

Association between Corneal Biomechanical Properties with Ocular Response Analyzer and Also CorvisST Tonometry, and Glaucomatous Visual Field Severity

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Purpose: To investigate the association between corneal biomechanical properties measured with the Ocular Response Analyzer (ORA) and also CorvisST (CST) tonometry, and glaucomatous visual field (VF) severity.

Methods: One hundred forty-six eyes of 91 patients with primary open-angle glaucoma who performed Humphrey Field Analyzer 30-2 or 24-2 SITA-Standard, ORA, and CST within 180 days were included in this multicenter, observational cross-sectional study. The association between ORA parameters (corneal hysteresis [CH] and corneal resistant factor [CRF]), CST parameters (A1 and A2 time, A1 and A2 length, A1 and A2 velocity, A1 and A2 deformation amplitude, highest deformation amplitude, highest concavity time, peak distance, and radius), and other basic parameters (age, intraocular pressure with Goldmann applanation tonometry, central corneal thickness, and axial length) against mean total deviation (mTD) were analyzed using a linear mixed-model and model selection with corrected Akaike Information Criterion (AICc).

Results: The optimal model of VF severity included ORA's CH as well as a number of CST parameters, including A1 length, A2 time, radius, and highest concavity deformation amplitude (AICc: 971.7). The possibility this model describes visual field severity more accurately than the optimal model without CST parameters was 99.98%.

Conclusion: Glaucomatous VF severity was best described by both ORA and CST parameters. Eyes with corneas that experience sharp and deep indentation at the maximum deformation, wide indentation at the first applanation, and early second applanation in the CST measurement are more likely to show advanced VF severity.

Translational Relevance: CorvisST tonometry parameters are related to VF severity in glaucoma patients.

Introduction

Glaucomatous visual field (VF) damage is irreversible, so it is essential to predict its progression so that appropriate interventions are given as soon as possible. As confirmed by previous clinical trials and research studies,¹⁻⁹ glaucomatous VF damage progression can be halted by appropriately reducing intraocular pressure (IOP). The IOP measurement is usually carried out using Goldmann applanation tonometry (GAT) in glaucoma clinics worldwide,

however it is now widely acknowledged that GAT measurement can be affected by central corneal thickness (CCT),¹⁰⁻²² and also that CCT itself is related to the progression of glaucoma.^{3,23} Recent studies have revealed that corneal biomechanical properties are related to the progression of glaucoma: corneal hysteresis (CH) and/or corneal resistance factor (CRF) measured with the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Depew, NY; Lascaratos G, et al. *IOVS.* 2014;55:AR-VO E-Abstract A0221).²⁴ Mansouri et al.²⁵ have

reported CH and CRF, as well as CCT, are related to the severity of glaucomatous VF damage, but the relationships were weak.

ORA measures air jet pressure at the events of first and second applanations, however many other corneal biomechanical properties can be measured using a rapid air puff application with the novel Corneal Visualization Scheimpflug Technology instrument (CorvisST tonometry [CST]; Oculus, Wetzlar, Germany) in which detailed corneal movement is examined using the integrated ultra-high-speed Scheimpflug camera.²⁶ The velocity of corneal deformation at the first and second applanations and the maximum depth of corneal deformation due to the air jet is recorded by this camera (Fig.). Thus, glaucomatous VF severity may be better analyzed and understood using CST tonometry, however the relationship between CST-measured corneal parameters and the severity of glaucomatous VF damage has not been reported in our knowledge. Therefore, the purpose of the current study was to investigate the association between ORA- and CST-measured parameters, and the severity of glaucomatous VF damage in patients with open angle glaucoma (OAG).

Methods

The Research Ethics Committee of the Graduated School of Medicine and Faculty of Medicine at The University of Tokyo approved this multicenter, observational cross-sectional study. Written consent was given by patients for their information to be stored in the hospital database and used for research. This study was performed according to the tenets of the Declaration of Helsinki.

