The Relationship Between Asymmetries of Corneal Properties and Rates of Visual Field Progression in Glaucoma Patients

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Précis: In this study, asymmetries in corneal hysteresis (CH) between eyes of glaucoma patients were significantly associated with asymmetries in rates of visual field loss, suggesting a role of hysteresis as a risk factor for disease progression.

Purpose: The purpose of this study was to investigate the relationship between asymmetries in rates of glaucoma progression and asymmetries of corneal properties between eyes of subjects with primary open-angle glaucoma.

Participants and Methods: This prospective study followed 126 binocular subjects with glaucoma for an average of 4.3 ± 0.8 years. CH was measured at baseline using the Ocular Response Analyzer. Standard automated perimetry (SAP) and intraocular pressure were measured at baseline and every 6 months. Rates of visual field progression were calculated using ordinary least square regression of SAP mean deviation (MD) values over time for each eye. Eyes were defined as "better" and "worse" based on the slopes of SAP MD. Pearson correlation test, and univariable and multivariable regression models were used to investigate the relationship between inter-eye asymmetry in CH and central corneal thickness and inter-eye differences in rates of visual field progression.

Results: Only asymmetry of CH was significantly associated with the asymmetry in SAP MD rates of change between eyes ($r = 0.22$; $P = 0.01$). In a multivariable model adjusting for age, race, central corneal thickness, mean intraocular pressure and baseline disease severity, CH asymmetry remained significantly associated with asymmetric progression ($P = 0.032$).

Conclusion: CH asymmetry between eyes was associated with asymmetry on rates of visual field change, providing further support for the role of CH as a risk factor for glaucoma progression.

Key Words: corneal hysteresis, asymmetry, glaucoma, progression

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Primary open-angle glaucoma (POAG) is a chronic eye disease that can potentially result in irreversible blindness. Although POAG tends to be an asymmetric disease, the factors associated with interocular differences in rates of disease progression have not been completely elucidated. Although intraocular pressure (IOP) is the most important and the only modifiable risk factor for the disease, many eyes with glaucoma still present progressive functional loss despite relatively low IOP levels.[1,2] Therefore, it is likely that other characteristics may play a role in explaining the susceptibility to glaucoma damage at a given level of IOP.

Specific characteristics of the cornea, such as corneal central thickness (CCT) and corneal hysteresis (CH), have been associated with the individual susceptibility to glaucomatous damage. Thinner CCT has been associated with increased risk for development and progression of glaucoma.[3–7] More recently, CH, which is measured by estimating the ability of the cornea to resist deformation, has also been shown to be an important risk factor for development and progression of glaucoma.[8,9] However, no previous study has assessed the impact of inter-eye asymmetries in CH and CCT on rates of progression in subjects with glaucoma, which could add to our current understanding of the influence of cornea's biomechanics to each eye's susceptibility to glaucoma damage in an asymmetric disease.

In this study, we propose to investigate how the asymmetry of corneal properties between eyes of a subject with binocular POAG may correlate to asymmetric rates of visual field loss, to identify potential risk factors for disease progression.

METHODS

This was an observational cohort study of participants from a prospective longitudinal study designed to evaluate structure and function in glaucoma. The Institutional Review Board approved all methods, and written informed consent was obtained from all participants. All methods adhered to the tenets of the Declaration of Helsinki for research involving human subjects and the study was conducted in accordance with regulations of the Health Insurance Portability and Accountability Act.

At baseline and every 6 months, all participants underwent comprehensive ophthalmologic biomicroscopy, IOP measurement, gonioscopy, ophthalmoscopy examination, stereoscopic optic disc photography, and standard automated perimetry (SAP). CCT measurements were obtained at the baseline visit by a trained technician using the Pachette DGH 500 ultrasound pachymeter (DGH

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Technology Inc., Philadelphia, PA). Qualified trained personnel obtained IOP measurements using the Goldmann applanation tonometry (Haag-Streit, Konig, Switzerland) during follow-up. The mean and maximum values among these measurements for each individual eye over time were defined as mean IOP and peak IOP, respectively.

