Association of Intereye Visual-Sensitivity Asymmetry With Progression of Primary Open-Angle Glaucoma

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Purpose. To investigate the relationship between intereye visual field defect (VFD) asymmetry and subsequent VF progression in primary open-angle glaucoma (POAG).

Methods. Moderate-stage patients with POAG (226 eyes of 113 patients) with a single hemifield defect were followed for 8.7 years. Participants were categorized into three groups by initial VF pattern: (1) unilateral VFD, (2) bilateral VFD within same hemifield (superior–superior, inferior–inferior), (3) bilateral VFD within opposite hemifield (superior–inferior). The mean deviation (MD) difference between the intereye was defined as the intereye MD asymmetry index (iMAI). Intereye visual-sensitivity difference within the same hemifield was calculated as the intereye hemifield visual-sensitivity asymmetry index. Functional progression was detected by Glaucoma Progression Analysis. The overall rate of MD change and the association between new indices were evaluated by linear regression. A Kaplan-Meier survival analysis was performed and the factors associated with glaucoma progression were evaluated by Cox proportional hazard modeling.

Results. Unilateral VFD eyes and bilateral VFD eyes within opposite VF hemifield showed significant progression and faster rate of MD change compared with bilateral VFD eyes within same VF hemifield (71.1% vs. 45.9% vs. 21.1% [$P = 0.001$]; −1.27 dB/y vs. −0.64 dB/y vs. −0.32 dB/y [$P = 0.001$]). Unilateral VFD eyes showed the fastest time to VF progression compared with other groups ($P = 0.002$). A faster rate of MD change was associated with greater intereye MD asymmetry index ($P = 0.001$) and greater intereye hemifield visual-sensitivity asymmetric index ($P = 0.031$), which were significant risk factors for glaucoma progression (all $P < 0.001$).

Conclusions. Among POAG eyes with comparable hemifield VFDs, eyes without a corresponding hemifield defect in the fellow eye showed faster rates of progression compared with those with a corresponding hemifield defect.

Keywords: asymmetric, intereye, primary open-angle glaucoma, visual field defect, hemifield

Glaucoma is the leading cause of irreversible blindness worldwide, affecting nearly 70 million people.[1] The disease is a progressive optic neuropathy with functional damage of gradual, irreversible loss of the visual field (VF). In landmark glaucoma studies, the evaluation of glaucoma progression has been largely predicated on VF assessment.[2] The detection of progression and risk assessment has been important to prevent progressive loss in patients with glaucoma.[3]

The risk factors for the progression of primary open-angle glaucoma (POAG) have been established in many studies, including large, randomized controlled trials: the Early Manifest Glaucoma Trial (EMGT),[4] the Advanced Glaucoma Intervention Study,[5] the Collaborative Initial Glaucoma Treatment Study,[6] and the Collaborative Normal Tension Study.[7,8] Well-known risk factors for the progression of POAG are older age,[4–6] higher IOP,[4–7] and disc hemorrhage (DH).[4,8] The knowledge of risk factors for VF progression allows for the identification of individuals who can be targeted for closer monitoring or augmentation treatment.

POAG generally affects both eyes, but often presents asymmetrically with asymmetric VF defect (VFD).[9–12] Previous studies have documented intereye asymmetry and its relationship with intraocular factors such as IOP, myopia, optic nerve head parameters, retinal nerve fiber layer (RNFL) thickness, and intereye vessel density asymmetry.[9,13–17] Also, intereye IOP asymmetry and VF asymmetry has been reported to increase the risk of POAG development

in patients with ocular hypertension.[18] However, intereye asymmetry of VFD in glaucoma and its relation to the rate of VF loss has not been investigated to the best of our knowledge.

In this longitudinal study, we compared the rate of disease progression in patients with POAG with intereye asymmetric and symmetric VFD. That is, we determined whether glaucoma progression in POAG eyes is affected by the condition of the fellow eye. In addition, we presented a novel index of asymmetric VFD and focused on uncovering the risk factors of POAG progression.

Methods

This was retrospective, longitudinal cohort study was designed to evaluate the visual function of glaucoma. The data were retrieved from the clinical data warehouse of Seoul National University Hospital Patients Research Environment (SUPREME) based on a medical records review. This study was approved by the Seoul National University Hospital Institutional Review Board, and informed consent was waived owing to the study's retrospective nature. All of the investigations and procedures adhered to the tenets of the Declaration of Helsinki.

Study Participants

Participants who had been diagnosed with POAG at the Glaucoma Clinic of Seoul National University Hospital from January 2008 to June 2018 and been followed up regularly at a 6-month interval for a minimum of 5 years were enrolled. The main inclusion criteria were moderate-stage POAG (mean deviation [MD] between −12 dB and −6 dB) with a single-hemifield defect. Additionally, the patients had a best-corrected visual acuity of better than 20/30, a spherical equivalent refractive error between –6.00 and +3.00 diopters, and reliable VF testing results (fixation loss <20%, false positive errors <15%, and false-negative errors <15%).