Subjects

A total of 146 eyes of 91 Japanese OAG patients were included in this study. The diagnosis of glaucoma was determined via a fundus examination using slit-lamp indirect ophthalmoscopy and 90-diopter (D) lens by glaucoma specialist and based on previous VF results. Primary open-angle glaucoma (POAG) was defined as (1) presence of typical glaucomatous changes in the optic nerve head such as a rim notch with a rim width of 0.1 disc diameters or a vertical cup-to-disc ratio of greater than 0.7, and/or a retinal nerve fiber layer defect with its edge at the optic nerve head margin greater than a major retinal vessel, diverging in an arcuate or wedge shape; and (2) gonioscopically wide-open angles of grade 3 or 4

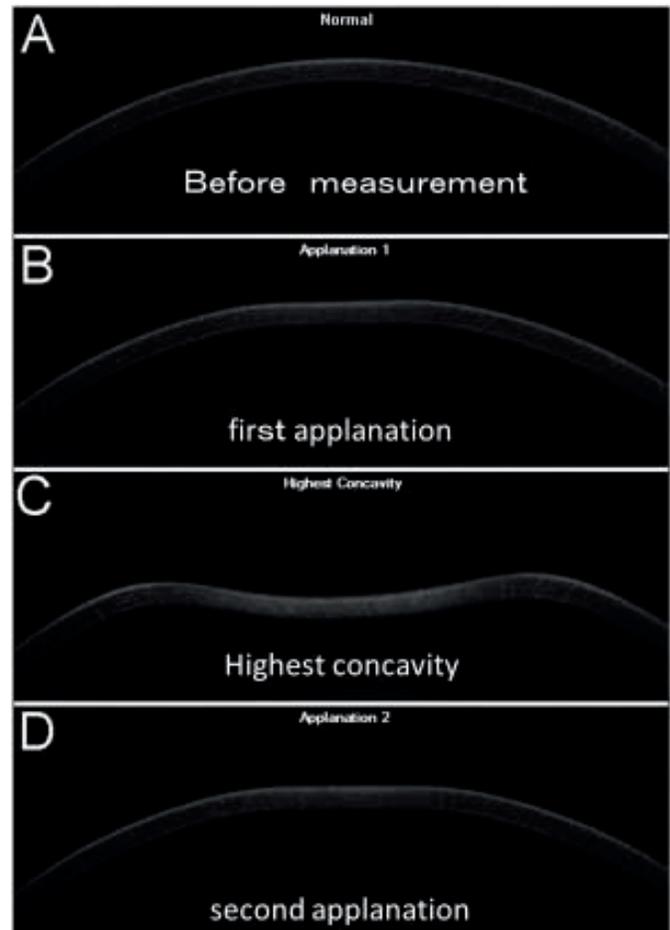


Figure. Corneal movement during the CST measurement. In the CST tonometry measurement, a rapid air puff is applied to cornea and cornea moves inward, whereas ORA measures air jet pressure at the events of first and second applanations. The figures show the corneal shape in each phase: (A) prior to air puff applanation, (B) first applanation, (C) highest concavity, (D) second applanation, and (E) posterior to air puff applanation.

based on the Shaffer classification. If patients showed structural glaucoma changes such as rim thinning, notching, and nerve fiber layer thinning or defects, and if they showed abnormal VF results corresponding with Anderson-Patella criteria,²⁷ patients were diagnosed as glaucoma. VF measured within 1 month from the ORA and CST measurements were used in the current analyses. All patients had reliable VF measurement with the Humphrey Field Analyzer II (HFA; Carl Zeiss Meditec Inc., Dublin, CA), with the 24-2 or 30-2 test point program with Swedish Interactive Threshold Algorithm Standard. Reliable VFs were defined as fixation loss rate less than 20% and false positive rate less than 15% following the

Table 1. Patient Demographics

Parameters	Mean \pm SD	Range
Male/female	51/40	
Right/left (eyes)	75/71	
Type of glaucoma (eyes)	NTG 81 POAG 65	
Age, y	62.4 \pm 10.8	34–85
Spherical equivalent, D	−2.91 \pm 3.29	−10.00–3.25
Visual acuity, LogMAR	−0.05 \pm 0.19	−1.08–1.00
Corneal power, D	43.74 \pm 1.33	41.00–46.50
GAT IOP, mm Hg	13.2 \pm 2.6	8–22
Axial length, mm	25.0 \pm 1.6	22.3–29.2
CCT, μ m	529.0 \pm 34.5	458.3–624.3
mTD, dB	−8.4 \pm 7.2	−26.7–3.0

criteria used in the HFA software; false negative was not used as an exclusion criterion.²⁸

Eyes with previous experience of any surgical procedure, including trabeculectomy and cataract surgery, were excluded. Inclusion criteria were no abnormal eye-related findings except for OAG on biomicroscopy, gonioscopy, and funduscopy. Eyes with a history of other ocular disease, such as age-related macular degeneration or diabetes mellitus were also excluded. Only subjects aged more than 20-years old were included. If both eyes satisfied the inclusion criteria, then both were included in the study. The details of patient demographic shown in Table 1.

