

# Comparison of corneal biomechanics among primary open-angle glaucoma with normal tension or hypertension and controls

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## Abstract

**Background:** Normal tension glaucoma (NTG) is a less pressure-dependent type of glaucoma with characteristic optic neuropathy. Recently, the biomechanical mechanism has been thought to account for glaucomatous optic neuropathy to some degree. We intended to compare dynamic corneal response parameters (DCRs) among patients with primary open-angle glaucoma with normal tension or hypertension and controls. The correlations between DCRs and known risk factors for glaucoma were also analyzed.

**Methods:** In this cross-sectional study, 49 NTG subjects, 45 hypertension glaucoma (HTG) subjects, and 50 control subjects were enrolled. We compared the differences in DCRs using corneal visualization Scheimpflug technology among the NTG, HTG, and control groups. We also analyzed the correlations between DCRs and known risk factors for glaucoma (eg, central corneal thickness [CCT], intraocular pressure [IOP], etc).

**Results:** The maximum inverse concave radius (NTG: 0.18 [0.17, 0.20] mm<sup>-1</sup>; control: 0.17 [0.16, 0.18] mm<sup>-1</sup>;  $P = 0.033$ ), deformation amplitude ratio of 2 mm (DAR 2 mm, NTG: 4.87 [4.33, 5.39]; control: 4.37 [4.07, 4.88];  $P < 0.001$ ), and DAR 1 mm (NTG: 1.62 [1.58, 1.65]; control: 1.58 [1.54, 1.61];  $P < 0.001$ ) were significantly higher in NTG than in the controls. The integrated radius (IR, NTG: 8.40 ± 1.07 mm<sup>-1</sup>; HTG: 7.64 ± 1.31 mm<sup>-1</sup>;  $P = 0.026$ ) and DAR 2 mm (NTG: 4.87 [4.33, 5.39]; HTG: 4.44 [4.12, 5.02];  $P < 0.007$ ) were significantly higher, whereas the stiffness parameter at the first applanation (SP-A1, NTG: 91.23 [77.45, 107.45]; HTG: 102.36 [85.77, 125.12];  $P = 0.007$ ) was lower in NTG than in HTG. There were no significant differences in the DCRs between HTG and control groups ( $P > 0.05$ ). In the univariate and multivariate analyses, some of the DCRs, such as IR, were negatively correlated with CCT and IOP, whereas SP-A1 was positively correlated with CCT and IOP.

**Conclusions:** The cornea was more deformable in NTG than in HTG or controls. There were no significant differences in corneal deformability between HTG and controls. The cornea was more deformable with the thinner cornea and lower IOP.

**Keywords:** Corneal biomechanics; Primary open-angle glaucoma; Normal tension glaucoma; Hypertensive glaucoma

## Introduction

Glaucoma is a disease defined as a progressive optic neuropathy with characteristic changes in the optic nerve head (ONH) and corresponding visual field defects, with or without elevated intraocular pressure (IOP). Normal tension glaucoma (NTG) is a special type of primary open-angle glaucoma (POAG), with glaucomatous optic nerve (GON) damage despite normal IOP; while POAG with hypertension is associated with elevated IOP. The interaction between IOP-related stress and biomechanical properties of the ONH has been postulated to determine the overall magnitude of the optic nerve damage, which

may account for why some patients are susceptible to glaucomatous damage even under normal levels of IOP.<sup>[1]</sup>

Some studies found that eyes with more deformable corneas may be at more risk for the development and worsening of glaucoma.<sup>[2-4]</sup> The biomechanical characteristics of the cornea reflect the deformability of the sclera and lamina cribrosa to some extent, and this may demonstrate the capacity of the optic nerve to endure the harm caused by glaucoma.

However, whether the cornea of POAG patients is more deformable becomes controversial, as more studies are

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carried out.<sup>[5,6]</sup> Some studies<sup>[5,6]</sup> found that the deformation amplitude (DA) was smaller in the glaucoma group than in the normal control group, which indicates that the corneas of glaucoma subjects were less deformable. Most of the studies reported POAG patients as a whole without separating NTG from hypertension glaucoma (HTG), which may result in confounding biomechanical characteristics in some cases due to the peculiarity of NTG.