Only subjects with POAG in both eyes were included in this study. Glaucoma was defined by the presence of 2 or more repeatable glaucomatous visual field defects at baseline, defined as a pattern standard deviation with *P*-value of < 0.05, or a Glaucoma Hemifield Test result outside normal limits, and corresponding optic nerve damage. Subjects were excluded if they presented any other ocular or systemic disease that could affect the optic nerve or the visual field, if best-corrected visual acuity was < 20/40, spherical refraction outside 5.00 D, or cylinder correction outside 3.00 D or if they underwent any corneal surgery before enrollment in study. Participants who underwent glaucoma surgeries (ie, trabeculectomy, tube shunt procedures) or minimally invasive glaucoma surgery after the beginning of the study had all tests after the procedure date censored from the analyses.

SAP

SAP tests were performed using the Swedish Interactive Threshold Algorithm (SITA) Standard with 24-2 strategy of the Humphrey Field Analyzer II-i, model 750 (Carl Zeiss Meditec Inc., Dublin, CA). Only patients with a minimum of 3 visual field tests and 1 year of follow-up with reliable visual field tests ($\leq 15\%$ false-positive errors and $\leq 33\%$ fixation losses) were included in the study. The visual field tests were also reviewed and excluded if they presented artifacts, learning effect, or abnormalities that could indicate diseases other than glaucoma. The first reliable visual field exam performed after inclusion in the study was considered as the baseline test.

CH Measurements

CH was measured at baseline visit with the Ocular Response Analyzer (ORA; Reichert Technologies Inc., Depew, NY). A trained technician obtained 3 measurements from each eye and the average of these measurements was calculated for analysis. The ORA is a noninvasive device that evaluates corneal biomechanical properties using an applied force-displacement relationship. Details of this technology have been previously described.[10] Briefly, this instrument precisely ejects an air pulse that causes the cornea to move inward past applanation, deforming into a slight concavity. Milliseconds later, the airflow is shut down and the cornea recovers its normal configuration, passing through a second applanated state. The difference between the 2 applanation pressures, measured in mm Hg, is the CH parameter.

Statistical Analyses

The primary outcome of this study was the relationship between asymmetries in rates of visual field loss and asymmetries in corneal biomechanical properties. Rates of visual field change were calculated using ordinary least squares linear regression of SAP mean deviation (MD) values over time for each eye. For this study, eyes were defined as "better" and "worse" based on the rates of change of SAP MD, with the worse eye having the most negative slope. The asymmetry between eyes was calculated by subtracting the value of the "worse" eye from the "better" eye for rates of MD change, CH, CCT, mean IOP, peak IOP, and baseline MD.

Continuous variables were tested for normality and variables considered normal were compared using Student paired *t* test and are presented as mean ± SD. Variables with skewed distribution were compared using Wilcoxon signed-rank tests and are presented as median with interquartile range.

Because the asymmetry in rates of SAP MD change did not have a normal distribution, we performed a logarithmic transformation of the asymmetry in rates of SAP MD change for statistical modeling purposes. Using a log transformation results in a normally distributed variable, which allows for easy inference using linear regression. However, the transformation should be kept in mind when interpreting the effect of the coefficients of the linear regression model. When interpreted in relation to the original untransformed variable, the effects of the coefficients are not linear, but multiplicative (see example in the results). Figure 1 shows the distribution of the rates of SAP MD change before and after the logarithmic transformation. We then evaluated the correlation of the logarithmic-transformed SAP MD asymmetry with age and with the asymmetry in each of the clinical characteristics (ie, CH, CCT, baseline MD, and IOP) using Pearson correlation analysis. Univariable and multivariable regression analyses were also performed. The multivariate model was used to assess asymmetry in the corneal properties as a predictive factor for asymmetry in rates of SAP MD change, adjusting for confounding factors such as age, race, and asymmetry in baseline MD and in IOP parameters.

