Original Article

Corneal Biomechanical Parameters and Asymmetric Visual Field Damage in Patients with Untreated Normal Tension Glaucoma

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Abstract

Background: High intraocular pressure (IOP) and low central corneal thickness (CCT) are important validated risk factors for glaucoma, and some studies also have suggested that eyes with more deformable corneas may be in higher risk of the development and worsening of glaucoma. In the present study, we aimed to evaluate the association between corneal biomechanical parameters and asymmetric visual field (VF) damage using a Corvis-ST device in patients with untreated normal tension glaucoma (NTG).
Methods: In this observational, cross-sectional study, 44 newly diagnosed NTG patients were enrolled. Of these, 31 had asymmetric VF damage, which was defined as a 5-point difference between the eyes according to the Advanced Glaucoma Intervention Study scoring system. Corneal biomechanical parameters were obtained using a Corvis-ST device, such as time from start until the first and second applanation is reached (time A1 and time A2, respectively), cord length of the first and second applanation (length A1 and length A2, respectively), corneal speed during the first and second applanation (velocity A1 and velocity A2, respectively), time from start until highest concavity is reached (time HC), maximum amplitude at the apex of highest concavity (def ampl HC), distance between the two peaks at highest concavity (peak dist HC), and central concave curvature at its highest concavity (radius HC).
Results: Time A1 (7.19 ± 0.28 vs. 7.37 ± 0.41 ms, $P = 0.010$), length A1 (1.73 [1.70–1.76] vs. 1.78 [1.76–1.79] mm, $P = 0.007$), length A2 (1.58 [1.46–1.70] vs. 1.84 [1.76–1.92] mm, $P < 0.001$), peak dist HC (3.53 [3.08–4.00] vs. 4.33 [3.92–4.74] mm, $P = 0.010$), and radius HC (6.20 ± 0.69 vs. 6.59 ± 1.18 mm, $P = 0.032$) were significantly lower in the worse eyes than in the better eyes, whereas velocity A1 and def ampl HC were significantly higher (0.156 [0.149–0.163] vs. 0.145 [0.138–0.152] m/s, $P = 0.002$ and 1.19 ± 0.13 vs. 1.15 ± 0.13 mm, $P = 0.005$, respectively). There was no significant difference in time A2, velocity A2, and time HC between the two groups. In addition, no difference was observed in IOP, CCT, and axial length. In the univariate and multivariate analyses, some of the Corvis-ST parameters, including time A1 and def ampl HC, were correlated with known risk factors for glaucoma, and there was also a significant positive correlation between def ampl HC and age.
Conclusions: There were differences in dynamic corneal response parameters but not IOP or CCT between the paired eyes of NTG patients with asymmetric VF damage. We suggest that the shape of the cornea is more easily altered in the worse eyes of asymmetric NTG patients.

Key words: Asymmetric Visual Field Damage; Corneal Biomechanical Parameters; Corvis-ST; Normal Tension Glaucoma; Untreated

Introduction

Glaucomatous disease is characterized by the progressive damage of the optic nerve and is associated with visual field (VF) damage. Patients with normal tension glaucoma (NTG) often display asymmetric VF damage, and the percentage of patients with unilateral VF damage has been estimated to be approximately 25%.[1] Previous studies have attempted to explain this asymmetry, although

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some of these studies have found an association between asymmetric intraocular pressure (IOP) and asymmetric VF.[1,2] Greenfield *et al*.[3] found, in a randomized controlled study, no relationship between VF asymmetry and mean, peak, and trough IOP in NTG patients. One research team first found in a retrospective study that asymmetric central corneal thickness (CCT) was associated with asymmetric primary open-angle glaucoma (POAG),[4] and then the same research team drew the opposite conclusion in a later study.[5] Many studies have recently focused on other potential risk determinants for glaucoma, including corneal biomechanical parameters.