In this study, POAG was divided into HTG and NTG groups based on 24-h IOP measurements. We explored the differences in corneal biomechanics among NTG, HTG, and control groups. The correlations between dynamic corneal response parameters (DCRs) and known risk factors for glaucoma were also assessed.

## Methods

### Ethical approval

The study was conducted in full accordance with the tenets of the *Declaration of Helsinki*, and the Peking University First Hospital Ethical Review Committee approved the study protocol. Informed patient and volunteers' consents were obtained before the study commenced.

### Patients

This was a cross-sectional, observational study. The patients were recruited consecutively from the Glaucoma Department of Ophthalmology at Peking University First Hospital diagnosed with POAG between July 2019 and December 2019. Volunteers were also enrolled during the same period.

POAG is defined as a glaucomatous optic disc (cup-to-disc ratio  $>0.6$ , asymmetry of the cup-to-disc ratio  $\geq 0.2$  between eyes, and the presence of local or diffuse retinal nerve fiber layer defects or neuroretinal rim defects in absence of any other abnormalities that could explain such findings) and/or with a corresponding glaucomatous visual field defect with an open angle. Patients were divided into HTG or NTG groups based on 24-h IOP measurements, which was measured using Goldmann applanation tonometry (GAT, Haag-Streit, Switzerland) when first diagnosed.

The inclusion criteria for POAG patients were as follows: age  $>40$  years, best-corrected visual acuity (BCVA) of 20/40 or better, and astigmatism  $<3.0$  diopters. Patients with any of the following criteria were excluded: corneal scarring, any trauma or a history of previous ocular surgery, inflammatory eye disease, and systemic disease conditions, with a known or anticipated effect on DCR measurements, including diabetes mellitus.

The control group consisted of volunteers with a BCVA over 40/60 and no glaucomatous optic neuropathy or history of IOP exceeding 21 mmHg. Other inclusion and exclusion criteria were the same as above.

All subjects underwent a thorough ophthalmic evaluation including slit-lamp biomicroscopy, fundus examination,

IOP measurement (GAT), and gonioscopy. All subjects underwent automated perimetry using a Humphrey Field Analyzer II (Carl Zeiss Meditec, Jena, Germany) with a full threshold 24-2 SITA standard program. Central corneal thickness (CCT) was measured using a Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany). Axial length (AL) was measured using an IOL-Master 500 (Carl Zeiss Meditec). The duration of prostaglandins (PGs) treatment was recorded in all POAG patients.

If both eyes of a POAG patient met the inclusion criteria, the eye with more severe glaucoma (defined as a lower mean defect [MD] value) was included in the analysis. In control subjects, one of the eyes was randomly selected by a random number table.

### Corneal visualization Scheimpflug technology (CST) measurements

All measurements obtained with the CST (Oculus, Wetzlar, Germany) were taken by the same experienced technicians and captured by automatic release to minimize the effect of operator dependence. Only CST examinations with a quality score of "OK" were included in the analysis.

The main DCRs used in this study were previously described.<sup>[7-10]</sup> The outputs of the Corvis-ST are as follows: Briefly, a higher maximum inverse concave radius (MICR), deformation amplitude ratio (DAR) (of 2.0 [DAR 2 mm] or 1.0 mm [DAR 1 mm]), and integrated radius (IR) indicated a more deformable cornea. A lower stiffness parameter at the first applanation (SP-A1) indicated an increased corneal deformity.

### Statistical analysis

Statistical analyses were performed using SPSS software (V.18, IBM Corp. Armonk, NY, USA). Categorical variables were compared with Pearson Chi-squared test. Before comparing the quantitative variables among different groups, the normality of the variables was verified using the Shapiro-Wilk test. Normally distributed continuous variables were expressed as the mean  $\pm$  standard deviation, while non-normally distributed variables were recorded as the median (first and third quartiles). One-way analysis of variance followed by Bonferroni corrections and Kruskal-Wallis tests was used for comparisons among the NTG, HTG, and control groups. Univariate and multivariate regression analyses were used to evaluate the correlations between DCRs and glaucoma risk factors (age, CCT, IOP, and AL). A  $P$  value  $< 0.05$  was considered statistically significant.