All statistical analyses were performed using the commercially available software Stata, version 15 (StataCorp LP, College Station, TX). The alpha level (type I error) was set at 0.05.

RESULTS

The study included 252 eyes of 126 subjects with POAG under treatment during a mean follow-up of 4.3 ± 0.8 years, with an average of 11 visits (range, 4 to 24). 65 (51%) of the patients were women. 71 (56.35%) were White and 55 (43.65%) were African American. The mean age at baseline was 67 ± 11 years.

The median (interquartile range) rate of MD change in the better eyes was −0.08 (−0.50, 0.30) dB/year and −0.38 (−0.94, −0.11) dB/year in the worse eyes. Clinical parameters from better and worse eyes are compared in Table 1. There was no statistically significant difference in mean IOP during follow-up between better and worse eyes (14.2 ± 3.3 vs. 14.3 ± 3.2 mm Hg, respectively; $P = 0.662$); and median peak IOP was 18 mm Hg for both groups ($P = 0.208$). Corneal parameters were not significantly different between better and worse eyes (CH: $P = 0.255$; CCT: $P = 0.466$). Figure 2 shows the distribution of asymmetries in CH, CCT, mean IOP, and peak IOP.

The correlation coefficients between asymmetries in CCT, peak IOP, mean IOP, baseline MD, and log of SAP MD rates of change asymmetry are presented in Table 2. Of note, the log of the asymmetry in SAP MD rates of change was significantly positively correlated with CH asymmetry only ($r = 0.22$, $P = 0.01$). Figure 3 shows the relationship between the log-asymmetry in rates of change of SAP MD and the asymmetry in CH. CH asymmetry remained significantly associated with asymmetry in rates of MD change in a multivariable model adjusting for asymmetries in mean IOP, baseline MD and CCT, as

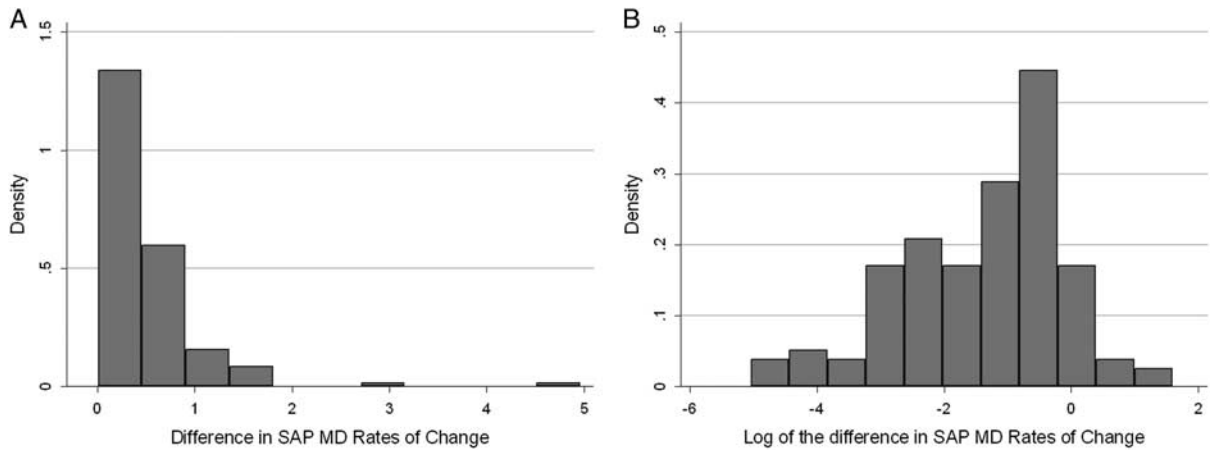

FIGURE 1. Distribution of the standard automated perimetry (SAP) mean deviation (MD) rates of change asymmetry values between worse and better eyes (A) before and (B) after logarithmic transformation. The asymmetry value is given as the difference in SAP MD rates of change (better—worse eye).