POAG was defined as the presence of glaucomatous optic disc with typical glaucomatous VF damage on standard automated perimetry (SAP) at three initial consecutive VF examinations, and an open angle. The IOP was not considered in the determination of patient eligibility for the POAG group. Glaucomatous VF change was defined as (1) glaucoma hemifield test values outside the normal limits or (2) three or more abnormal contiguous points with a probability of $P < 0.05$, of which at least one point has a probability of $P < 0.01$ on a pattern deviation plot, or (3) a pattern standard deviation of $P < 0.05$. The determination of glaucoma severity was based on baseline MD measurements using the Hodapp–Parrish–Anderson grading scale.[19] The criteria for single-hemifield defect were based on the previous literature[20–22]: (1) VFD with a sharp border along the horizontal meridian and (2) both nasal and temporal involvement. Normal VFs were required to have consistently normal and reliable VF results from at least two SAP tests. In addition, they could not have any test points with a probability level less than 2% and no clusters of three or more adjacent points with a probability of less than 5% on the pattern deviation probability plots.[23] The first one to two VF results were excluded so as to minimize learning effects, and unreliable results also were excluded. The first recorded MD, having excluded the VF for learning effects, was subsequently referred to as the baseline MD. For tests showing unreliable results or suspected progression, clinicians were allowed to check the test more frequently, and more than five reliable VF tests at separate visits were required for analysis. All of the participants received treatment consisting of medication, laser trabeculoplasty, or both. The better eye and worse eye were defined based on the baseline MD values from the first eligible VF report. The worse eye, which is to say, the eye with the lower MD value, was selected as the study eye for further analysis.

Participants were excluded for the following reasons: secondary OAG (i.e., steroid-induced glaucoma); evidence of pseudoexfoliation or pigment dispersion syndrome; ocular surgery history such as cataract surgery, glaucoma surgery, or vitrectomy possibly affecting the VF test; a history of strabismus; a history of uveitis, trauma, or inflammatory disease; and any retinal or neurologic disease possibly affecting the VF examination results.

All of the patients were reviewed for demographic and systemic factors including history of diabetes mellitus and systemic hypertension, and all had undergone a complete ophthalmic examination including visual acuity assessment, refraction, slit-lamp biomicroscopy, Goldmann applanation tonometry (Haag-Streit, Koniz, Switzerland), gonioscopy, dilated fundus examination, digital color disc photography, red-free RNFL photography (TRC-50IX; Topcon Corporation, Tokyo, Japan), central corneal thickness measurement (Orbscan 73 II, Bausch & Lomb Surgical, Rochester, NY), axial length measurement (Axis II PR; Quantel Medical, Inc., Bozeman, MT), Cirrus spectral-domain optic coherence tomography (Carl Zeiss Meditec, Dublin, CA), as well as SAP 24-2, 30-2 testing (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) with the Swedish interactive threshold algorithm standard strategy.

The baseline IOP was defined as the average IOP of two consecutive visits in the absence of IOP-lowering medication use. All of the eyes were aimed to decrease their baseline IOP by 20% or more. The mean IOP was calculated as the average of IOPs taken at the respective visits during the VF examination visits. IOP fluctuation was defined based on the standard deviation of those values. Disc and RNFL photography were taken after full dilation of the pupil. DH was defined as an isolated flame-shaped or splinter-like hemorrhage on the optic disc or in the parapapillary area extending to the border of the optic disc. Beta-zone (ß-zone) parapapillary atrophy was characterized by marked atrophy of the retinal pigment epithelium and choriocapillaris, with good visibility of the sclera and large choroidal vessels.

Intereye VFD Pattern

Participants were classified into three categories according to the intereye pattern of hemifield defect at baseline:

(1) Unilateral VFD: one superior or inferior hemifield defect in the study eye and normal VF results in the contralateral eye (Fig. 1A);
(2) Bilateral VFD within the same hemifield: bilateral superior or bilateral inferior hemifield defect (Fig. 1B);
(3) Bilateral VFD within the opposite hemifield: one superior hemifield defect and contralateral–inferior hemifield defect (Fig. 1C).

Intereye Visual-Sensitivity Asymmetry Index

The intereye visual sensitivity asymmetry index was determined based on the intereye VF examination difference of

