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Correlation of Blue Chromatic Macular Sensitivity with Optic Disc Change in Early Glaucoma Patients

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Purpose: To investigate the relationship between morphological changes of the optic nerve head (ONH) and macular sensitivity determined with blue on yellow (B on Y) and white on white (W on W) perimetry in normal subjects and patients with glaucoma.

Methods: One randomly chosen eye was evaluated in each of 28 healthy subjects, 23 patients with ocular hypertension (OH), and 23 patients with early primary open-angle glaucoma (POAG). The mean macular sensitivity determined with B on Y and W on W perimetry was obtained by a macular program using a modified Humphrey field analyzer. The Heidelberg retina tomograph with software version 2.01 was used to evaluate the temporal topographic measurements of ONH.

Results: There was no significant difference in temporal ONH parameters among the three clinical groups. The mean macular sensitivity of B on Y and W on W perimetry in early POAG patients was significantly lower than that in healthy subjects and in patients with OH. The mean macular sensitivity of W on W perimetry showed no significant correlation with temporal ONH parameters in any clinical groups. In patients with early POAG, the mean macular sensitivity of B on Y perimetry was significantly related to cup area and volume, cup/disc area ratio, and rim volume in the temporal sector of the ONH.

Conclusion: The measurement of the mean macular sensitivity of B on Y perimetry might make it possible to detect functional damage prior to morphological changes in the ONH due to elevated intraocular pressure in glaucoma. **Jpn J Ophthalmol 2002;46:89–94**

Key Words: Blue on yellow perimetry, Heidelberg retina tomograph, Humphrey field analyzer, macular sensitivity, optic nerve head.

Introduction

Many authors have described blue-yellow or blue-green color vision deficiencies in patients with ocular hypertension (OH) and glaucoma. Lakowski et al found that a significant number of suspected glaucoma patients showed poorer color sensitivity than healthy persons of the same age, particularly in the blue-yellow or blue-green spectrum measured at the fovea.[1,2] According to the introduction of the selective chromatic adaptation technique, when using yellow background, an approximate isolation of the blue chromatic mechanism is obtained.[3] Yamazaki et al have reported that blue chromatic sensitivity was strongly related to highest intraocular pressure (IOP),[4] and that patients with primary open-angle glaucoma (POAG) showed significant losses in blue chromatic sensitivity when compared with normal tension glaucoma patients matched for similar visual field defects.[5] This phenomenon indicated that the dysfunction of the blue chromatic pathway might be caused by elevated IOP.

It has been demonstrated recently that larger diameter optic nerve fibers are more vulnerable to elevated IOP than smaller fibers,[6] and that there is a high prevalence of large diameter fibers present dominantly in the magnocellular (M cell) pathways and the subtype of the parvocellular (P cell) pathways.[6] The subpopulation of larger diameter P cells handle inputs from short-wavelength sensitive cones and have cell bodies approximately 50% larger than those handling middle- and long-wavelength cone in-

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puts.[7] These results are consistent with the view that the dysfunction of the blue chromatic pathway is vulnerable to elevated IOP.

Recently, short-wavelength automated perimetry or blue on yellow (B on Y) perimetry has been developed by the use of a modified Humphrey Field Analyzer (HFA; Carl Zeiss, San Leandro, CA, USA).[8,9] B on Y perimetry is thought to be more effective in detecting visual field defects earlier than conventional white on white (W on W) perimetry.

Changes in the optic nerve head (ONH) are widely recognized as important and definite signs of glaucoma. The introduction of computerized instruments such as the Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany) has made it possible to obtain rapid and reproducible three-dimensional analysis of the ONH structure by the quantitative serial point-by-point comparison of the surface contour, and it has been reported that sector-based ONH shape measurement with HRT was closely correlated with differential light sensitivity anatomically matched to the visual field.[10] We had earlier reported a significant correlation between the global cup/disc area ratio of the ONH and the macular blue chromatic sensitivity in patients with POAG.[11] It is not yet certain whether losses in macular blue chromatic sensitivity take place prior to the morphological changes of the ONH in glaucoma.

The purpose of this study was to determine how the results of B on Y macular sensitivity correlate with temporal ONH parameters obtained with HRT and to compare the strength of the association of the ONH morphological values with the macular sensitivity of B on Y and W on W in normal subjects, patients with OH, and those with early POAG.

Materials and Methods

Seventy-four participants were enrolled consecutively for this study. Patients with OH and early POAG were recruited from the outpatient clinic of the Department of Ophthalmology of Nihon University School of Medicine. Healthy subjects were volunteers and employees of the Nihon University School of Medicine. All participants underwent a full ophthalmic examination, including an automated visual field (HFA program 30-2) and optic-disc analysis with a confocal scanning laser ophthalmoscope (HRT).