ORA

ORA records two applanation pressure measurements, before and after the application of an air puff. Cornea resists the air puff because of the viscoelastic property, and this causes a measureable difference in two applanation pressures. This difference is called CH, while CRF represents an indicator of the overall ‘resistance’ of the cornea.²⁹

CorvisST Tonometer

The principles of CST are described in detail elsewhere.²⁶ In short, the instrument’s camera records a sequence of images (capable of capturing 4330 images per second) that capture corneal deformation due to the application of a rapid air puff (Fig.). More specifically, each measurement is detailed as follows: ‘A1 and A2 time’ is the length of time from the initiation of the air puff to the first and inward or second and outward applanations, respectively; ‘A1

and A2 length’ is the length of the flattened corneal surface at the first or second applanation, respectively; ‘A1 and A2 velocity’ is the velocity of the movement of cornea apex during the first or second applanation, respectively; ‘A1 and A2 deformation amplitude’ is the magnitude of the movement of the corneal apex at the first or second applanation, respectively; ‘peak distance’ is the distance between the two surrounding peaks of the cornea at the highest concavity; ‘highest concavity deformation amplitude’ is the magnitude of movement of the corneal apex from before deformation to the highest concavity, ‘highest concavity time’ is the duration taken to reach highest concavity from predeformation of the cornea; and ‘radius’ is the central curvature radius at the highest concavity.

Measurement

Both ORA and CST were carried out three times on the same day in a random order with researchers (MM or YN), but prior to the GAT-IOP measurement because oxybuprocaine hydrochloride and fluorescein were used in the GAT-IOP measurement. All ORA data had the quality index greater than 7.5, which guarantees sufficient quality. All of the CST measurements were considered reliable according to the “OK” quality index displayed on the CST device monitor. Three measurements with ORA and CST (software version, 1.2r1092; Oculus, Wetzlar, Germany) were performed with at least a 1-minute interval between each repeat measurement of ORA and CST, and the averages of ORA and CST parameters were calculated. CCT was derived from the CST measurement.

The mean total deviation (mTD) of the 52 test points in the 24-2 HFA VF test pattern was calculated. Axial length (AL) was measured in all patients using the IOL Master, ver. 5.02 (Carl Zeiss Meditec). All of the measurements were performed within the period of 180 days.

Statistical Analysis

The association between ORA (CH and CRF), CST parameters (A1 and A2 time, A1 and A2 length, A1 and A2 velocity, A1 and A2 deformation amplitude, highest deformation amplitude, highest concavity time, peak distance, and radius), and other parameters (age, GAT-IOP, CCT, and AL) against mTD was analyzed using a linear mixed-model in which patient was a random effect (because one or two eyes of a patient were included). The linear

Table 2. ORA and CST Parameters

Parameters	Mean \pm SD	Range
ORA		
CH, mm Hg	9.1 \pm 1.1	6.5–11.7
CRF, mm Hg	8.4 \pm 1.5	4.9–13.2
CST		
A1 time, ms	7.2 \pm 0.3	6.5–8.4
A1 length, mm	1.7 \pm 0.1	1.4–1.8
A1 velocity, m/s	0.16 \pm 0.01	0.10–0.20
A1 deformation amplitude, mm	0.12 \pm 0.01	0.11–0.16
A2 time, ms	21.9 \pm 0.4	20.9–23.2
A2 length, mm	1.6 \pm 0.2	0.83–2.3
A2 velocity, m/s	–0.39 \pm 0.08	–0.64 to –0.16
A2 deformation amplitude, mm	0.41 \pm 0.07	0.25–0.57
Highest deformation amplitude, mm	1.1 \pm 0.1	0.8–1.3
Highest concavity time, ms	16.9 \pm 0.6	15.0–18.4
Peak distance, mm	3.4 \pm 0.9	2.1–5.5
Radius, mm	7.5 \pm 0.8	5.7–10.3