## Results

In this study, we recruited 49 consecutive NTG and 45 HTG patients who met the criterion mentioned above. Fifty controls with age and gender matched were also included. The clinical characteristics of the subjects are shown in Table 1. Although NTG group had a thinner CCT, there was no significant difference among the three groups (NTG:  $526 \pm 39$   $\mu\text{m}$ ; HTG:  $547 \pm 50$   $\mu\text{m}$ ; controls:

**Table 1: Clinical characteristics of the control, NTG, and HTG patients.**

Items	Control	NTG	HTG	P value
Numbers of eyes	50	49	45	–
Sex (F/M)	26/24	29/20	22/23	0.320*
Age (years)	62.5 (53.8, 70.3)	63.0 (55.0, 69.0)	66.0 (52.0, 72.5)	0.849†
GAT-IOP (mmHg)	14.0 ± 2.3	14.0 ± 1.9‡	15.4 ± 2.8‡	0.051
CCT (µm)	541 ± 33	526 ± 39	547 ± 50	0.082
AL (mm)	23.9 ± 1.3	24.3 ± 1.6	24.5 ± 1.8	0.217
MD (dB)	–2.6 ± 1.5	–6.4 ± 1.4	–10.6 ± 5.9	<0.001§
PGs use (months)	–	50.3 ± 49.2	37.9 ± 37.1	0.870

Data are presented as mean ± SD or median (Q25 and Q75). \* Pearson Chi-squared test among three groups. †Kruskal-Wallis H test. Other P values were obtained from one-way analysis of variance among the three groups. ‡ IOP under anti-glaucoma medication. §The P value of MD comparison between the NTG and HTG groups was 0.791. AL: Axial length; CCT: Central cornea thickness; GAT-IOP: Intraocular pressure measured by Goldmann applanation tonometry; HTG: Hypertension glaucoma; MD: Mean deviation of the visual field; NTG: Normal tension glaucoma; PGs: Prostaglandins; SD: standard deviation; –: Not applicable.

