

Assessment of Corneal Biomechanical Properties in Normal Tension Glaucoma and Comparison With Open-angle Glaucoma, Ocular Hypertension, and Normal Eyes

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Purpose: To assess the biomechanical properties of corneas in patients with normal tension glaucoma (NTG) and to compare them with those of patients with primary open-angle glaucoma (POAG), ocular hypertension (OHT), and normal controls (N).

Methods: Corneal hysteresis (CH), corneal resistance factor (CRF), Goldmann intraocular pressure (IOPg), and corneal compensated IOP (IOPcc) were obtained using an ocular response analyzer for 28 eyes in 14 patients with NTG, 75 eyes in 38 patients with chronic POAG, 53 eyes of 27 patients with OHT, and 44 eyes of 22 N controls. IOP using Goldmann applanation tonometry (IOPGA) and ultrasonic central corneal thickness (CCT) were also measured for each eye. Analysis of variance test was used for statistical analysis.

Results: CH was significantly lower in the NTG group (9.88 ± 2.02 mm Hg) compared with the N group (11.05 ± 1.53 mm Hg; $P < 0.01$). CRF was significantly lower in the NTG group (9.5 ± 1.89 mm Hg) compared with the POAG group (11.15 ± 2.35 mm Hg; $P < 0.01$) and to the N group (11.00 ± 1.75 mm Hg; $P < 0.01$). CCT was not considered significantly different between the 4 groups. However, IOPcc was found to be significantly lower in NTG group compared with the POAG group and OHT group ($P < 0.001$).

Conclusion: NTG was associated with significantly lower CRF than chronic POAG and N patients. CH and CRF could be a useful tool in early diagnosis of NTG.

Key Words: normal tension glaucoma, ocular response analyser, hysteresis, corneal resistance factor

(*J Glaucoma* 2011;00:000–000)

Normal tension glaucoma (NTG), also known as normal pressure or low tension glaucoma, is unique among glaucomas in that damage to the optic nerve can occur with eye pressure below 21 mm Hg.¹ The prevalence of NTG over the age of 40 years is 0.2%, and the condition accounts for 20% to 40% of open-angle glaucoma.^{2,3} NTG is characterized by a mean intraocular pressure (IOP), arbitrarily chosen by pasted studies, lower than 21 mm Hg on diurnal testing, an open angle on gonioscopy, optic disc

damage and visual field loss. Although the causes of NTG are not well known, it has been associated with various other diseases such as migraine, nocturnal systemic hypotension, reduced blood flow velocity in the ophthalmic artery, and obstructive sleep apnea syndrome.⁴

Glaucoma progression depends on many parameters, but ocular hypertension is the main risk factor to develop or to aggravate glaucoma.⁵ Recent studies have demonstrated that central corneal thickness (CCT) could be an independent risk factor for glaucoma progression. However, the Ocular Hypertension Treatment study showed a correlation between the IOP response to topical hypotensive medication and the CCT.⁶ Moreover, it is now well accepted that CCT must be considered in analyzing IOP measurements that are performed using Goldmann Applanation.

More recently, it has been shown that corneal viscoelasticity also has an impact on IOP measurements.^{7–9} The Reichert Ocular Response Analyzer (ORA, Reichert) is the first simple device capable of determining in vivo biomechanical properties of the cornea. It quantifies corneal viscoelasticity by measuring corneal hysteresis (CH). Hysteresis corresponds to ocular resistance due to the combined effect of various parameters such as CCT and viscoelastic properties. Corneal viscoelastic properties have been studied in various ocular diseases. Most studies have been reported on keratoconus but less often on glaucoma.¹⁰

The aim of our study was to evaluate and compare CH and CRF between NTG, chronic open-angle glaucoma, ocular hypertension, and normal eyes.

PATIENTS AND METHODS

Patients

Two hundred eyes were included in this retrospective study. The study was conducted according to the tenets of the Helsinki Declaration, and all patients gave their informed consent after the nature and intent of the study had been explained.