mixed-model is similar to ordinary linear regression in that the model describes the relationship between the predictor variables and a single outcome variable. However, standard linear regression analysis is based on the assumption that all samples are independent of each other. In the current study, measurements (1 or 2 eyes) were nested within patients and, thus, not independent of each other. Ignoring this grouping of the measurements will lead to the underestimation of standard errors of regression coefficients. The linear mixed-model adjusts for the hierarchical structure of the data, modeling in a way in which measurements are grouped within subjects. The optimal linear mixed-model (model_{basic}) to describe mTD using ocular and systemic parameters (age, GAT-IOP, CCT, and AL) was selected according to the second order bias corrected Akaike Information Criterion (AICc) index. Three further models were selected adding only ORA parameters, only CST parameters and also both ORA and CST parameters (model_{ORA}, model_{CST}, and model_{ORA_CST}, respectively). The AIC is the common statistical measure with which optimal variables can be determined without having an overfit problem, unlike the coefficient of determination.³⁰ In addition, there is no established method to determine if correlation coefficient can be applied to linear mixed-model, and hence model selection with AIC was used in the current study.³⁰ AICc gives an accurate estimation even when the sample size is small.³¹ It is recommended to use model selection methods, instead of multivariate regression, to

improve the model fit by removing redundant variable, because the degrees of freedom decreases as the number of variables increases.^{32,33} Any magnitude of reduction in AICc is suggestive of the improvement of the model, but the probability that one particular model is the model that minimizes ‘information loss’ is calculated as: when there are n candidate models and the AICc values of those models are AIC₁, AIC₂, AIC₃, ..., AIC _{n} . For AIC_{min} the minimum of these values, $\exp[(AIC_{min} - AIC_i)/2]$ describes the relative probability that the i th model minimizes the information loss (i.e., is the ‘optimal model’).³⁴ All statistical analyses were performed using the statistical programming language ‘R’ (R version 3.2.3; The foundation for Statistical Computing, Vienna, Austria).

Results

Summary statistics of ORA and CST measurements are shown in Table 2. None of ORA and CST parameters were significantly different between the NTG and POAG groups ($P > 0.05$, linear mixed-model). The relationship between age and CST and ORA parameters are shown in Table 3. There was no significant correlation between age and CST and ORA parameters. Also, there was no significant difference in age, mTD, CCT, and AL between the two groups ($P > 0.05$, linear mixed-model).

The modeled relationships between mTD and basic parameter including age, GAT, CCT, AL, ORA, and

Table 3. The Relationship between Age and CST and ORA Parameters (All Parameters Were Analyzed Separately)

Parameters	Coefficient	SE	P value
ORA			
CH, mm Hg	-0.000082	0.0089	0.99
CRF, mm Hg	-0.0019	0.012	0.87
CST			
A1 time, ms	0.00099	0.0022	0.65
A1 length, mm	0.00044	0.00054	0.41
A1 velocity, m/s	-0.000087	0.00010	0.41
A1 deformation amplitude, mm	-0.0000062	0.000065	0.92
A2 time, ms	-0.0026	0.0035	0.45
A2 length, mm	0.0025	0.0019	0.20
A2 velocity, m/s	0.00031	0.00064	0.63
A2 deformation amplitude, mm	-0.00032	0.00056	0.56
Highest deformation amplitude, mm	-0.00053	0.00083	0.52
Highest concavity time, ms	0.0050	0.0047	0.29
Peak distance, mm	-0.0043	0.0071	0.55
Radius, mm	0.0089	0.0066	0.18

CST parameters are shown in Table 4. A significant relationship was observed for CH ($P = 0.002$, linear mixed-model), CRF ($P = 0.002$), A1 time ($P = 0.003$), A1 velocity ($P = 0.003$), A2 velocity ($P < 0.001$), highest deformation amplitude ($P < 0.001$), and radius ($P < 0.001$). There was no significant relationship in basic parameter including age, GAT, CCT, and AL.

The equation for model_{basic} was: $mTD = -23.7 + 0.029 \times CCT$ (AICc = 997.6); thus all other variables (age, GAT IOP, AL) were not deemed to improve the model. The equation for model_{ORA} was: $mTD = -23.7 + 1.70 \times CH$ (AICc = 990.1). The equation for model_{CST} was: $mTD = -94.3 - 14.8 \times A1 \text{ length} - 98.3 \times A1 \text{ velocity} + 6.4 \times A2 \text{ time} + 1.9 \times \text{Radius} - 24.4 \times \text{highest concavity deformation amplitude}$ (AICc = 972.5). The equation for model_{ORA_CST} was: $mTD = -79.7 - 15.6 \times A1 \text{ length} + 4.9 \times A2 \text{ time} + 1.7 \times \text{radius} - 27.5 \times \text{highest concavity deformation amplitude} + 1.0 \times CH$ (AICc = 971.7).