Some studies have suggested that eyes with more malleable corneas may be more at risk for the development and worsening of glaucoma.[6] The Ocular Response Analyzer (ORA; Reichert, Inc., Depew, NY, USA) is the first device designed to measure corneal biomechanics *in vivo*. This device is used to measure the following two dynamic corneal response parameters: Corneal hysteresis (CH) and corneal resistance factor (CRF). There is substantial evidence showing that low CH is an independent risk factor for glaucoma, while low CH has been associated with VF progression.[6]

More recently, a new noncontact tonometer, the Corvis-ST (Oculus, Wetzlar, Germany), has been used in clinics. The Corvis-ST is an automated air-puff tonometer that takes advantage of ultra-high-speed Scheimpflug technology and provides information about corneal biomechanical parameters. The Corvis-ST Scheimpflug imaging system allows more accurate registration of the corneal deformation process than ORA by defining the corneal deformation amplitude and other nine parameters.

In our study, we compared corneal biomechanical parameters between the paired eyes of untreated NTG patients with asymmetric VF. All parameters were acquired using the Corvis-ST. We sought to evaluate the association between Corvis-ST parameters and asymmetric VF damage in NTG patients. The correlations between Corvis-ST parameters and risk factors for glaucoma were also assessed.

Methods

This was an observational, prospective, cross-sectional study. A total of 44 patients were enrolled in this study. They were recruited from patients who were newly diagnosed with bilateral NTG at the Glaucoma Department of Ophthalmology at Peking University First Hospital between May 2016 and October 2016. The Review Board of Peking University First Hospital approved the study protocol, and the study was conducted in full accordance with the tenets of the *Declaration of Helsinki*. Informed patient consent was obtained before the study commenced.

The diagnostic criteria used for NTG were the following: Presents glaucomatous optic neuropathy and VF defects without IOP elevation (including a 24-h IOP curve under 21 mmHg) but with open angles. IOP was measured using Goldmann applanation tonometry (GAT).

The inclusion criteria were corneal astigmatism <3 D, refractive error between − 6 and + 3 D, and anisometropia <2 D. The exclusion criteria were best-corrected visual acuity <20/40, previous intraocular surgery within 3 months and any keratorefractive surgery, corneal scarring, inflammatory eye disease, ocular trauma, and systemic disease conditions with a known or anticipated effect on dynamic corneal response parameter measurement, including diabetes mellitus.

We used a Humphrey Field Analyzer to measure perimetry (24-2 SITA standard, Humphrey Field Analyzer model 750, Carl Zeiss Meditec, Dublin, CA, USA). Perimetry was measured at least twice to diagnose NTG and determine the baseline level of VF damage. We selected the second or third reliable test result. A reliable VF analysis was considered to be <15% fixation loss and <15% false positive or false negative. Each VF was scored using the Advanced Glaucoma Intervention Study (AGIS) II numeric scoring system. When patients' AGIS scores appeared to be equal between both eyes (defined as a difference in AGIS scores of four or less between paired eyes), they were excluded from this study.

The Corvis-ST (Oculus, Wetzlar, Germany) device applies an air impulse to the corneal apex. The corneal deformation process was recorded using a high-speed Scheimpflug camera, which records 4330 frames per second and covers 8.5 mm of the central cornea. For each measurement, the camera collects a sequence of 140 images of the cornea over 30 ms. The outputs of the Corvis-ST are as follows: Time from start until the first and second applanation is reached (time A1 and time A2, respectively), cord length of the first and second applanation (length A1 and length A2, respectively), corneal speed during the first and second applanation (velocity A1 and velocity A2, respectively), time from start until highest concavity is reached (time HC), maximum amplitude at the apex of highest concavity (def ampl HC), distance between the two peaks at highest concavity (peak dist HC), central concave curvature at its highest concavity (radius HC), IOP, and CCT. IOP measurements were based on the first applanation, and CCT measurements were based on the sectional corneal images that were taken before the influence of the air puff.

Although the Corvis-ST can measure IOP (Corvis IOP), we also used GAT to measure IOP. GAT was performed using a BQ 900 slit-lamp (Haag Streit International, Koniz-Bern, Switzerland) under local anesthetic (0.4% benoxinate hydrochloride) and with fluorescein sodium 2% strips. To reduce the impact of the anesthetic drops on Corvis-ST measurements, in all patients, Corvis-ST measurements were obtained before GAT measurements. Three readings were obtained with each instrument, and the mean of the three readings was used for comparisons.