Eyes were separated in 4 groups according to the type of the glaucomatous disease. Twenty-eight eyes of 14 patients had NTG, 75 eyes of 38 patients had chronic primary open-angle glaucoma (POAG), and 53 eyes of 27 patients had isolated intraocular hypertension (OHT). They were compared with a normal (N) group of 44 eyes of 22 normal controls.

The diagnosis of glaucoma was based on optic nerve excavation associated with visual field loss. POAG group and NTG group had optic nerve disc damage and visual field loss and were separated into POAG or NTG based on whether their baseline IOP was over or below 21 mm Hg,

Received for publication August 20, 2010; accepted April 18, 2011.
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Conflict of Interest: None.

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DOI:10.1097/IJG.0b013e318220daf0

respectively. Patients with IOP over 21 mm Hg on 2 consecutive visits without optic nerve disc damage and visual field loss were considered as patients with isolated ocular hypertension. Seventeen healthy volunteers were recruited from patients attending the ophthalmologic consultation for refractive or cataract surgery. Their IOP was below 21 mm Hg, and they had neither optic disc excavation nor visual field loss.

Exclusion criteria were corneal diseases (based on history and slit lamp examination), previous eye surgery, and generalized diseases that could affect the eyes.

All patients had a complete slit lamp examination, an IOP measurement by Goldmann applanation tonometry (IOPGA), and a corneal central thickness measurement using an ultrasound pachymeter (CCT).

ORA Analysis

All patients included in the study had an ORA examination. The ORA (Reichert, Inc., Buffalo, NY) is a noncontact device that provides measurements of corneal biomechanical properties, referred to as CH and Corneal resistance factor (CRF). In addition, the device provides a Goldmann correlated IOP measurement (IOPg) and a corneal compensated IOP measurement (IOPcc) which is reported to be less influenced by corneal properties than other tonometric methods. An overview of the device has been described in detail by Luce.¹¹

The patient was seated in front of the ORA device and was asked to fixate on a green light. A fully automated alignment system positions an air tube to a precise position relative to the apex of the cornea. Four measurements were taken for each eye and then the results were averaged.

Statistical Analysis

All numerical results were entered into a database and statistical analyses were performed with XLSTAT2009 (Addinsoft) using analysis of variance. A *P* value < 0.05 was considered statistically significant.

RESULTS

Patients

Table 1 compares demographic data for the 4 groups. The mean age of the patients was 56.8 ± 2.2 years. No significant difference was observed between age in the 4 groups. Mean CCT was $556.6 \mu\text{m}$ (± 9.1). Even if CCT was higher in the OHT group, it was also not significantly different from the 3 other groups. IOPGA was significantly lower in NTG and N groups compared with IOPGA in POAG and OHT groups.

ORA Measurement

IOPg was significantly lower in NTG and N groups compared with POAG and OHT groups. For each of the 4 groups, IOPGA and IOPg were well correlated and no significant difference was noticed between these 2 measurements (Table 1).

IOPcc was significantly lower in NTG group compared with POAG and OHT groups ($P < 0.01$) but it was not significantly different from the N group (Fig. 1).

CH of the 2 glaucomatous groups, NTG (9.88 ± 2.02 mm Hg) and POAG (10.03 ± 2.31 mm Hg), was significantly lower than CH of the N group (11.05 ± 1.53 mm Hg). No significant difference was found between OHT (10.06 ± 2.47 mm Hg) and N patients (Fig. 2).

CRF was significantly lower in the NTG group (9.5 ± 1.89 mm Hg) compared with the POAG group (11.15 ± 2.35 mm Hg; $P < 0.01$) and to the N group (11.00 ± 1.75 mm Hg; $P < 0.01$). On the contrary CRF of OHT (12.11 ± 1.89) patients was significantly higher than the one of normal controls ($P < 0.01$) (Fig. 3).

DISCUSSION

Even if the ORA is a relatively recent device, its measurements have been proven to be reproducible and it seems to be useful in glaucoma diagnosis and management. Wasilica-Poslednik et al¹² demonstrated that interobserver and intraobserver reproducibility of ORA measurements was almost perfect for IOPcc, CRF, and CH.