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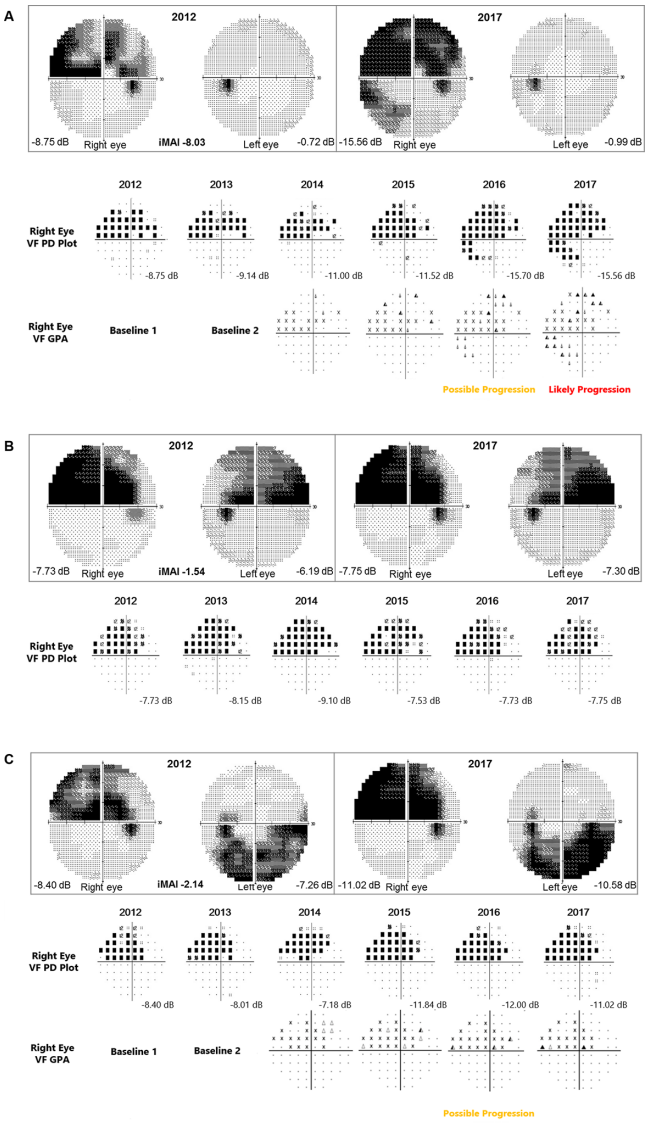

Figure 1. Representative cases of POAG with (**A**) unilateral VFD, (**B**) bilateral VFD within same hemifield, (**C**) bilateral VFD within opposite hemifield.

(1) the overall MD and (2) hemifield deviation (HD) value of intereye mirrored hemifields (bilateral–superior or bilateral–inferior hemifield). The HD value used the same test locations of each hemifield in the glaucoma hemifield test: central, paracentral, nasal, arcuate 1, and arcuate 2 regions.[24] This was a subset of the 24-2 test pattern, excluding locations at and near the blind spot, resulting in 22 test points. The HD values of each hemifield were calculated as the mean values of total deviation in 22 test points.[25] The intereye hemifield visual sensitivity asymmetric index (ihVAI) was calculated as the difference of HD value between the affected hemifield in the study eye (HD_1) and the intereye mirrored hemifield in the fellow eye (HD_2).

The new indices were defined as the absolute values as follows (1: study eye, 2: fellow eye):

(a) intereye MD asymmetry index (iMAI) = $|MD_1 - MD_2|$
(b) ihVAI = $|HD_1 - HD_2|$

Assessment of Glaucoma Progression

Glaucoma progression was defined as functional change on VF tests. Progression of VF was evaluated by two methods: (1) an "event-based" analysis and (2) a "trend-based" analysis. The event-based analysis using the Humphrey field analyzer with guided progression analysis was used to determine progression, and only likely progression was considered to be VF progression. In the trend-based analysis, the rate of progression based on the change of MD against time was calculated. Also, the hemifield progression rate of each hemifield in both eyes were analyzed. One glaucoma specialist (Y.K.K.) reviewed all of the patients' VF results to ensure the absence of any artifactual results.

Statistical Analysis

The categorical data were analyzed by χ^2 test, and continuous variables were compared with the *t* test and ANOVA test results that had been corrected for multiple comparisons according to the Bonferroni method. The κ coefficients for the independent examiners' (EB and AH) assessment of the presence or absence of DH and parapapillary atrophy were calculated as a measure of the reliability of interobserver agreement. The κ coefficient adjusts the observed proportional agreement that would be expected by chance, with $\kappa = 1$ indicating perfect agreement and $\kappa = 0$ indicating no agreement.[26] Linear regression analysis was used to calculate the rate of MD change. It was also used to evaluate the association between the new indices and the rate of MD change. The area under the receiver operating characteristic (AUROC) curve and 95% confidence limits was calculated and compared by pairwise comparison to evaluate predictive power. The intergroup cumulative risk ratios of functional progression were compared by Kaplan–Meier survival analysis and log-rank test. The first time progression detection was found was regarded as the endpoint in survival analyses. The hazard ratios of glaucoma progression were estimated with covariates using Cox proportional hazard modeling. In the univariate model, the variables with significance less than 0.10 were included in a multivariate model, because the traditional level of 0.05 can fail in identifying potential predictor variables.[27] The final multivariate model was developed by means of backward elimination, and the hazard ratios with 95% confidence intervals (CIs) were calculated. The model was validated using the Hosmer-Lemeshow test. A bootstrap resampling procedure was used to derive 95% CIs and *P* values. We used 10,000 iterations of the bootstrap to estimate the parameter distribution and the sample size for each iteration was the same as the number of observations in the original sample. Statistical analyses were performed using statistical software SPSS (version 22.0; SPSS Inc., Chicago, IL), MedCalc (version 19.6.1; MedCalc Software, Mariakerke, Belgium), and STATA (version 16.0; StataCorp LLC, College Station, TX). All of the *P* values were two sided and were considered statistically significant when less than 0.05.