Only 1 eye of each subject was randomly chosen. The selective criteria were as follows: a corrected visual acuity of 20/20 or better, spherical refraction within ± 6.0 diopters, cylindrical error within ± 2.5 diopters, no evidence of media opacity, no history of intraocular surgery or ocular/systemic disease potentially associated with optic neuropathy, and age less than 70 years.

A glaucomatous visual field was defined as an HFA program 30-2 visual field with (a) 3 adjacent test points having a deviation ≥ 5 dB lower than the age-matched controls, with 1 point >10 dB lower; or (b) at least 2 adjacent points >10 dB lower; or (c) at least 2 adjacent points ≥ 5 dB across the nasal horizontal meridian.[12]

Both W on W and B on Y perimetry were carried out using the macular program of the HFA. The method of B on Y perimetry has been described in detail elsewhere.[13] Each of the participants underwent two separate perimetric sessions. The first examination was a training session involving standard W on W perimetry (achromatic stimulus : Goldmann size III, achromatic background luminance: 10 cd/m^2), and B on Y perimetry (blue stimulus : Goldmann size V, yellow background luminance : 100 cd/m^2). The same protocol was used at the second visit. Appropriate refractive error correction was used for the viewing distance of the perimetric bowl. The results of the first visit were discarded, and those of the second examination with no fixation loss, false positive, or false negative were used for the evaluation in this study.

Three-dimensional topographic analysis of the ONH was carried out using the HRT. In this study, three images, $10° \times 10°$, and the mean topographic image were created using software version 2.01 of the HRT. Mean topographic images with measured standard deviation <30 μm were used in the study. The contour line of the optic disc margin, at the inner edge of the scleral ring (Elschnig's ring), was manually traced on the HRT screen by a trained observer using a computer mouse, while simultaneously viewing the stereoscopic ONH photograph. The outline was verified by one of the authors (Y.Y.) The reference plane was automatically determined at 50 μm below the mean peripapillary vertical height along the temporal sector between 350° and 356°, based on the tilted disc system. The operating software provided by the HRT calculates a number of predefined topographic parameters. In this study, the ONH parameters used were rim area and volume, cup area and volume, cup/disc area ratio, mean and maximum cup depth, mean retinal nerve fiber layer (RNFL) thickness, and RNFL cross-section area. The system calculated for each parameter in the temporal sector ($330° - 30°$) involved the pap-

illo-macular bundle, anatomically matched for the macular region.[14]

The participants were divided into the following groups: healthy, OH, and early POAG patients. Criteria in each group were based on clinical findings, disc appearance, visual field, and IOP. Patients with early POAG were defined as having IOP >21 mm Hg on three or more occasions, glaucomatous visual field defect and/or an abnormal disc and/or RNFL on stereoscopic slit-lamp biomicroscopy, an open angle on gonioscopy, and no clinically apparent secondary cause for their glaucoma. Participants with early POAG who had a mean deviation of more than −5 dB obtained with STATPAC 2 (Carl Zeiss) built-in HFA program 30-2 in spite of a value of corrected pattern standard deviation were accepted into this study. Patients with OH were defined as having IOP >21 mm Hg measured on at least three separate occasions, a normal visual field, and a normal optic disc and RNFL on routine stereoscopic slit-lamp biomicroscopy. Healthy subjects were defined as having IOP <21 mm Hg measured on at least three separate occasions, a normal visual field, a normal optic disc and RNFL, and no gross myopic features.

Macular sensitivity of W on W and B on Y perimetry was measured with the macular program of HFA. The mean macular sensitivity was manually calculated using the value of thresholds of 16 tested points in the macular program, as shown on the HFA printout. Only reliable results with no fixation loss, no false positive or false negative, were analyzed in the study.

This study followed the tenets of the Declaration of Helsinki, and informed consent was obtained from all participants after the purpose of the study had been explained.

The data were analyzed using the SPSS statistic package (SPSS, Chicago, IL, USA) by analysis of variance to compare morphologic and perimetric results among the three clinical groups. We also calculated the Spearman rank correlation between the temporal ONH parameters and the mean macular sensitivity of W on W and B on Y perimetry.