well as age and race. The coefficient in the multivariable model for CH was 0.29 on the log-scale. This implies that for a 1 mm Hg increase in CH asymmetry, we would expect a 0.29 increase in log-difference of the SAP MD rates. On the original scale, it means that for a 1 mm Hg increase in CH asymmetry we would expect the difference in SAP MD rates to increase by 34% [ie, exp (0.29) = 1.34] (Table 3). When asymmetry in peak IOP was included in the multivariable model (see Table A, Supplementary Digital Content 1, http://links.lww.com/IJG/A433, which shows the results of the multivariable model including peak IOP along other clinical variables for predicting log-asymmetry in SAP MD rates of change), the effect of asymmetry in CH in predicting asymmetry on rates of SAP MD change was very similar.

DISCUSSION

In the current study, we observed that a difference in CH between eyes was significantly associated with asymmetric rates of visual field progression in a cohort of individuals with POAG. Our results suggest that investigating asymmetry in CH can provide clinicians with additional information to help predict asymmetric glaucoma progression, potentially aiding in the decision of treating eyes of the same patient differently.

In our study, we found the difference in baseline CH between eyes of a same patient to be the only clinical characteristic significantly correlated with asymmetry in the rates of SAP MD loss over time. Although this correlation was not strong ($r = 0.22$, $P = 0.01$), the relationship remained significant even after adjustment for potential confounders in the multivariable model ($P = 0.032$). It is important to note that the majority of subjects included in our study had only relatively small asymmetries in CH which correlated to small asymmetries in rates of visual field change. However, ~20% of subjects presented relatively large asymmetries in CH and large differences in rates of visual field change between the eyes. Our findings are in accordance with previous studies that found association of CH and faster progression rates of SAP MD loss in glaucoma patients,[8,9,11] and therefore reinforce that CH should be seen as an additional risk factor for glaucoma progression.

It is interesting that the asymmetries in well-established risk factors for glaucoma progression such as mean IOP and peak IOP were not associated with asymmetry in rates of visual field loss. This might be related to the design of the study. During follow-up, patients were treated at the discretion of the ophthalmologist. It is likely that eyes with higher IOP may have been treated more aggressively and it is possible that differences in treatment between eyes may have been driven by IOP differences. This can potentially decrease the impact of these risk factors on progression over time, explaining at least in part the lack of significance in our analyses. Future studies should be prospectively designed with the aim of developing predictive models, including CH and other risk factors, to attempt to better predict individual risk for progression.

Few studies have investigated differences in CH between eyes of the same subject. A study by Carbonaro et al[12] found a significant correlation of $r = 0.61$ ($P < 0.001$) between right and left eyes of healthy individuals. Similarly, in our study the correlation between the better and worse eyes in glaucoma patients was significant ($r = 0.80$; $P < 0.001$). Despite this result, CH difference between eyes showed a clinically relevant association with asymmetric rates of SAP MD in the log-linear models in our analyses.

TABLE 1. Clinical Parameters of the Eyes Included in the Study, as Classified in Worse and Better Eye According to the Rate of Change in SAP MD

Parameters	Better Eye	Worse Eye	*P*
Corneal hysteresis (mm Hg)	9.0 ± 1.6	9.1 ± 1.6	0.255
Central corneal thickness (μm)	533.0 ± 42.6	533.9 ± 42.9	0.466
Mean IOP (mm Hg)	14.2 ± 3.3	14.3 ± 3.2	0.662
Peak IOP (mm Hg)*	18.0 (15.0-20.0)	18.0 (16.0-21.0)	0.208
Baseline SAP 24-2 MD (dB)*	−4.19 (−8.61 to −2.32)	−3.98 (−7.88 to −2.03)	0.121

Data are presented as mean ± SD, unless otherwise noted.
*Median (interquartile range).
IOP indicates intraocular pressure; MD, mean deviation; SAP, standard automated perimetry.