Results

A total of 3770 patients with moderate stage POAG were assessed for eligibility and 3602 patients without fulfilling the definition of a single hemifield defect at baseline were ineligible. Among the 168 participants with a single hemifield defect at baseline, 17 were excluded from further

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Table 1. Comparison of Demographic and Clinical Characteristics of POAG Study Eyes

Characteristics	Unilateral VFD (n = 38)	Bilateral VFD Within the Same VF Hemifield (n = 38)	Bilateral VFD Within the Opposite VF Hemifield (n = 37)	P Value
Demographic data				
Age, y	54.3 ± 11.3 (32 to 82)	59.4 ± 12.9 (33 to 88)	55.0 ± 9.5 (32 to 80)	0.19
Male, n (%)	19 (50.0)	20 (52.6)	18 (48.6)	0.82
Hypertension, n (%)	6 (15.8)	10 (26.3)	8 (21.6)	0.15
Diabetes mellitus, n (%)	6 (15.8)	5 (13.1)	5 (13.5)	0.65
Follow-up duration, y	8.5 ± 1.9 (5 to 13)	8.9 ± 2.5 (5 to 13)	8.6 ± 2.6 (5 to 13)	0.13
Mean glaucoma medications	2.2 ± 1.2 (1 to 4)	2.2 ± 1.1 (1 to 4)	2.3 ± 1.7 (1 to 4)	0.42
Clinical data				
Spherical equivalence (diopters)	–2.79 ± 2.80 (–6.00 to 2.63)	–2.80 ± 2.16 (–6.00 to 2.17)	–2.75 ± 2.98 (–6.00 to 2.00)	0.43
Axial length, mm	24.71 ± 1.55 (22.21 to 25.92)	24.94 ± 1.47 (22.40 to 26.02)	24.79 ± 1.79 (22.96 to 26.21)	0.33
Central corneal thickness, µm	537.8 ± 37.6 (443 to 628)	525.9 ± 36.2 (482 to 599)	524.6 ± 36.4 (423 to 592)	0.69
Baseline IOP, mm Hg	17.9 ± 2.3 (9 to 25)	17.8 ± 4.3 (10 to 23)	17.8 ± 3.9 (9 to 23)	0.53
Mean follow-up IOP, mm Hg	14.2 ± 2.2 (10.1 to 19.3)	14.1 ± 2.3 (10.1 to 19.3)	13.9 ± 2.2 (10.1 to 19.3)	0.90
IOP fluctuation, mm Hg	2.2 ± 1.1 (1.0 to 4.3)	2.0 ± 0.9 (1.1 to 4.2)	1.9 ± 0.7 (1.0 to 3.1)	0.58
Cup-to-disc ratio	0.75 ± 0.04 (0.49 to 0.90)	0.78 ± 0.03 (0.58 to 0.91)	0.77 ± 0.03 (0.59 to 0.93)	0.57
Optic DH, n (%)	14 (36.8)	15 (39.5)	13 (35.1)	0.82
Parapapillary atrophy, n (%)	37 (97.3)	36 (94.7)	35 (94.6)	0.36
MD, dB	–8.51 ± 1.81 (–11.7 to –6.0)	–8.92 ± 2.10 (–11.8 to –6.1)	–8.83 ± 1.90 (–11.9 to –6.1)	0.12
PSD, dB	12.50 ± 2.71 (7.6 to 17.1)	12.18 ± 2.59 (6.3 to 17.2)	11.49 ± 2.81 (6.8 to 17.1)	0.82
VFI, dB	76.6 ± 8.0 (59 to 89)	74.7 ± 9.3 (57 to 90)	79.6 ± 7.1 (61 to 91)	0.42

Comparison was performed using one-way ANOVA with post hoc Bonferroni correction for multiple comparisons. Values are mean ± standard deviation (range) or number (%).

PSD, pattern standard deviation; VFI, VF index.