AGIS scores were compared between the two eyes of each patient, and all eyes were classified into two groups: The eye with the greater AGIS score (the worse eye) and the eye with the lower AGIS score (the better eye). Measurement data were presented as mean ± standard deviation or median

(Q_{25}–Q_{75}). All data were analyzed using statistical software (SPSS version 16.0; SPSS Inc., Chicago, IL, USA). Student's paired *t*-test and Wilcoxon signed-rank test were used to assess differences in IOP, CCT, AGIS, and the corneal biomechanical parameters obtained using the Corvis-ST between the two groups. Univariate and multivariate linear regression models were used to evaluate the relationship between dynamic corneal response parameters (in both worse eyes and better eyes) and known glaucoma risk factors, including age, IOP, and CCT. $P < 0.05$ was considered statistically significant.

Results

We enrolled 44 patients (median age, 61.4 ± 12.2 years) with NTG. Based on the study definition, 31 (70.5%) patients had asymmetric VF defects. A larger proportion of the patients were women (21, 67.7%), and there were ten men (32.3%).

The mean IOP that was obtained using GAT was similar between the two groups (worse eye: 14.77 [13.82–15.73] mmHg, better eye: 14.87 [13.87–15.87] mmHg; $P = 0.403$). Only nine (29.0%) worse eyes had a higher IOP than their paired better eyes, whereas in 12 patients, IOP was equal in both eyes. Although twenty (64.5%) worse eyes had a thinner CCT, no significant difference was found between the two groups (worse eye: 525.29 ± 38.82 μm, better eye: 526.94 ± 37.33 μm; $P = 0.369$). In paired eyes, the AGIS score of the VF was significantly different (worse eye: 9.45 [8.24–10.66], better eye: 3.58 [2.14–5.02]; $P < 0.001$). Worse eyes were associated with a lower time A1, length A1, length A2, peak dist HC and radius HC, and a higher velocity A1 and def ampl HC. There was no asymmetry between the worse and the better eyes in time A2, velocity A2, and time HC. The clinical and dynamic corneal response parameters in the worse and better eyes of the study patients are shown in Table 1.

The ten included biomechanical variables were assessed with regard to their correlations with known risk factors[7] for glaucoma [Table 2]. Def ampl HC had strong correlations with age and IOP in both eyes ($r = 0.673$, 0.624, 0.702, and 0.692; all $P < 0.05$). Similarly, time A1 was strongly correlated with IOP ($r = 0.776$ and 0.689, all $P < 0.05$) in both eyes but only moderately correlated with age and CCT ($r = 0.417$, 0.360, 0.386, and 0.145; all $P < 0.05$). In contrast, there were no correlations between length A2 and the three analyzed risk factors, and the correlations between time HC and these risk factors were also weak. In line with these results, our analysis using a multiple linear regression model also demonstrated that length A1, time A2, and time HC were independent (all $P > 0.05$ for the three variables) of age, IOP, and CCT. The correlation coefficients and *P* values are shown in Table 3. Notably, a positive correlation was found between def ampl HC and age [$r^2 = 0.4081$, $P < 0.001$, Figure 1].

Discussion

The relationship between corneal biomechanical parameters and glaucoma has attracted an increasing amount of attention. Previous studies have shown that there are differences in corneal biomechanical characteristics between glaucoma and nonglaucoma patients.[7-10] The characteristics of the cornea, such as CH and CRF, may reflect, to some extent, the deformability of the sclera and lamina cribrosa, and this may, in turn, demonstrate the capacity of the optic nerve to endure the harm caused by glaucoma.[11] Past studies that have explored this relationship have mainly been based on the use of ORA. While studies that use the Corvis-ST provide us with access to more direct parameters with more details, no previous studies on the corneal biochemical characteristics of the NTG with two asymmetric eyes have used Corvis-ST.