Results

Of the 74 participants, 28 were considered to be normal subjects, 23 had OH, and 23 were patients with POAG. There was no statistically significant difference in age, refraction, and temporal ONH parameters measured with HRT among the three clinical groups (Table 1). The mean macular sensitivity of B on Y and W on W perimetry showed a statistically significant difference among the three clinical groups ($P < .05$). In addition, the mean macular sensitivity of B on Y and W on W perimetry in patients

Table 1. Descriptive Analysis of Clinical Background for All Subjects*

	Healthy Subjects (n = 28)	Patients with OH (n = 23)	Patients with Early POAG (n = 23)	ANOVA *P* Value
Age (y)	57.0 ± 9.9	55.5 ± 7.2	54.4 ± 9.8	NS
Refraction (D)	−0.9 ± 1.8	−0.8 ± 2.0	−1.1 ± 2.4	NS
W on W mean macular sensitivity (dB)	33.2 ± 1.4	32.9 ± 1.9	31.0 ± 2.7†	.001
B on Y mean macular sensitivity (dB)	25.6 ± 3.7	24.6 ± 2.8	22.7 ± 3.1†	.027
Disc area (mm^2)	0.35 ± 0.07	0.34 ± 0.09	0.34 ± 0.11	NS
Cup area (mm^2)	0.24 ± 0.09	0.24 ± 0.10	0.24 ± 0.11	NS
Rim area (mm^2)	0.11 ± 0.05	0.11 ± 0.04	0.10 ± 0.04	NS
Cup/Disc area ratio	0.67 ± 0.18	0.66 ± 0.17	0.68 ± 0.15	NS
Cup volume (mm^3)	0.054 ± 0.038	0.062 ± 0.039	0.051 ± 0.044	NS
Rim volume (mm^3)	0.009 ± 0.006	0.008 ± 0.005	0.007 ± 0.003	NS
Mean cup depth (mm)	0.29 ± 0.10	0.31 ± 0.11	0.29 ± 0.14	NS
Maximum cup depth (mm)	0.56 ± 0.15	0.60 ± 0.18	0.57 ± 0.18	NS
Mean RNFL thickness (mm)	0.071 ± 0.016	0.069 ± 0.018	0.072 ± 0.021	NS
RNFL cross-section area (mm^2)	0.059 ± 0.013	0.058 ± 0.017	0.060 ± 0.020	NS
Mean deviation (dB)	−0.31 ± 0.86	−0.61 ± 1.32	−3.12 ± 0.84†‡	.000
Corrected patter SD (dB)	1.49 ± 1.19	1.30 ± 1.00	3.88 ± 3.24†‡	.000

*Values are mean ± SD.

OH: ocular hypertension, POAG: primary open angle glaucoma, ANOVA: analysis of variance, W on W: white on white perimetry, B on Y: blue on yellow perimetry, RNFL: retinal nerve fiber layer, NS: not significant.

†Significant dfference from normal subjects ($P < .05$: Scheffé test for multiple comparisons).

‡Significant difference from ocular hypertension ($P < .05$: Scheffé test for multiple comparisons).

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Table 2. Correlation Coefficients for Temporal ONH Parameters and White Mean Macular Sensitivity in Each Clinical Group

Temporal ONH Parameters	Healthy Subjects (n = 28)	Patients with OH (n = 23)	Patients with Early POAG (n = 23)
Disc area	0.134	−0.175	−0.349
Cup area	0.115	−0.252	−0.336
Rim area	0.119	0.336	0.111
Cup/disc area ratio	−0.014	−0.248	−0.336
Cup volume	0.155	−0.072	−0.295
Rim volume	0.054	0.233	0.295
Mean cup depth	0.178	−0.157	−0.154
Maximum cup depth	0.282	−0.170	0.013
Mean RNFL thickness	0.307	−0.044	0.133
RNFL cross-section area	0.287	−0.096	−0.139

ONH: optic nerve head, OH: ocular hypertension, POAG: primary open angle glaucoma, RNFL: retinal nerve fiber layer.

with early POAG was significantly lower than in healthy subjects ($P < .05$). The mean deviation and the corrected pattern standard deviation of the conventional W on W perimetry, measured with HFA program 30-2, showed statistically significant differences among the three clinical groups ($P < .05$). The mean deviation and the corrected pattern standard deviation in patients with early POAG were significantly lower than those in normal subjects and patients with OH ($P < .05$).

The correlation coefficients between the temporal ONH parameters and the mean macular sensitivity of W on W and B on Y perimetry in the three clinical groups are summarized in Tables 2 and 3. There were no significant correlations between the temporal ONH parameters and the mean macular sensitivity of W on W perimetry for the three clinical groups. In patients with POAG, the mean macular sensitivity of B on Y perimetry showed significant correlation with cup area and volume, cup/disc area ratio, and rim volume of temporal ONH ($P < .05$), whereas in healthy subjects and patients with OH, there was no significant correlation between the mean macular sensitivity of B on Y perimetry and the temporal ONH parameters.