**Table 2: Corvis ST parameters of patients in the control, NTG, and HTG groups.**

Parameter	Control	NTG	HTG	P value (Overall)	P value (NTG vs. control)	P value (NTG vs. HTG)	P value (HTG vs. control)
MICR (mm <sup>-1</sup> )	0.17 (0.16, 0.18)	0.18 (0.17, 0.20)	0.17 (0.16, 0.19)	0.040	0.033	0.408	1.000
DAR 2 mm	4.37 (4.07, 4.88)	4.87 (4.33, 5.39)	4.44 (4.12, 5.02)	<0.001	<0.001	<0.001	1.000
DAR 1 mm	1.58 (1.54, 1.61)	1.62 (1.58, 1.65)	1.58 (1.52, 1.63)	<0.001	<0.001	0.110	1.000
IR (mm <sup>-1</sup> )	7.99 ± 0.99	8.40 ± 1.07	7.64 ± 1.31	<0.001*	0.321	0.026	0.688
SP-A1	94.41 (85.84, 109.23)	91.23 (77.45, 107.45)	102.36 (85.77, 125.12)	0.010	0.647	0.007	0.160
A1-DFL (mm)	2.62 (2.55, 2.71)	2.56 (2.49, 2.67)	2.62 (2.50, 2.76)	0.190	–	–	–
HC-DFL (mm)	6.31 (5.96, 6.74)	6.13 (5.74, 6.77)	6.05 (5.57, 6.77)	0.293	–	–	–
A2-DFL (mm)	4.05 (3.24, 6.03)	4.91 (3.05, 6.15)	3.23 (2.81, 5.74)	0.109	–	–	–
A1-DFA (mm)	0.11 (0.11, 0.11)	0.11 (0.10, 0.11)	0.11 (0.10, 0.12)	0.365	–	–	–
HC-DFA (mm)	0.91 ± 0.11	0.94 (0.86, 1.00)	0.85 (0.77, 0.98)	0.105	–	–	–
A2-DFA (mm)	0.12 (0.12, 0.13)	0.12 (0.11, 0.13)	0.12 (0.11, 0.13)	0.133	–	–	–
DFA Max (mm)	0.93 ± 0.11	0.96 ± 0.11	0.90 ± 0.14	0.105*	–	–	–
WEM (mm)	0.37 ± 0.08	0.39 ± 0.10	0.36 ± 0.11	0.376*	–	–	–
DFA Max (ms)	16.48 (15.81, 16.92)	16.17 (15.41, 16.75)	16.19 (15.29, 16.73)	0.427	–	–	–
WEM (ms)	22.78 (22.28, 22.99)	22.86 (22.56, 23.05)	22.53 (22.32, 22.93)	0.310	–	–	–
A1-DF Area (mm <sup>2</sup> )	0.21 (0.20, 0.23)	0.20 (0.19, 0.21)	0.20 (0.19, 0.22)	0.298	–	–	–
HC-DF Area (mm <sup>2</sup> )	3.39 ± 0.56	3.46 ± 0.60	3.18 ± 0.76	0.158*	–	–	–
A2-DF Area (mm <sup>2</sup> )	0.28 (0.27, 0.31)	0.27 (0.24, 0.30)	0.27 (0.23, 0.30)	0.063	–	–	–
A1-dDFL (mm)	–0.02 (–0.02, –0.02)	–0.02 (–0.02, –0.02)	–0.02 (–0.02, –0.02)	0.247	–	–	–
HC-dDFL (mm)	–0.15 ± 0.03	–0.14 ± 0.03	–0.14 ± 0.04	0.539*	–	–	–
A2-dDFL (mm)	–0.03 (–0.03, –0.03)	–0.03 (–0.03, –0.03)	–0.03 (–0.03, –0.02)	0.163	–	–	–
dDFL Max (mm)	–0.18 (–0.20, –0.16)	–0.20 (–0.21, –0.16)	–0.18 (–0.23, –0.15)	0.257	–	–	–

Data are presented as the mean ± SD or median (Q25 and Q75). \* Indicates P values that are from One-way analysis of variance. Other P values are from the Kruskal-Wallis H test. The slashes indicate no need to perform *post hoc* analysis due to the overall P values > 0.05. A1: The first applanation; A2: The second applanation; DAR: Deformation amplitude ratio; dDFL: Delta deflection arc length; DF Area: The overall surface area “displaced” due to corneal deformation in the horizontal section analyzed; DFA: Deflection amplitude; DFL: Deflection length; HC: Highest cavity; HTG: Hypertensive glaucoma; IR: Integrated radius; Max: Maximum; MICR: Maximum inverse concave radius; NTG: Normal tension glaucoma; SD: Standard deviation; SP-A1: Stiffness parameter at A1; WEM: Whole eye movement; –: Not applicable.

541 ± 33 µm; P = 0.082). There was also no significant difference in IOP among NTG, HTG, and controls (NTG: 14.0 ± 1.9 mmHg; HTG: 15.4 ± 2.8 mmHg; controls: 14.0 ± 2.3 mmHg; P = 0.051) as IOP was measured under anti-glaucoma medications in POAG patients. There was a significant difference in visual field severity (MD) among the three groups, but the difference between NTG and HTG groups was not significant (P = 0.791). No difference in PGs usage duration between the NTG and HTG groups was found (P > 0.05).

The comparisons of DCRs among the NTG, HTG, and control groups are shown in Table 2. The MICR (NTG: 0.18 [0.17, 0.20] mm<sup>-1</sup>; control: 0.17 [0.16, 0.18] mm<sup>-1</sup>; P = 0.033), DAR 2 mm (NTG: 4.87 [4.33, 5.39]; control: 4.37 [4.07, 4.88]; P < 0.001), and DAR 1 mm (NTG: 1.62 [1.58, 1.65]; control: 1.58 [1.54, 1.61]; P < 0.001) were higher in the NTG group than in the control group. These showed that cornea was more deformable in NTG group than in the controls. The DAR 2 mm (NTG: 4.87 [4.33, 5.39]; HTG: 4.44 [4.12, 5.02]; P < 0.001) and IR (NTG:

**Table 3: Regression coefficients in the univariate and multivariate linear regression of the associations between DCRs variables and age, CCT, IOP, and AL in all subjects.**

Parameters	Age				CCT			
	Univariate		Multivariate		Univariate		Multivariate	
	Coefficient	P	Coefficient	P	Coefficient	P	Coefficient	P
MICR	-	0.512	-	0.522	-0.502	<0.001	-0.238	0.020
DAR 2 mm	-	0.653	-	0.070	-0.752	<0.001	-0.520	<0.001
DAR 1 mm	-	0.953	-	0.609	-0.673	<0.001	-	0.374
IR	-	0.873	-	0.060	-0.736	<0.001	-0.529	<0.001
SP-A1	-	0.762	-	0.690	0.791	<0.001	0.560	<0.001

  

Parameters	IOP				AL			
	Univariate		Multivariate		Univariate		Multivariate	
	Coefficient	P	Coefficient	P	Coefficient	P	Coefficient	P
MICR	-0.287	0.004	-	0.515	-	0.879	-	0.058
DAR 2 mm	-0.560	<0.001	-	0.234	-	0.551	-	0.083
DAR 1 mm	-0.460	<0.001	-	0.329	-	0.536	-	0.616
IR	-0.611	<0.001	-0.650	0.002	-	0.433	-	0.098
SP-A1	0.672	<0.001	0.642	<0.001	-	0.204	-	0.264

AL: Axial length; CCT: Central cornea thickness; DAR: Deformation amplitude ratio; DCRs: Dynamic corneal response parameters; IOP: Intraocular pressure; IR: Integrated radius; MICR: Maximum inverse concave radius; SP-A1: Stiffness parameter at the first applanation; -: Not applicable.

8.40 ± 1.07 mm<sup>-1</sup>; HTG: 7.64 ± 1.31 mm<sup>-1</sup>; P = 0.026) were higher in the NTG group than in the HTG group. SP-A1 (NTG: 91.23 [77.45, 107.45]; HTG: 102.36 [85.77, 125.12]; P = 0.007) was lower in the NTG group than in the HTG group. These showed that the cornea was also more deformable in NTG compared with HTG group. There were no significant differences in any of the DCRs between the HTG and control groups.

The correlations between DCRs and age, IOP, CCT, and AL were examined in all subjects as well as in the NTG, HTG, and control groups separately. The results analyzed for all subjects were similar to each group separately. A previous study<sup>[6]</sup> also indicated that the correlations between DCRs and influencing factors were basically consistent between POAG and normal subjects. Thus, the correlations in all subjects are presented in Table 3. In univariate correlation analysis, there were correlations between CCT and MICR, DAR 2 mm, DAR 1 mm, IR, and SP-A1 (r = -0.502, -0.752, -0.673, -0.736, and 0.791, respectively; all P < 0.05). IOP was also correlated with DAR 2 mm, IR, and SP-A1 (r = -0.560, -0.611, and 0.672, respectively; all P < 0.05). The analysis using a multivariate linear regression model also demonstrated that there were correlations between CCT and MICR, DAR 2 mm, IR, and SP-A1 (r = -0.238, -0.520, -0.529, and 0.560, respectively; all P < 0.05). IOP was also correlated with IR and SP-A1 (r = -0.650 and 0.642, respectively; both P < 0.05). No correlations were found between age and AL with the DCRs in either univariate or multivariate analysis.

**Discussion**

In the present study, we compared the corneal biomechanical properties of NTG, HTG, and non-glaucoma subjects

*in vivo* using CST. The meanings of biomechanical parameters were described in previous reports.<sup>[7-10]</sup> In brief, the MICR is calculated as the reciprocal of the radius of curvature at the highest concavity between inward and outward applanation. IR represents the area under the inverse concave radius curve. Higher MICR and IR are associated with more deformable corneas. The DAR 2/1 mm represents the ratio between the DA of the apex and the average of 2 points located 2.0/1.0 mm on either side of the apex. A higher DAR 2/1 mm also shows a more deformable cornea. SP-A1 describes the rigidity of the cornea.<sup>[11]</sup> A lower value of SP-A1 indicates a more deformable cornea. Compared with the control group, the NTG group presented higher MICR, DAR 2 mm, and DAR 1 mm values. These results indicate that cornea in NTG subjects was more deformable than that in the control group. The NTG group also had higher DAR 2 mm and IR, as well as lower SP-A1 than the HTG group, indicating that cornea with NTG subjects was also more deformable than the HTG group. In addition, there were no significant differences in all the DCRs between HTG and control groups.