In this study, we found that in patients who had only recently developed NTG with asymmetric VF, it takes less time for the cornea of the worse eye to first take on a flattened state after it has been exposed to outer airflow with a greater velocity and that the corneas of these eyes have a smaller flattened horizontal section length. This indicates that eyes with a worse VF are quicker to reach first-degree applanation. When the shape of the cornea changes to its largest extent, the maximum deformation extent of the worse eye is more extreme than that of the better eye, the distance between the two peaks is smaller at its highest concavity, and its central concave curvature is smaller. This translates into a larger deformation in the cornea of the worse eye when it is influenced by an outer force. The above-described deformation parameters of the cornea directly demonstrate that in patients with asymmetric NTG, the worse eye is the one with a larger degree of corneal deformability. Anand *et al*.[12] used ORA to study POAG patients whose eyes have asymmetrical VF and determined that their worse eyes had a smaller CH and that this made the cornea less able to absorb energy from the outside. The unabsorbed energy then exerts an effect on the eyeball that leads to the development of glaucoma.[13] In our study, we described a more direct understanding, with more details, regarding how this deformation of the cornea occurs. When exposed to airflow, the cornea of the worse eye exhibits a larger degree of displacement and a higher displacement velocity during

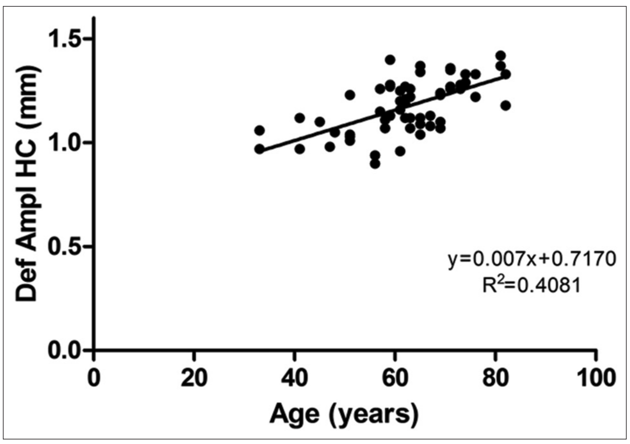

Figure 1: The correlation between the def ampl HC and age in patients with normal tension glaucoma ($n = 62$ eyes). Def ampl HC: Maximum amplitude at the apex of highest concavity.

Table 1: Interocular comparison of clinical data, visual fields, and Corvis-ST metrics in patients with asymmetric NTG

Items	Worse eye (n = 31 eyes)	Better eye (n = 31 eyes)	Statistics	P
Clinical data				
IOP (mmHg)	14.77 (13.82–15.73)	14.87 (13.07–15.87)	−0.835*	0.403
Corvis IOP (mmHg)	12.37 (11.28–13.67)	12.66 (11.40–13.93)	−0.824*	0.410
CCT (μm)	525.29 ± 38.82	526.94 ± 37.33	−0.912†	0.369
Axial length (mm)	23.72 ± 1.36	23.81 ± 1.43	−1.061†	0.052
AGIS score	9.45 (8.24–10.66)	3.58 (2.14–5.02)	10.787†	<0.001
Corvis-ST parameters				
Time A1 (ms)	7.19 ± 0.28	7.37 ± 0.41	−2.738†	0.010‡
Length A1 (mm)	1.73 (1.70–1.76)	1.78 (1.76–1.79)	−2.811†	0.007‡
Velocity A1 (m/s)	0.156 (0.149–0.163)	0.145 (0.138–0.152)	3.309†	0.002‡
Time A2 (ms)	21.85 ± 0.48	21.03 ± 3.89	1.167†	0.248‡
Length A2 (mm)	1.58 (1.46–1.70)	1.84 (1.76–1.92)	−4.415†	<0.001‡
Velocity A2 (m/s)	−0.36 ± 0.10	−0.33 ± 0.08	−1.561†	0.124‡
Time HC (ms)	16.81 ± 0.79	16.71 ± 0.77	0.507†	0.616‡
Def ampl HC (mm)	1.19 ± 0.13	1.15 ± 0.13	3.005†	0.005‡
Peak dist HC (mm)	3.53 (3.08–4.00)	4.33 (3.92–4.74)	−2.644†	0.010‡
Radius HC (mm)	6.20 ± 0.69	6.59 ± 1.18	−1.721†	0.032‡