The probability that model_{ORA} minimizes information loss compared with model_{basic} was 98.8%. The probability that model_{CST} minimizes information loss compared with model_{ORA} was 99.97%. The probability that model_{ORA_CST} minimizes information loss compared with model_{CST} was 33.0%.

Discussion

In the current study, CST and ORA measurements were carried out in 146 eyes of 91 patients with OAG.

In models describing the severity of VF damage (mTD), the inclusion of ORA parameters resulted in the more favorable model compared with when only age, GAT-IOP, CCT, and AL were used. Further improvement was observed by adding CST parameters. The final optimal model (model_{ORA_CST}) included $-15.6 \times A1 \text{ length}$ (larger length is associated with more pronounced damage) + $4.9 \times A2 \text{ time}$ (shorter A2 time is associated with severe damage) + $1.7 \times \text{radius}$ (smaller radius is associated with severe damage) - $27.5 \times \text{highest concavity deformation amplitude}$ (deeper highest concavity deformation amplitude is associated with severe damage) + $1.0 \times CH$ (smaller CH is associated to severe damage).

There are many previous studies that analyzed ORA parameters in glaucoma.³⁵⁻³⁹ The reported CH and CRF values varied among these studies. Previous studies have reported that CH was 7.7 to 10.0 and CRF was 7.8 to 11.2 in POAG³⁶⁻³⁸ or NTG,³⁷⁻³⁹ whereas CH have been reported as between 9.5 to 11.1 and reported CRF values were between 9.2 to 11.0 in normal control.^{37,38} In the current study, mean ORA CH and CRF values were 9.1 and 8.4, respectively, which are within the range of these reports with POAG. To the best of our knowledge, this is the first report suggesting the CST parameter values in POAG patients.

There is no doubt that high IOP is a risk factor of the progression of glaucoma, despite its undoubted influence on VF progression,^{1,2,40-42} however, mod-

Table 4. The Relationship between mTD and CST, ORA, and Basic Parameters (All Parameters Were Analyzed Separately)

Parameters	Coefficient	SE	P value	AICc
ORA				
CH, mm Hg	1.70	0.52	0.002	990.1
CRF, mm Hg	1.25	0.39	0.002	990.3
CST				
A1 time, ms	6.40	2.10	0.003	991.7
A1 length, mm	-7.70	8.90	0.390	999.6
A1 velocity, m/s	-136.8	44.4	0.003	991.0
A1 deformation amplitude, mm	126.5	73.5	0.090	997.6
A2 time, ms	-0.15	1.40	0.910	1000.3
A2 length, mm	3.1	2.5	0.210	998.9
A2 velocity, m/s	26.30	7.20	<0.001	987.2
A2 deformation amplitude, mm	-3.7	8.6	0.670	1000.2
Highest deformation amplitude, mm	-19.50	5.60	<0.001	988.7
Highest concavity time, ms	1.9	1.0	0.065	996.8
Peak distance, mm	-0.82	0.67	0.220	998.9
Radius, mm	2.90	0.68	<0.001	982.9
Basic parameter				
Age, y	0.0039	0.0057	0.490	999.9
GAT IOP, mm Hg	-0.05	0.23	0.830	1000.3
CCT, mm	0.029	0.017	0.095	997.6
Axial length, mm	0.094	0.370	0.800	1000.3

Bold characters represent $P < 0.05$.