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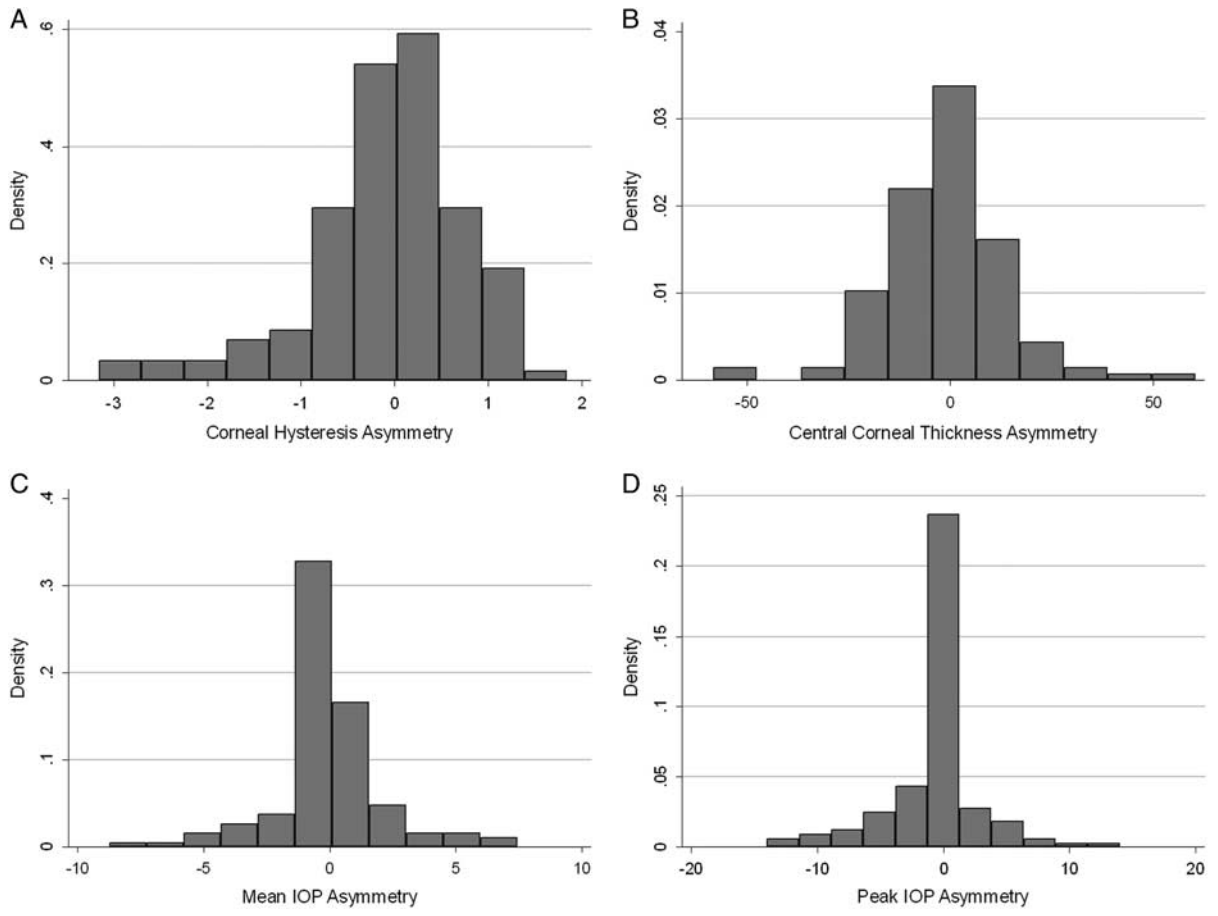

FIGURE 2. Distribution of asymmetry in: corneal hysteresis (A), central corneal thickness (B), mean intraocular pressure (C), and peak intraocular pressure (D). IOP indicates intraocular pressure.