Data are presented as the mean ± standard deviation or median (Q_{25}–Q_{75}). *Z value; †t value; ‡Linear mixed-effect models were used to control the influences of IOP, CCT, and axial length. Time A1: Time from start until the first applanation is reached; Length A1: Cord length of the first applanation; Velocity A1: Corneal speed during the first applanation; Time A2: Time from start until the second applanation is reached; Length A2: Cord length of the second applanation; velocity A2: Corneal speed during the second applanation; Time HC: Time from start until highest concavity is reached; Def ampl HC: Maximum amplitude at the apex of highest concavity; Peak dist HC: Distance between the two peaks at highest concavity; Radius HC: Central concave curvature at its highest concavity; NTG: Normal tension glaucoma; IOP: Intraocular pressure; CCT: Central corneal thickness; AGIS: Advanced Glaucoma Intervention Study; SD: Standard deviation.

Table 2: Correlations between Corvis-ST variables and age, IOP, and CCT in worse/better eyes of patients with asymmetric NTG (n = 31)

Items	Time A1 (ms)	Length A1 (mm)	Velocity A1 (m/s)	Time A2 (ms)	Length A2 (mm)
Age (years)	0.417*/0.360*	0.289/0.107	0.146/0.226	0.411*/0.385*	0.148/0.134
IOP (mmHg)	0.776*/0.689*	0.033/0.352	0.494*/0.570*	0.741*/0.106	0.189/0.033
CCT (μm)	0.386*/0.145	0.272/0.057	0.190/0.166	0.067/0.046	0.485*/0.126

Items	Velocity A2 (m/s)	Time HC (ms)	Def Ampl HC (mm)	Peak dist HC (mm)	Radius HC (mm)
Age (years)	0.367*/0.257	0.345/0.284	0.673*/0.624*	0.477*/0.152	0.152/0.027
IOP (mmHg)	0.608*/0.595*	0.264/0.052	0.702*/0.692*	0.117/0.037	0.160/0.188
CCT (μm)	0.485*/0.166	0.086/0.385*	0.234/0.042	0.068/0.273	0.366*/0.038

Data were presented as r values in worse/better eyes. The r values were calculated as the correlations between Corvis-ST variables and known risk factors for glaucoma. r<0.2 indicates a weak correlation, 0.2<r<0.6 indicates a moderate correlation, and r>0.6 indicates a strong correlation. *P<0.05. IOP: Intraocular pressure; CCT: Central corneal thickness. Time A1: Time from start until the first applanation is reached; Length A1: Cord length of the first applanation; Velocity A1: Corneal speed during the first applanation; Time A2: Time from start until the second applanation is reached; Length A2: Cord length of the second applanation; Velocity A2: Corneal speed during the second applanation; Time HC: Time from start until highest concavity is reached; def ampl HC: Maximum amplitude at the apex of highest concavity; Peak dist HC: Distance between the two peaks at highest concavity; Radius HC: Central concave curvature at its highest concavity.

deformation. We, therefore, hypothesized that because it was difficult for the sclera and the lamina cribrosa to bear this pressure, the glaucoma develops asymmetrically. According to our results, there were no significant differences in time A2, velocity A2, and time HC between the groups. These data demonstrate that there is no significant difference between the groups in the resilience of the cornea and the time it takes to reach its highest concavity.

In our study, we also included evaluations of the effect of known risk factors[13] for glaucoma (i.e., age, IOP, and CCT) on corneal biomechanical parameters in glaucoma patients. We found that there was a strong correlation between these risk factors and def ampl HC [Tables 2 and 3], and we also found that def ampl HC values were higher in older patients [Figure 1]. These data are in line with the results described in Leung *et al*.[14] and Tian *et al*.[15] However, in another study that explored collagen fibrils in the human cornea, Daxer *et al*.[16] found that the strength of the cornea can increase with age, a lower def ampl HC instead of a higher one. The reason that def ampl HC becomes higher with age remains to be further studied. According to our study, time A2, length A1, radius HC, and time HC are not correlated with age, IOP, or CCT, whereas other biomechanical properties, including length A2, velocity A1,

Table 3: Regression coefficients of multivariate linear regression of the associations between Corvis-ST variables and age, IOP, and CCT in worse/better eyes of patients with asymmetric NTG (n = 31)