el_{basic} did not include GAT-IOP. The current study analyzed clinical data from an actual glaucoma clinic, and hence the measured IOP is the value after intervention. On the contrary, CCT was included in the $model_{\text{basic}}$. This implies eyes with thin CCT are associated with severity of glaucomatous VF damage, agreeing with previous reports.^{3,23} Importantly, recent studies have reported that CH is a greater risk factor for the progression of glaucoma than CCT (Lascartos G, et al. *IOVS*. 2014;55:ARVO E-Abstract A0221) and our current results also showed severity of glaucoma can be better described using CH than CCT, as shown in $model_{\text{ORA}}$. The reason the eyes with low CH is a risk factor for the advancement of glaucoma is not entirely clear, but it may be because the eye is deformed and possibly associated with IOP change in daily life, such as postural change,⁴³ eye lid blinking,⁴⁴ ocular pulsatility due to ocular hemodynamics,⁴⁵ Valsalva maneuver,⁴⁶ and also eye movement.⁴⁷ An eye with high hysteresis is more likely to absorb these external strains, which would be advantageous to prevent retinal nerve fiber damage at the optic nerve and also retinal ganglion cell

damage. A further study is needed be carried out shedding light on the relationship between these eye deformation and hysteresis of cornea using both ORA and CST.

Age is an independent risk factor of the progression of glaucoma,^{3,48-50} however age was not included in any optimal models in the current study. As the current study is a cross-sectional observation, the stage of glaucoma at the initiation of treatment and also the duration from the initiation of the treatment are variable among eyes. Different results could be observed when the effect of age on the glaucomatous VF severity, not cross-sectional severity of VF damage, is investigated. CH and CST parameters are related to age; more specifically, CH decreases as age increases⁵¹ and CST-derived highest deformation amplitude increases as age increases.⁵² Nonetheless age was not included in all of $model_{\text{ORA}}$, $model_{\text{CST}}$, $model_{\text{ORA_CST}}$. Thus, CH and CST parameters included in $model_{\text{CST}}$ or $model_{\text{ORA_CST}}$ are risk factors for the severity of glaucoma, independent from age.

Both of the ORA parameters of CH and CRF were associated with the severity of glaucoma (see Table 3).

However, the AICc of model_{CST} was significantly smaller than the AICc of model_{ORA} (according to their AICc values, model_{CST} is deemed to be the better model with a probability of 99.97%), and also model_{ORA_CST} obtained further decrease of AICc. Thus, it may be advantageous to use CST, ideally in addition to ORA, to better interpret VF severity/progression in glaucoma patients.

The model_{CST} and model_{ORA_CST} suggest that eyes with corneas experiencing a deep indentation following the CST air-puff are likely to have a severe glaucoma. The hysteresis or the viscoelastic property of cornea is identical to the amount of energy absorption during the 'loading/unloading' stress/strain cycle and the magnitude of the energy absorption can be calculated as the area surrounded by the loading and unloading curves.⁵³ Importantly, a deeper highest deformation amplitude indicates the change of shape of the loading/unloading curves is large. Eyes with high IOP would have shallower highest deformation amplitude (same magnitude of air-puff is applied in the CST measurement), because high IOP serves to help resisting to the indentation of cornea. This would further suggest this CST parameter is a risk factor for the severity of glaucoma, independent from IOP. Interestingly, eyes with smaller radius tended to have severe VF damage, as shown in model_{CST} and model_{ORA_CST}. This implies that eyes with deep and sharp indentation of cornea at the maximum deformation are likely to have more severe glaucomatous VF damage. The model_{CST} suggests that eyes with fast A1 velocity are related to more severe glaucomatous VF damage. Also, shorter A2 time is related to severe VF damage (model_{CST} and model_{ORA_CST}). The fast A1 velocity would suggest the 'energy absorption' was poor and whole amount of air puff forced cornea to indent. Shorter A2 time may be related to early 'energy absorption' phase termination.

A limitation of the current study is that we could not control for the influence of antiglaucomatous eye drops on corneal biomechanical properties.^{54–57} As all participants were recruited from real world glaucoma clinic this could not be avoided, but it could have a nonnegligible effect on the study findings. Nonetheless, all of the CST and ORA parameter values were not significantly different between those with and without these eye drops ($P > 0.05$, linear mixed-model), and hence the influence of these eye drops would be negligible (125 eyes of 79 patients were taking prostaglandins, 80 eyes of 53 patients were taking beta blockers, and 63 eyes of 42 patients were taking

carbonic anhydrase inhibitors; not shown in the Results). Also, a further study should be carried out in the future to investigate the relationship between the progression rate of glaucomatous VF damage and CST parameters.

In conclusion, CST tonometry parameters were associated with the severity of glaucomatous VF change. Assessing detailed biomechanical properties of cornea using the CST tonometry, in addition to ORA, resulted in better description of the severity of VF damage.

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