRT II were to be used as a screening instrument, then disc photos would not be available. Watkins and Broadway[21] reported no difference in the defined ROI when 2 experienced observers defined ROIs from stereoscopic or nonstereoscopic optic disc photographs, or without any photographic guide. Therefore, contour lines may be drawn with or without a photographic aid, and the results are unaffected. However, in this study, we used stereoscopic optic disc photographs to draw contour lines to reduce dependency on operator's skill.

In this study, costs associated with recruiting eligible subjects or management of contact information were negligible because this study was performed as part of a community health screening project. Personnel costs were $8765 whereas direct costs were almost $2600. Since we detected 54 new definite glaucoma patients, the estimated cost of the initial screening per new case was approximately $210. However, this does not include medical equipment.

Although HRT II did not detect glaucoma as well as optic nerve stereophotographs in this Japanese population, it may play a role in community health screening. Furthermore, HRT II retains the potential to increase the detection rate of glaucoma in conjunction with other diagnostic techniques such as FDT.

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In Vivo Imaging and Quantitative Evaluation of the Rat Retinal Nerve Fiber Layer Using Scanning Laser Ophthalmoscopy

Ichiro Kawaguchi, Tomomi Higashide, Shinji Ohkubo, Hisashi Takeda, and Kazuhisa Sugiyama

Purpose. To determine whether scanning laser ophthalmoscopy (SLO) is useful for in vivo imaging and quantitative evaluation of rat retinal nerve fiber layer (RNFL) using an optic nerve crush model.

Methods. The optic nerve of the right eye was crushed intraorbitally with a clip. The left eye served as the untreated control. Fundus images of both eyes were recorded by SLO using an argon blue laser before and 1, 2, and 4 weeks after optic nerve crush. The focused plane was sequentially moved by changing the refractive values in the SLO setting. The range of refractive values (ΔF) in which the RNFL reflex was clearly observed was determined. The RNFL thickness in retinal sections was measured and compared to the ΔF value from SLO images taken before histologic preparation.

Results. Striations of RNFL radiating from the optic disc were clearly visible by SLO. No obvious changes in the RNFL reflex were observed 1 week after optic nerve crush. However, striations of RNFL became uniformly darker and thinner 2 weeks after the crush and were barely visible 4 weeks after the crush. The ΔF value was unchanged 1 week after the crush, but then decreased significantly and progressively after the second week. ΔF was unchanged in the control eyes during the experimental period. The ΔF value correlated significantly with the histologically determined RNFL thickness.

Conclusions. SLO is a useful and valuable tool for in vivo imaging and quantitative evaluation of rat RNFL. (*Invest Ophthalmol Vis Sci.* 2006;47:2911-2916) DOI:10.1167/iovs.05-1169

Retinal nerve fiber layer (RNFL) defects are one of the most critical factors to assess in the evaluation of the degree and distribution of retinal ganglion cell loss in patients with glaucoma. In routine fundus examinations, red-free or green light rather than white light is suitable for visualization of RNFL, because of the optical properties of RNFL.[1] A scanning laser ophthalmoscope (SLO; Rodenstock Instruments, Munich, Germany) provides argon blue laser illumination and confocal apertures which are ideal for RNFL observation as the wavelength of the laser is optimal for RNFL visualization, and a small confocal aperture allows high-contrast imaging by reducing the scattered light arising from defocused tissues.[2] Accordingly, highly reproducible RNFL evaluation can be performed by SLO.[2] However, there are no detailed reports on RNFL in rat eyes visualized with an SLO, although in one study an SLO was used for imaging the rat fundus and assessing retinal circulation.[3]

Ocular hypertension, ischemia-reperfusion, and optic nerve crush rodent models have been used to elucidate the pathophysiology of glaucoma and other optic neuropathies.[4] In these models, loss of retinal ganglion cells has usually been evaluated histologically by counting the number of cell bodies in the retina or their axons in the optic nerve.[5-8] For intraretinal axons of retinal ganglion cells, qualitative assessment of the effect of axotomy has been performed by staining the axons in the flatmount retina.[6,9] However, there have been no reports of in vivo evaluation of RNFL changes in rodent models of optic nerve injury.

In this study, we determined whether the SLO is useful for in vivo imaging and quantitative evaluation of the rat RNFL using the optic nerve crush model.

Methods

Animals

Male Brown Norway rats, 12 weeks of age and weighing 200 to 250 g, were used in this study. The rats had free access to food and water and were maintained in cages in an environmentally controlled room with a 12-hour light-dark cycle. All experiments were conducted on rats anesthetized by an intraperitoneal injection (65 mg/kg) of sodium pentobarbital (Somnopentil; Schering-Plough Animal Health, Omaha, NE). All animals were treated in accordance with the ARVO statement for the Use of Animal in Ophthalmic and Vision Research.

Optic Nerve Crush Model

The conjunctiva of the right eye was incised in the supratemporal quadrant to expose the optic nerve by careful blunt dissection under an operating microscope. The optic nerve was crushed 2 mm behind the globe for 30 seconds with a 60-g vascular clip (Micro Vascular Clip; Roboz Surgical Instrument Co., Gaithersburg, MD). Special care was taken not to damage the blood supply to the eye traveling along the inferior side of the optic nerve.[10] Immediate recovery of retinal blood supply after removal of the clip was observed by indirect ophthalmoscopy in each eye. The left eye served as the untreated control.

In Vivo Imaging of RNFL over Time Using SLO

Before and 1, 2, and 4 weeks after optic nerve crush, the retinal images of both eyes were recorded by SLO (SLO 101; Rodenstock Instruments) with argon blue laser illumination (wavelength: 488 nm, output: 190-210 μW) in 21 rats. The eyes were dilated with 0.5% tropicamide and 0.5% phenylephrine hydrochloride eye drops (Santen Pharmaceuticals, Osaka, Japan). To preserve corneal clarity throughout the experiment, a custom-made contact lens with a radius of curvature

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