Table 2. Comparison of Intereye Visual-Sensitivity Asymmetry Index

Intereye Visual-Sensitivity Asymmetry Index	Unilateral VFD (A) (n = 38)	Bilateral VFD Within the Same VF Hemifield (B) (n = 38)	Bilateral VFD Within the Opposite VF Hemifield (C) (n = 37)	P Value	Post Hoc Analysis
iMAI, dB	7.93 ± 1.93	2.62 ± 1.57	2.50 ± 1.69	**<0.001**	B, C<A
ihVAI, dB	12.93 ± 4.49	5.84 ± 3.46	11.46 ± 4.79	**<0.001**	B<A, C

Comparison was performed using one-way ANOVA with post hoc Bonferroni correction for multiple comparisons. Values with statistical significance are shown in bold.

analysis, 13 having undergone intraocular surgery (11 eyes, uncomplicated cataract surgery; 2 eyes, combined vitrectomy) and 4 having been diagnosed with combined retinal diseases during the course of the follow-up. Of the remaining 151 eyes, a further 38 failed to attend follow-up visits for 5 years. We found no significant difference in the follow-up rates between the three groups: unilateral VF group (38 of 49 [77.6%]) vs. bilateral VFD within opposite VF hemifield group (37 of 51 [72.5%]) vs. bilateral VFD within same VF hemifield group (38 of 51 [74.5%]; P = 0.84). Finally, a total of 113 participants (226 eyes) were included in the study (mean age, 57.4 ± 12.0 years; range, 32–88 years; mean follow-up period, 8.7 ± 2.4 years). A total of 1246 VF tests were performed and baseline tests affected by the learning curve (125 tests) and unreliable VF results (32 tests) were discarded.

Demographic and Clinical Characteristics of Study Participants

The demographics and clinical characteristics of the patients are summarized in Table 1, and an intereye comparison is provided in Supplementary Table S1. There were no significant differences in any of the baseline clinical characteristics, including age, self-reported history of diabetes mellitus and systemic hypertension, IOP, presence of DH, and VF parameters (all $P > 0.05$). There was an almost perfect agreement between graders for the presence of DH (κ = 0.909; 95% CI, 0.861–0.973; $P < 0.001$), and for the presence of parapapillary atrophy (κ = 0.889; 95% CI, 0.788–0.934; $P < 0.001$).

Comparison of Intereye Asymmetry Indices

Table 2 summarizes the comparison of intereye visual sensitivity asymmetry index among the three groups at baseline. The iMAI was significantly greater in the unilateral VFD group relative to the groups of bilateral VFD within same and opposite VF hemifield group (7.93 dB [1.93 dB] vs. 2.62 dB [1.57 dB] vs. 2.50 dB [1.69] dB; $P < 0.001$). Additionally, the ihVAI was significantly greater in the unilateral VF group and bilateral VFD within opposite VF hemifield group compared with the bilateral VFD within same VF hemifield group (12.93 [4.49] vs. 11.46 [4.79] vs. 5.84 [3.46]; $P < 0.001$).

Comparison of VF Progression

During the 8.7 ± 2.4-year follow-up period, 27 of 38 unilateral VFD eyes (71.1%), 17 of 37 bilateral VFD eyes within the opposite VF hemifield (45.9%), and 8 of 38 bilateral VFD eyes within the same VF hemifield (21.1%) showed

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Table 3. Comparison of VF Progression

VF Progression	Unilateral VFD (A) ($n = 38$)	Bilateral VFD Within the Same VF Hemifield (B) ($n = 38$)	Bilateral VFD Within the Opposite VF Hemifield (C) ($n = 37$)	*P* Value	Post Hoc Analysis
GPA progression, *n* (%)	27 (71.1)	8 (21.1)	17 (45.9)	**0.001**	B<C< A
Rate of MD change, dB/y	–1.27 ± 0.94	–0.32 ± 0.37	–0.64 ± 0.73	**0.001**	A<C<B
Hemifield progression rate, dB/year	–1.32 ± 0.66	–0.38 ± 0.42	–1.27 ± 0.44	**<0.001**	A, C<B

Comparison was performed using one-way ANOVA with post hoc Bonferroni correction for multiple comparisons. Values with statistical significance are shown in bold.

GPA, guided progression analysis.

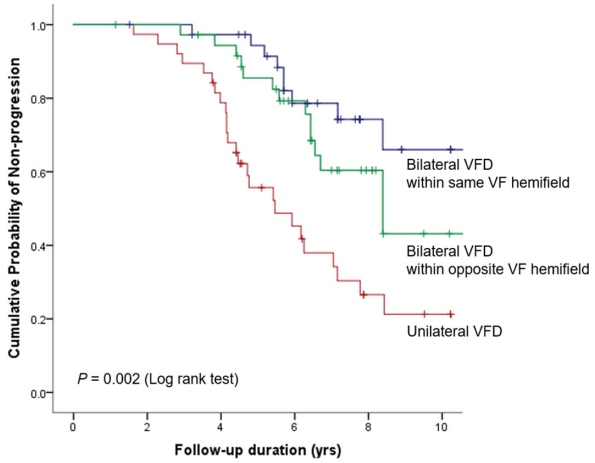

Figure 2. Kaplan–Meier curves comparing cumulative progression probability. Patients with unilateral VFD had a greater cumulative progression probability than those with bilateral VFD within same and opposite hemifield defect (log-rank test, $P = 0.002$).