Anand et al[13] investigated CH differences between eyes of patients with asymmetric glaucoma. In their study, the worse eyes were associated with a lower mean CH, but asymmetry in CH was not correlated with asymmetric glaucoma. However, their study did not evaluate the effect of CH asymmetry on rates of visual field progression longitudinally, as done in our study. Our results give further support for the overall understanding that differences in corneal biomechanics may have a different effect on the severity of glaucoma over time, even if in eyes of the same patient.

TABLE 2. Pearson Correlation Coefficients Between the Log of Asymmetry in Standard Automated Perimetry MD Rates of Change and the Asymmetry in Other Clinical Characteristics

Characteristics	Correlation (*r*)	*P*
Corneal hysteresis difference (mm Hg)	0.22	0.01
Central corneal thickness difference (μm)	−0.05	0.57
Age (y)	0.14	0.12
Mean IOP difference (mm Hg)	−0.13	0.15
Peak IOP difference (mm Hg)	−0.16	0.07
Baseline MD difference (dB)	−0.09	0.32

IOP indicates intraocular pressure; MD, mean deviation.

There are a several reasons why CH has been hypothesized to be related to risk of glaucoma progression. The viscoelastic properties of the cornea may be an indirect indicator of the viscoelastic properties of the posterior segment of the eye, such as lamina cribrosa and peripapillary sclera. It is likely that the connective tissues of the anterior and posterior structures of the eye share similar properties and therefore similar response to IOP peaks and fluctuations.[14,15] In an experimental study, Wells et al[16] found a significant association between CH and mean cup depth in individuals with glaucoma, showing that this biomechanical property may be related with the susceptibility of IOP-induced damage to the optic nerve in glaucoma patients. Moreover, CH has been pointed as a risk factor for glaucoma progression; in a longitudinal study, Medeiros et al[9] found that eyes with lower CH measurements tended to progress significantly faster than eyes with higher CH levels. They also found an interaction between IOP and CH suggesting that the effect of IOP on rates of glaucoma progression may be dependent on CH levels.

Of note, we found no significant correlation between interocular CCT asymmetry and asymmetry in rates of visual progression and ($r = -0.05$, $P = 0.57$). Our results are in agreement with previous studies suggesting that CH measurements are more closely related with ocular biomechanics than CCT[16] and, therefore, may be more