Table 3. Correlation Coefficients for Temporal ONH Parameters and Blue on Yellow Mean Macular Sensitivity in Each Clinical Group

	Healthy Subjects (n = 28)	Patients with OH (n = 23)	Patients with Early POAG (n = 23)
Disc area	−0.329	−0.253	−0.340
Cup area	−0.342	−0.278	−0.631*
Rim area	0.293	0.069	0.375
Cup/disc area ratio	−0.298	−0.218	−0.549*
Cup volume	−0.092	−0.115	−0.528*
Rim volume	0.328	0.086	0.542*
Mean cup depth	−0.023	0.150	−0.282
Maximum cup depth	0.178	0.206	−0.197
Mean RNFL thickness	0.257	−0.041	0.147
RNFL cross-section area	0.099	−0.125	−0.122

OH: ocular hypertension, POAG: primary open angle glaucoma, RNFL: retinal nerve fiber layer.
*$P < .01$.

Discussion

A blue-yellow color vision deficiency is the most common form of acquired color vision deficiency found in patients with OH and POAG. This suggests that blue chromatic sensitivity or its neural connections are more vulnerable to damage due to elevated IOP than achromatic sensitivity.[4,5] According to the histopathological investigation of the distribution of the blue-sensitive cones, they were found to be absent in the limited center of the fovea, reach peak density at 0.75–1.5° eccentricity, and decrease with greater eccentricity.[15–17] Therefore, in order to identify the relationship between blue chromatic sensitivity and morphological changes of the ONH in patients with early POAG, we used blue chromatic and achromatic macular sensitivity measured with the macular program of HFA and the temporal ONH parameters, including the papillo-macular bundle, measured with HRT.

There was no significant difference in the temporal ONH parameters among the three clinical groups. The mean macular sensitivity of B on Y and W on W perimetry in patients with early POAG showed significant losses compared with that in healthy subjects, suggesting that macular sensitivity is vulnerable to diffuse RNFL functional damage due to elevated IOP. Furthermore, regardless of the lack of any correlation between the mean macular sensitivity of W on W perimetry and the temporal ONH parameter in the three clinical groups, in patients with early POAG, significant correlations were found between cup area and volume, cup/disc area ratio, and rim volume, and the mean macular sensitivity of B on Y perimetry, showing that the losses of blue chromatic sensitivity are more affected by the temporal morphological changes of the ONH than the changes in achromatic sensitivity. These results supported the previous studies,[18,19] indicating that diffuse RNFL damage due to elevated IOP involving the papillo-macular bundle is significantly related to the losses in the blue chromatic sensitivity, and that the dys-

function of the blue chromatic pathway may precede the occurrence of the morphological changes in glaucomatous ONH damage. Therefore, our results revealed that the measurement of the blue chromatic threshold obtained by B on Y perimetry could make it possible to detect functional damage in glaucoma patients prior to ONH morphological changes.

It is well known that there is a decrease in the light transmission of the short-wavelength spectrum of the crystal lens because of the development of cataract,[20] the functional changes in myopia,[21] and the short-term fluctuation of the threshold in the examination sessions.[22] These factors explain the variability in the test results of B on Y perimetry.

Sample et al proposed a light transmission index of the lens calculated from the measurement of the autofluorescence of the lens obtained by fluorometry.[23] He commented that the most significant and rapid increase in lens density occurs in the 6th and 7th decades of life, and that subjects younger than 70 years of age showed apparently smaller discrepancies in the threshold radiance between the short-wavelength and long-wavelength spectrums compared with subjects older than 70 years.[24] However, our selection criteria could exclude the differences in age, visual acuity, and ocular findings among the three clinical groups.

Kawabata et al reported that the blue chromatic threshold was affected by myopic refractive errors because the population of blue sensitive cones is much smaller than that of green and red sensitive cones. The enlargement of the posterior part of the eye due to the anatomical change in myopia leads to a decrease of photoreceptor density in the macular region.[21] In this study, as high myopic eyes with a spherical refraction less than −6.0 D were excluded, there was no significant difference in the values of spherical equivalence among the three clinical groups, and the discrepancies in macular sensitivity between B on Y and W on W perimetry were significantly smaller than those of the peripheral visual field in the myopic eyes. Our results therefore are not likely to be influenced by myopia.

Takahashi et al mentioned that short-term fluctuation of B on Y and W on W perimetry was significantly different between the initial and second sessions, but that there was no difference between the second and subsequent sessions.[22] In order to minimize the short-term fluctuation of the tested thresholds, in the present study we held separate sessions of B on Y and W on W perimetry, and only the more reliable results of the second examination were considered in the analysis.

In conclusion, the present study demonstrated no significant correlation of the temporal ONH parameters and the mean macular sensitivity of W on W perimetry for the three clinical groups. There were significant correlations between the mean macular sensitivity of B on Y perimetry and cup area and volume, cup/disc area ratio, and rim volume of the temporal ONH in patients with early POAG. No correlation was found between the mean macular sensitivity of B on Y perimetry and the temporal ONH parameters. These findings suggested that the measurement of blue chromatic thresholds in the macular region might make it possible to detect functional damage due to elevated IOP prior to morphological changes of the ONH of glaucoma patients.

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