progression ($P = 0.001$) (Table 3). A Kaplan–Meier survival analysis revealed that patients with unilateral VFD had a greater cumulative probability of progression than those with bilateral VFD within same and opposite VF hemifield group (log rank test, $P = 0.002$) (Fig. 2). The overall mean rate of MD was significantly faster in the eyes of unilateral VFD group and bilateral VFD within opposite VF hemifield group, compared with the eyes of bilateral VFD within same VF hemifield group: −1.27 ± 0.94 dB/y vs. –0.64 ± 0.73 dB/y vs. −0.32 ± 0.37 dB/y ($P = 0.001$). Also in the adjusted analysis, overall mean rate of MD was significantly faster in the eyes of unilateral VFD group and bilateral VFD within opposite VF hemifield group, compared with the eyes of bilateral VFD within same VF hemifield group: −1.28 ± 0.17 dB/y (bootstrap 95% CI, –1.380 to –0.524) dB/y vs. –0.64 ± 0.12 dB/y; (bootstrap 95% CI, –0.752 to 0.109 dB/y) vs. −0.32 ± 0.06 dB/y (bootstrap 95% CI, –0.109, 0.752 dB/year) ($z = 2.92$; $P = 0.004$). The mean rates of hemifield change were significantly faster in the unilateral VFD group and bilateral VFD within opposite VF hemifield group compared with the bilateral VFD within same VF hemifield group: −1.32 ± 0.66 dB/y vs. −1.27 ± 0.44 dB/y vs. –0.38 ± 0.42 dB/year ($P < 0.001$) (Table 3). Box plots comparing the rates of hemifield change of all hemifields of both eyes in the three groups are shown in Supplementary Figure S1. There was a significant difference between the intereye hemifields in the unilateral VFD group and bilateral VFD eyes within opposite VF hemifield group (all $P < 0.001$).

Factors Associated With Glaucoma Progression

A faster rate of MD change was associated with greater iMAI ($R^2 = 0.202$; $P = 0.001$) and ihVAI ($R^2 = 0.041$; $P = 0.031$) (Fig. 3). Comparing the asymmetry indices, the AUROC for

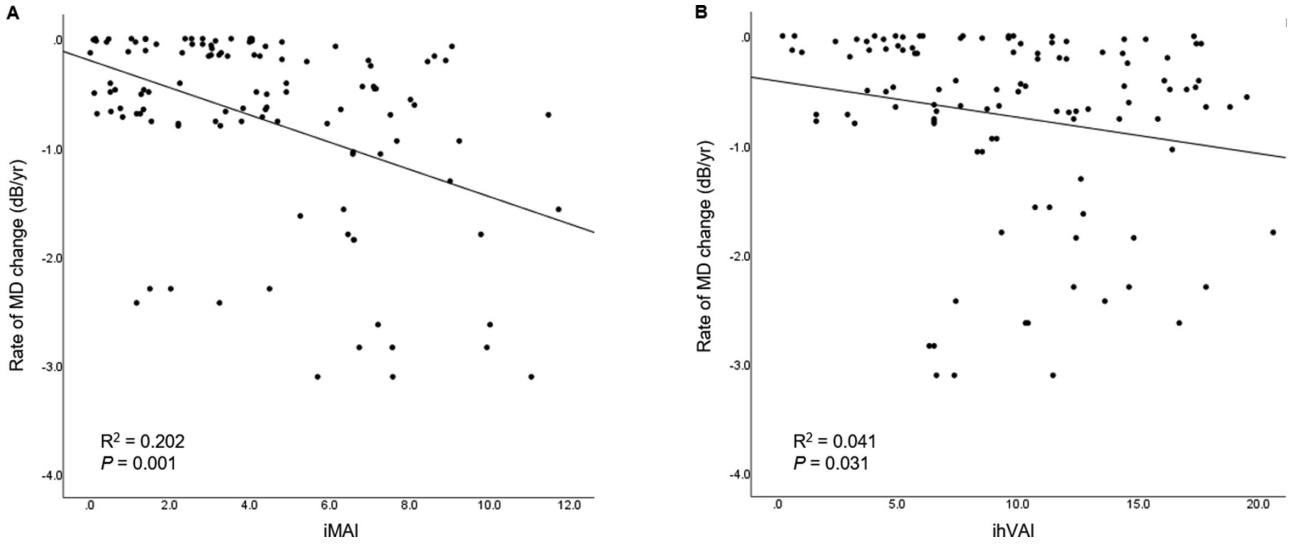

Figure 3. Scatterplots demonstrating relationships between new indices and rate of VF MD loss by linear regression analysis. The black line is the best-fit linear regression line.