Many studies have shown that CH and CRF were correlated with CCT and Mangouritsas et al⁸ demonstrated that there was a strong correlation between CH and CCT in both normal and glaucomatous eyes. In contrast, Congdon et al¹³ showed that lower CH but not CCT is associated with progressive visual field loss. In our study, CCT was not different between the 4 groups. Thus, by matching our 4 groups to CCT, we were able to analyze CH and CRF measurements independently of CCT.

Copt et al¹⁴ demonstrated that patients with NTG have a thinner CCT compared with patients with POAG or controls. In some cases, underestimating the IOP of patients with POAG who have thin corneas may lead to a misdiagnosis of NTG.¹⁵

Both CRF and CH were significantly lower in NTG group compared with the N group in our study. Age and CCT were not different between those 2 groups. As only CH and CRF, which are characteristics of the viscoelastic properties of the cornea, were different among the studied factors between the 2 groups, we hypothesized that the glaucoma disease itself could be associated to modifications of the biomechanical properties of the corneas in NTG.

TABLE 1. Demographic Data for the 4 Groups

	NTG	POAG	OHT	N
No. Eyes (n)	28	75	53	44
No. Patients (n)	14	38	27	22
Age(y) \pm SD	56.1 ± 5.1	59.9 ± 4.9	56.1 ± 4.8	57.5 ± 5.9
CCT(μm) \pm SD	552.5 ± 35.6	551.5 ± 38.9	570.2 ± 53.8	550.7 ± 29.3
IOPGA (mm Hg) \pm SD	13 ± 2.63	18 ± 4.42	20 ± 3.59	14 ± 3.47
IOPg (mm Hg) \pm SD	13.5 ± 2.63	18.4 ± 4.3	19.7 ± 5.5	13.8 ± 3.22

Mean age and CCT were not significantly different between the 4 groups. IOPGA and IOPg were significantly lower in NTG and N groups compared with POAG and OHT groups.

CCT indicates central corneal thickness; IOP, intraocular pressure; IOPGA, IOP measurement by Goldmann applanation tonometry; IOPg, Goldmann intraocular pressure; NTG, normal tension glaucoma; POAG, primary open-angle glaucoma; OHT, ocular hypertension; N, normal.

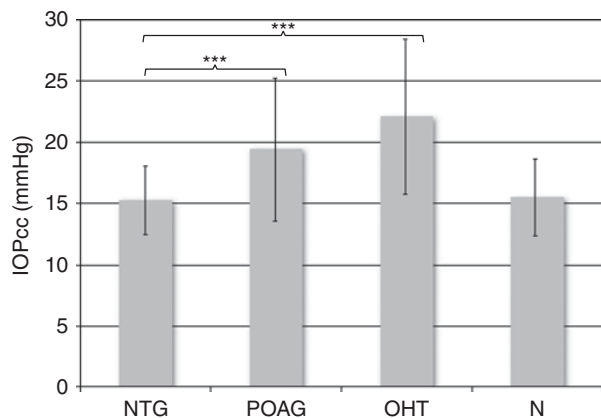


FIGURE 1. Corneal compensated intraocular pressure (IOPcc) was significantly lower in normal tension glaucoma (NTG) group compared with the primary open-angle glaucoma (POAG) group and ocular hypertension (OHT) group ($P < 0.001$) but not different from the normal (N) group.

Eyes with a more deformable cornea, less viscous damping, and lower CH could have optic discs more susceptible to glaucoma damage from increased IOP. CH could be interpreted as a parameter of properties of the entire eye and not just of the cornea itself.¹⁶ Further studies will be necessary to elucidate if patients with lower CH and CRF are more susceptible to glaucoma than patients with normal parameters or if glaucoma is responsible for the decrease of CH and CRF.

In our study, NTG and POAG had both lower CH and CRF than the N group. NTG and POAG groups were different by IOPcc and CRF that were both lower in the NTG group.