Items	Time A1 (ms)	Length A1 (mm)	Velocity A1 (m/s)	Time A2 (ms)
Age (years)	−0.005 (0.105)/−0.004 (0.468)	−0.002 (0.099)/0.000 (0.161)	0.000 (0.040)/−0.000 (0.837)	0.008 (0.163)/0.140 (0.420)
IOP (mmHg)	0.072 (<0.001)/0.102 (<0.001)	−0.004 (0.516)/−0.005 (0.054)	−0.004 (0.001)/−0.004 (0.003)	−0.129 (0.939)/0.069 (0.802)
CCT (μm)	0.002 (0.028)/0.002 (0.125)	0.001 (0.127)/−0.000 (0.497)	−0.000 (0.563)/−0.000 (0.497)	0.001 (0.567)/0.008 (0.681)

Items	Length A2 (mm)	Velocity A2 (m/s)	Time HC (ms)
Age (years)	−0.003 (0.548)/0.003 (0.452)	−0.002 (0.161)/0.000 (0.766)	0.020 (0.137)/0.018 (0.161)
IOP (mmHg)	0.008 (0.719)/0.003 (0.838)	0.017 (0.002)/0.016 (0.003)	−0.060 (0.308)/0.001 (0.986)
CCT (μm)	0.004 (0.010)/0.001 (0.473)	0.001 (0.007)/0.000 (0.495)	0.003 (0.456)/−0.008 (0.410)

Items	Def ampl HC (mm)	Peak dist HC (mm)	Radius HC (mm)
Age (years)	0.006 (<0.001)/0.005 (0.002)	0.053 (0.011)/−0.018 (0.338)	−0.007 (0.529)/0.006 (0.793)
IOP (mmHg)	−0.026 (<0.001)/−0.025 (<0.001)	0.012 (0.885)/−0.025 (0.751)	0.014 (0.778)/0.093 (0.302)
CCT (μm)	0.000 (0.275)/−0.000 (0.939)	0.003 (0.632)/−0.008 (0.126)	0.006 (0.063)/0.002 (0.739)

Data were presented as correlation coefficients and P values in worse/better eyes. Time A1: Time from start until the first applanation is reached; Length A1: Cord length of the first applanation; Velocity A1: Corneal speed during the first applanation; Time A2: Time from start until the second applanation is reached; Length A2: Cord length of the second applanation; Velocity A2: Corneal speed during the second applanation; Time HC: Time from start until highest concavity is reached; Def ampl HC: Maximum amplitude at the apex of highest concavity; Peak dist HC: Distance between the two peaks at highest concavity; Radius HC: Central concave curvature at its highest concavity; IOP: Intraocular pressure; CCT: Central corneal thickness.

velocity A2, and peak dist HC, are moderately correlated with these risk factors [Table 3]. In a study by Lee *et al*.,[13] the authors found that velocity A2 and peak dist HC were moderately correlated with IOP and CCT, whereas time HC was not.

In our study, we strictly controlled other risk factors for glaucoma, such as CCT and IOP, for which there are no known significant differences [Table 1]. Although CCT and IOP are considered important risk factors for the development of glaucoma,[17-21] we found in this study that an eye with a worse VF did not necessarily have a thinner cornea and a higher IOP. This led us to take a new understanding of the development of NTG. During our study, we carefully controlled the order of the test for applanation tonometry and Corvis-ST – we tested Corvis-ST first to avoid the test for contact-type applanation tonometry having an effect on Corvis-ST results.[22]

The limitations of our study include the following. First, our results need to be analyzed more carefully because our sample size was small. Second, because this is a cross-sectional study, the data can only be used to determine relationships among the biomechanical features of the cornea and glaucoma in patients with asymmetrical glaucoma development in both eyes. More forward-looking studies are needed before we can judge the causality of these factors.

In conclusion, VF defects are not symmetrical between bilateral eyes in NTG patients, in which corneal biomechanical parameters are different between eyes. More specifically, time A1, length A1, length A2, peak dist HC, and radius HC are lower in the worse eye whereas velocity A1 and def ampl HC are higher. These data indicate that the shape of the cornea is more easily changeable in this eye. We predict that this may result in the unbalanced development of glaucoma, but our data do not establish causality. Further follow-up studies conducted over longer periods of time are required.

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Conflicts of interest

There are no conflicts of interest.

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