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Table 4. Cox Proportional Hazard Model for Glaucoma Progression

	Univariate Model		Multivariate Model With iMAI Included		Multivariate Model With ihVAI Included	
Variable	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Demographic variables						
Age, y	0.991 (0.959–1.025)	0.60				
Sex, male	1.481 (0.701–3.129)	0.31				
Hypertension	0.595 (0.220–1.611)	0.32				
Diabetes mellitus	0.502 (0.093–2.705)	0.51				
Follow-up duration, y	0.963 (0.834–1.112)	0.61				
Clinical variables						
Spherical equivalence, diopters	0.936 (0.852–1.190)	0.94				
Axial length, mm	0.848 (0.595–1.208)	0.36				
Central corneal thickness, µm	0.996 (0.986–1.006)	0.42				
Baseline IOP, mm Hg	1.026 (0.945–1.113)	0.54				
Mean IOP, mm Hg	1.039 (0.879–1.228)	0.65				
IOP fluctuation, mm Hg	1.211 (0.804–1.824)	0.36				
Optic DH	**2.513 (1.166–5.414)**	**0.019**	**2.512 (1.199–5.599)**	**0.027**	**2.623 (1.180–5.831)**	**0.028**
Parapapillary atrophy	0.159 (0.048–2.198)	0.16				
Functional parameters						
Baseline MD, dB	1.070 (0.884–1.296)	0.49				
Baseline PSD, dB	0.988 (0.861–1.134)	0.86				
Baseline VFI, %	0.990 (0.947–1.035)	0.67				
Intereye VF index						
iMAI, dB	**1.242 (1.085–1.423)**	**0.002**	**1.251 (1.089–1.438)**	**0.001**		
ihVAI, dB	**1.111 (1.029–1.199)**	**0.003**			**1.116 (1.030–1.209)**	**0.001**

Factors with a *P* value of <0.10 in the univariate analysis were included in the multivariate analysis. Values with statistical significance are shown in bold.

PSD, pattern standard deviation; VFI, VF index.

diagnostic probability of glaucoma progression was determined: ihVAI had the best predictive power (AUROC = 0.800; 95% CI, 0.719–0.881), followed by iMAI (AUROC = 0.736; 95% CI, 0.639–0.825), without a significant difference ($P = 0.25$; Supplementary Fig. S2). By the initial model ($\chi^2 = 25.609$; degrees of freedom = 18; $P = 0.082$) and multivariate Cox proportional hazard model ($\chi^2 = 40.693$; degrees of freedom = 3; $P < 0.001$), the presence of DH (HR, 2.512; $P = 0.027$), greater iMAI (HR, 1.251; $P = 0.001$), and greater ihVAI (HR, 1.116; $P = 0.001$) were significant factors of glaucoma progression (Table 4). The model seemed to be well-calibrated (Hosmer–Lemeshow test; $P = 0.69$). Representative cases of POAG in each group are presented in Figure 1 (unilateral VFD, bilateral VFD within same hemifield, and opposite hemifield) during a follow-up period of 5 years.

Discussion

In the current longitudinal study, we compared the rate of disease progression in patients with POAG with intereye asymmetric and symmetric VFD. Eyes with unilateral VFD showed a greater probability and faster rates of VF progression than did eyes with bilateral VFD over the course of a mean of 8.7 years of follow-up. More interestingly, a positive association between the degree of VFD asymmetry index and the probability of glaucomatous progression in POAG eyes was established. To our knowledge, this study is the first to suggest the VFD asymmetry index between eyes as a risk factor for glaucoma progression.

The intereye correspondence between patterns of VF loss on SAP has been evaluated in glaucoma. Hoffmann et al.[12] reported that patterns of VF loss between eyes often correspond within the same VF hemifield and less commonly affect opposite hemifields. Boden et al.[11] found that a spatial relationship exists with defective locations between intereye concordance. Levine et al.[18] demonstrated that asymmetries of the VF between eyes predict the onset of glaucomatous VFDs in OHTS participants. However, all of these studies did not describe the progressive VF loss in glaucoma. Thus, in our study we investigated the intereye asymmetry in hemifield loss with glaucoma progression. We found that there was clinical significance of progressive VF change in the intereye asymmetric hemifield compared with the intereye symmetric VFD hemifield.

Previous studies have defined asymmetric VFD based on an intereye MD difference of at least 2 to 6 dB, and symmetric VFD as being less than that MD difference.[14,28–30] Meanwhile, our study presented asymmetry by first categorizing the pattern of VFD and calculating the novel asymmetry index afterward, based on the intereye MD difference (total and hemifield). The intereye VFD patterns were introduced to categorize the possible hemifields affected by glaucoma hemifield test, and new indices were devised to present the intereye MD difference with quantitative values. The unilateral VFD group presented a minimum iMAI of 6 dB, with significantly greater iMAI compared with bilateral VFD within opposite and same VF hemifield group (iMAI: –7.93 dB vs. –2.50 dB vs. –2.62 dB; $P < 0.001$). The unilateral VFD group and bilateral VFD within opposite VF hemifield group showed a greater ihVAI compared with the bilateral VFD within same VF hemifield group (ihVAI: –12.93 dB vs. –11.46 dB vs. –5.84 dB; $P < 0.001$). A greater probability

of glaucoma progression with faster rates of VF progression was demonstrated in eyes with unilateral VFD and bilateral VFD within opposite VF hemifield. These finding suggest that a high intereye asymmetry index may be associated, at least in part, with s higher probability and faster rates of disease progression.