Our results confirmed previous studies that had shown that CH was reduced in chronic open-angle glaucoma compared with eyes of normal controls.⁸ Nevertheless, CRF was more specifically lowered in NTG compared with POAG.

As all NTG and POAG patients were treated with local eyedrops and none had undergone previous eye surgery, we reached the hypothesis that CH and CRF reduction could be related to modification of the biomechanical properties of the cornea induced by the glaucoma

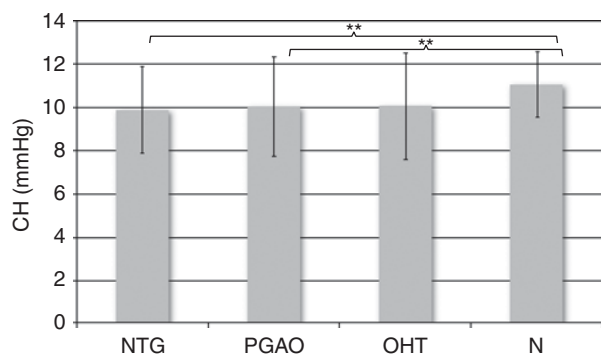


FIGURE 2. Corneal hysteresis (CH) of the 2 glaucomatous groups [normal tension glaucoma (NTG) and primary open-angle glaucoma (POAG)] was significantly lower than CH of the normal (N) group. No significant difference was found between ocular hypertension (OHT) and normal controls.

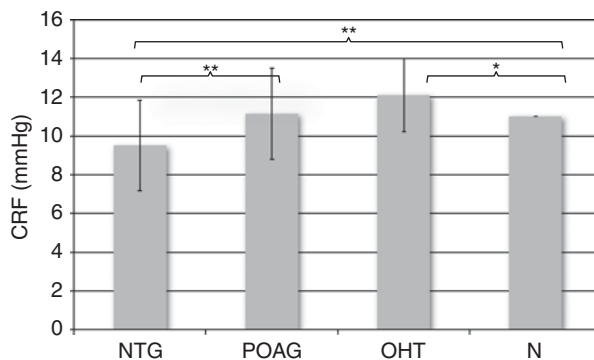


FIGURE 3. Corneal resistance factor (CRF) was significantly lower in the normal tension glaucoma (NTG) group compared with the primary open-angle glaucoma (POAG) group ($P < 0.01$) and to the normal (N) group ($P < 0.01$).

disease itself or that eyes with altered viscoelasticity properties could be more susceptible to glaucoma than normal eyes.¹⁷

A difference of pathogenesis between NTG and POAG has been suggested by many investigators.^{18,19} Different patterns of visual field defects, optic nerve head configuration, and nerve fiber layer defects have been observed for the 2 types of glaucoma, suggesting that a different pathogenesis of glaucomatous damage could be associated with each type of glaucoma. The idea of a pressure tolerance level of the head of the optic nerve which would be lower in NTG than in POAG, has been evocated by several investigators.¹⁶ We hypothesized that pressure tolerance of the cornea could also be lower in NTG than in POAG. Submitted to the same IOP level, corneal resistance of NTG would be lower than POAG corneal resistance.

Several cases of association of NTG or POAG with corneal dystrophy have been described.²⁰ Although the mechanism of this association still remains unknown, similar morphologic modification of cornea and trabecular meshwork could be involved. No corneal dystrophies were found in patients with NTG, but their cornea could be affected by infraclinical modifications which may modify their biomechanical properties.

Comparing NTG to OHT groups, IOPcc was significantly lower in the NTG group. CH in OHT group was found similar to NTG group whereas CRF was clearly higher.

A high level of CRF seemed to be associated with the absence of optic nerve alteration.

In conclusion, ORA measurements provide important information for corneal biomechanics analysis in NTG. NTG was associated with low CH and CRF in an independent way to CCT. Further studies will be required to confirm these results.

ACKNOWLEDGMENT

The authors thank Richard Medeiros, Rouen University Hospital Medical Editor, for editing the article.

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