The results showed that the corneal biomechanics of NTG and HTG subjects were different. Our results of corneal biomechanical characteristic comparisons among NTG, HTG, and control groups were consistent with Vinciguerra report.<sup>[12]</sup> However, we proved that cornea of NTG was more deformable than the HTG group more directly. We found that DAR 2 mm, IR, and SP-A1 were all significantly different between these two groups, while only SP-A1 was found in their study. In addition, we separated NTG from the HTG group with diurnal measurement of GAT-IOP rather than one measurement. As it was reported that approximately 40% to 50% of the peak IOP period in POAG patients occurs at times when clinics do not operate,<sup>[13-15]</sup> diurnal IOP could provide more reliable



results in some cases by comparing the biomechanical characteristics between NTG and HTG groups.

It is well known that the overall susceptibility of the ONH is determined by the level of IOP and the mechanical properties of the lamellar and scleral canal wall extracellular matrix. Previous studies<sup>[1]</sup> suggested that since the cornea, sclera, and lamina cribrosa were continuous collagenous sheaths and made up of similar extracellular matrix constituents,<sup>[16,17]</sup> the corneal biomechanical properties and those of the ONH were similar to some extent. We hypothesized that in more deformable cornea, such as those with NTG, the ONH is more susceptible to the same IOP stress conditions, which may be attributed to GON damage despite normal IOP. The direct measurement of the lamellar and scleral biomechanical properties *in vivo* cannot be realized yet. Thus, corneal biomechanics measurement may offer a convenient and valuable indication for glaucoma assessment. Corneal biomechanics can be influenced by several glaucoma risk factors. In this study, CCT was negatively correlated with MICR, DAR 2 mm, and IR and positively correlated with SP-A1. IOP was also negatively correlated with IR and positively correlated with SP-A1. These results suggested that corneal deformability increased as the CCT thinned and IOP decreased, in line with the observation that NTG patients tend to have thinner CCT values and lower IOP.

Age and myopia are considered important risk factors for the development of glaucoma.<sup>[18,19]</sup> In this study, no correlations were observed between age and AL with DCRs. The correlation results between age and DCRs in previous studies were contradictory, some of which showed that the cornea became more deformable with older age,<sup>[4,20]</sup> whereas another showed the opposite result.<sup>[21]</sup> There were also different opinions on the relationship between myopia and corneal biomechanics in previous studies. Consistent with our results, Matalia *et al*<sup>[22]</sup> also showed that corneal deformation parameters were unaffected by myopia. However, some other studies<sup>[23,24]</sup> found that the cornea became more deformable with elongation of the AL with corresponding increases in myopia. The effect of age and AL with DCRs needs to be further verified.

The limitations of our study include the following. First, because this was a cross-sectional study, the data could only be used to determine relationships among the corneal biomechanical features of NTG, HTG, and control groups. Further prospective studies are needed before we can determine if there are any causal relationships among these factors. Second, our results need to be analyzed more carefully because our sample size was relatively small.

In conclusion, patients with NTG had significantly higher MICR and DAR 2/1 mm than the controls and higher IR and DAR 2 mm and lower SP-A1 values than obtained in the HTG group. There was no difference between the HTG and control groups. These results indicated that the cornea of NTG patients was more deformable than the control and HTG patients. The results suggested that in more deformable eyes, such as NTG eyes, the ONH was more susceptible to the same IOP stress conditions to some

extent. Our data did not establish causality and further follow-up studies conducted over longer periods are required. The cornea was more deformable with a thinner cornea and lower IOP. We should pay more attention to these glaucoma risk factors in glaucoma development.

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### Conflicts of interest

None.

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