Some controversy surrounds the clinical significance of bilateral glaucoma and progression of glaucoma. The EMGT reported that bilateral glaucoma had association with VF progression.[4,31] In contrast, in other large, randomized controlled trials (i.e., Advanced Glaucoma Intervention Study, Collaborative Initial Glaucoma Treatment Study, Collaborative Normal Tension Glaucoma Study), they did not find a relationship between bilateral glaucoma affecting glaucoma progression.[5–8] In our study, we included patients with moderate stage OAG with a single hemifield defect in one or both eyes. We found that greater intereye VF asymmetry (unilateral VFD and bilateral VFD within opposite VF hemifield) was associated with glaucoma progression. However, patients enrolled in the EMGT study were early stage OAG. Additionally, the patients with bilateral glaucoma presented more severe VF damage (average MD of 2.17 dB) compared with the unilateral glaucoma participants at baseline. In early stage glaucoma, the severity of VF loss at presentation has a positive relationship with the rate of VF progression.[32] This issue may have affected the results of the study and further studies with controlled baseline characteristics are needed to confirm the clinical significance of bilateral glaucoma in progression.

Our study found that novel intereye asymmetry indices were strongly associated with glaucoma progression. Why there is a positive association between a high asymmetry index and glaucoma progression is not clear and needs further study. One possible explanation is the use of the better eye with suppression of the worse eye, which may accelerate the progression of visual sensitivity deficit in the worse eye. Amblyopia, defined as the degradation of spatial vision in the absence of any detectable organic cause, results from disuse of inadequate foveal or peripheral retinal stimulation and/or abnormal binocular interaction.[33,34] Stronger suppression of the amblyopic eye has been associated with poorer amblyopic eye visual function. To overcome the issue in adults, neuroplasticity, and perceptual learning has been shown to enhance visual function by increasing the efficiency of neural processing, which has also been studied in a variety of ophthalmic disorders, such as optic neuropathy.[35–37] Although amblyopia and glaucoma are not the same disease entity, the fundamental idea behind the concept of those disease entities potentially gives a new aspect in eyes with intereye asymmetric glaucoma. Therefore, further studies evaluating the nonocular site implicated in intereye asymmetry are needed.

Intereye asymmetry such as in IOP, myopia, optic nerve head parameters, RNFL thickness, intereye vessel density, vessel narrowing, and VF, has been an issue in glaucoma.[9,13–17] Cartwright and Anderson[38] reported that in asymmetric normal-tension glaucoma (NTG), eyes with a higher IOP showed greater glaucomatous damage than eyes with lower IOP. In the Low-Pressure Glaucoma Study, however, there was no correlation between baseline IOP asymmetry and VF damage in NTG.[39] It is assumed that glaucoma is a multifactorial disorder having multiple active mechanisms. Through the present study, we addressed the issue of another mechanism, this one related to intereye VFD asymmetry, which may contribute to disease progression.

The present study has several limitations to be considered. First, although the skewness of the sample shows a normal distribution close to zero, caution should be made in generalizing our findings, because the proportion of NTG was high (75.2%) and only patients with moderate glaucoma with a single hemifield defect were included. This design may not extrapolate directly to other subtypes of glaucoma and permutations of glaucomatous severity and underscores the discrimination power of intereye asymmetry VF index in early or advanced glaucoma. The retrospective nature of this study may have resulted in significant limitations, such as selection bias. To overcome these potential issues, we identified all eyes from the clinic that would be eligible and used a statistical bootstrapping procedure, which is classified as a resampling method among statistical estimation procedures. Our findings should be interpreted with caution and future prospective studies are warranted.

Second, one may be concerned about the possibility that amblyopia patients might have been included in this study. However, only patients with a best-corrected visual acuity of 20/30 or higher in both eyes were included, and the difference in best-corrected visual acuity between eyes was less than two lines. Third, systemic vascular disorders were not compared in the characteristics between the study groups. Impaired systemic circulation with decreased ocular blood flow is known to play a role in the development and progression of glaucoma.[40,41] Fourth, the treatment approach had not been standardized in the cohorts. However, we targeted to reduce their baseline IOP by 20% or more and aimed to simulate the reality of typical progression analysis studies. The number of glaucoma medications and mean IOP was not different between the groups in our study. Fifth, our study was not suited for elucidating the deep structure evaluated by OCT. However, we performed a structural analysis using a glaucoma progression analysis, and there was no significant difference in OCT progression between the three groups: 27 eyes (71.1%) with unilateral VFD, 23 eyes (60.5%) with bilateral VFD within same VF hemifield, and 25 eyes (67.6%) with bilateral VFD within opposite VF hemifield (χ^2, $P = 0.39$). Further studies speculating the asymmetric deep structure of optic nerve head would be necessary to elucidate the relationship of intereye asymmetry and glaucoma progression.

In conclusion, intereye VFD asymmetry played a role in glaucoma progression. A greater intereye asymmetry index showed a greater probability and faster rate of glaucoma progression. Further studies determining whether augmented or differentiated treatment strategies would be beneficial for glaucoma patients with asymmetric VFD are needed.

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