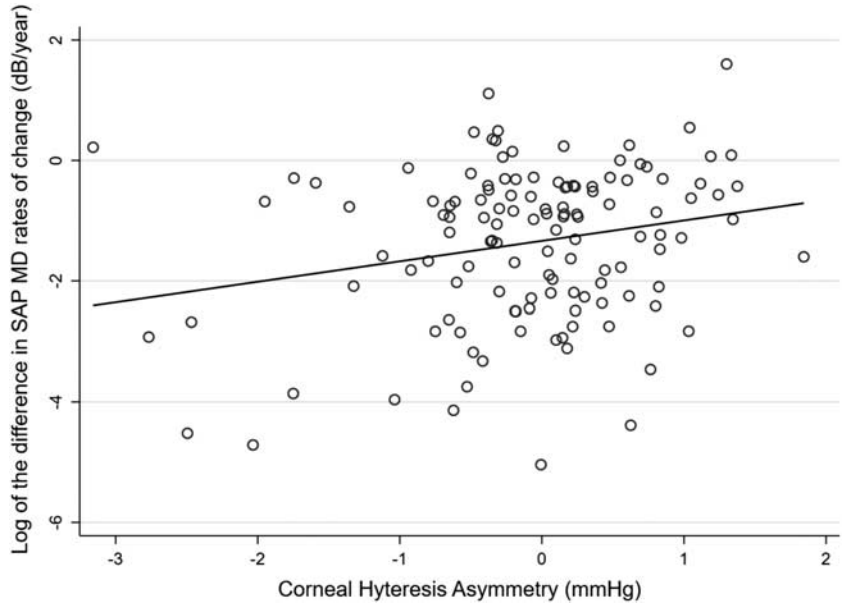

FIGURE 3. Scatterplot illustrating the relationship between asymmetry in rates of change of standard automated perimetry (SAP) mean deviation (MD) and asymmetry in corneal hysteresis. Differences are calculated by subtracting the value of the worse eye from the better eye.

correlated with glaucoma progression. Congdon et al[17] in a retrospective study found that CH measurements were associated with glaucoma progression, but not CCT. In a longitudinal study, Zhang et al[8] found lower CH but not CCT to be associated with faster retinal nerve fiber layer loss over time, suggesting that CH measurements at baseline may be of a greater value than baseline CCT in determining risk of glaucoma progression.

Our study had limitations. Progression was assessed solely based on trend-based analysis of MD rates of change. This could have missed subtle, localized progression. However, a recent study has shown that trend-based analysis of MD performs very similarly to other more sophisticated methods for analysis of visual field progression, such as the Guided Progression Analysis, when matched for specificity.[18] Another limitation was that no treatment protocol was established to set IOP targets and patients were treated at the discretion of the clinician. It is likely that different management strategies would have influenced the progression rates, however, this would in general be translated into differences in the measured rates of change. Notwithstanding, this may have influenced the impact of certain parameters on risk of progression, as discussed above. In addition, previous studies have suggested potential effects of treatment on CH measurements, although these seem to be of relatively small magnitude.[19,20] Of note, the IOP parameters used in our study were based on single daytime measurements taken during office hours from a limited number of visits. This may have precluded a more comprehensive assessment of the impact of asymmetry of IOP on the asymmetry in progression. Finally, CH was measured once, at baseline. Although it is possible that CH might vary over time,[21] the long-term reproducibility of CH and its potential effect on progression are yet to be determined.

In conclusion, our study showed that asymmetries in CH between eyes of a glaucoma patient were correlated with asymmetries in visual field rates of change. Our findings confirm that assessment of corneal biomechanical properties provides valuable information for the management of glaucoma and give further support for the role of CH as a risk factor for glaucoma progression.

TABLE 3. Univariable and Multivariable Analyses Assessing the Effect of Different Clinical Characteristics on the Asymmetry in Rates of Change on Standard Automated Perimetry MD (Logarithmic Transformation)

	Univariable Models		Multivariable Model	
Variables	**Coefficient (95% CI)**	***P***	**Coefficient (95% CI)**	***P***
Corneal hysteresis difference (each 1 mm Hg)	0.339 (0.080-0.599)	0.01	0.29 (0.026-0.056)	0.032
Central corneal thickness difference (each 10 μm)	−0.004 (−0.019 to 0.010)	0.57	−0.021 (−0.171 to 0.129)	0.78
Age (each 1 y older)	0.016 (−0.004 to 0.036)	0.12	0.016 (−0.004 to 0.037)	0.112
Race (African American)	−0.023 (−0.481 to 0.435)	0.92	0.101 (−0.366 to 0.568)	0.669
Mean IOP difference (each 1 mm Hg)	−0.076 (−0.181 to 0.029)	0.15	−0.051 (−0.157 to 0.055)	0.347
Peak IOP difference (each 1 mm Hg)	−0.05 (−0.115 to 0.004)	0.07	—	—
Baseline MD difference (each 1 dB)	−0.02 (−0.062 to 0.021)	0.32	−0.013 (−0.055 to 0.028)	0.520

CI indicates confidence interval; IOP, intraocular pressure; MD, mean deviation.

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