DOES THE CORNEAL CONFIGURATION OF THE EYES WITH NORMAL TENSION GLAUCOMA LEAD TO UNDERESTIMATION OF INTRAOCULAR PRESSURE ?

TAKUYA MATSUMOTO and HIROYUKI MAKINO
Department of Ophthalmology, Hoshigaoka Welfare Pension Hospital

HIROSHI UOZATO and MOTOTSUGU SAISHIN
Department of Ophthalmology, Nara Medical University
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Abstract : [Purpose] The intraocular pressure (IOP) is the only parameter that distinguishes normal tension glaucoma (NTG) from primary open angle glaucoma (POAG). NTG may be misdiagnosed as a result of underestimation of IOP due to corneal configuration. Whether the corneal configuration of the eye with NTG can cause underestimation of IOP was investigated.

[Methods] The corneal thickness and curvature were measured in 57 eyes of 38 NTG patients, and the IOP measurements were corrected for corneal configuration using Ehlers' formula. The incidence of disc hemorrhage (DH) was compared between eyes with a high corrected IOP and those with a normal corrected IOP.

[Results] Measurements of the corneal thickness and curvature in NTG eyes were similar to those in normal eyes. The corrected IOP was above the normal range (≥20 mmHg) for 12 eyes and remained normal (<20 mmHg) for 45 eyes. DH did not develop in any of the eyes with a high corrected IOP, but did develop in 15 eyes with a normal corrected IOP ($p < 0.05$).

[Conclusions] Some cases of NTG can be misdiagnosed as a result of underestimation of IOP. The incidence of DH in eyes with an underestimation IOP suggests that the correct diagnosis may be POAG in some eyes. (奈医誌. J. Nara Med. Ass. **50**, 294～302, 1999)

Key words : corneal configuration, corneal thickness, disc hemorrhage, intraocular pressure, normal tension glaucoma,

INTRODUCTION

The corneal configuration influences corneal rigidity and thus tonometric measurement of intraocular pressure (IOP). Since eyes diagnosed as having ocular hypertension (OHT) have a significantly greater corneal thickness when compared to normal eyes, their measurements of IOP are overestimated[1,2]. Conversely, eyes with normal tension glaucoma (NTG) may have a smaller corneal thickness and therefore have the IOP underestimated. The central corneal thickness and the radius of corneal curvature have been extensively studied in eyes with NTG. Tomlinson & Leighoton[3] reported that NTG had a greater radius of corneal curvature compared with normal eyes, although the central corneal thickness was similar to that in NTG and normal eyes. Morad et al.[4] found that there were no significant differences between NTG eyes and normal eyes with respect to the radius of corneal curvature, but noted that the corneal thickness was smaller for NTG eyes. They speculated that the IOP of some of these NTG eyes might be underestimated due to the thinner cornea. Both investigators speculated that the corneal configuration of NTG eyes could lead to underestimation of the IOP, although no consistent data had been obtained at that time on the radius of corneal curvature and the corneal thickness of NTG eyes. NTG differs from primary open angle glaucoma (POAG) in various clinical and pathophysiological features, including the prevalence of headache (which is higher in patients with NTG than in patients with POAG or in healthy individuals)[5], fluorescein angiographic findings[6], finger tip blood flow before and after hand immersion in 4 ℃ water(significantly lower in patients with NTG)[7], changes in the optic disc[8,9], and the pattern of visual field defects[10]. These differences between NTG and POAG cannot be explained solely by underestimation of the IOP for NTG eyes due to the influence of corneal configuration on tonometric measurements. Many NTG eyes may have a normal IOP and may develop glaucoma by another mechanism, despite this normal IOP.

In the present study, the corneal thickness and the radius of the corneal curvature were measured in NTG eyes and were compared with similar measurements obtained from normal control eyes. The IOP data obtained from NTG eyes were then corrected for the observed corneal thickness based on the predetermined influence of corneal thickness on manometric measurements of IOP[11]. Furthermore, the incidence of disc hemorrhage (DH), a clinical feature that distinguishes NTG from POAG, was compared between eyes with a high corrected IOP and those with a normal corrected IOP.

MATERIALS AND MATHODS

Subjects

The study involved 38 Japanese patients (57 eyes) [aged 67.1(SD 7.8), range : 51-83 years], including 17 men (20 eyes) and 21 women (37 eyes) who had been followed up as outpatients at our institution for at least 1 year after the diagnosis of NTG. The diagnostic criteria[12] included : 1) IOP$<$20 mmHg throughout the follow-up period ; 2) glaucomatous visual field defects consistent with glaucomatous disc changed ; and 3) absence of other conditions that might cause disc or visual field changes. None of the patients had corneal disease or had undergone intraocular surgery.

Control eyes

For comparison, the study also involved 49 age-matched normal controls (98 eyes) aged 63.3 (SD 6.7) years (range : 51-74 years), including 24 men (48 eyes) and 25 women (50 eyes). The corneal thickness and the radius of corneal curvature were measured in their eyes.

Correction of IOP for corneal thickness

Ehlers at al.[11] measured the IOP in 29 eyes undergoing cataract surgery using a monometer and studied the relationship between the corneal thickness and the disparity between the actual IOP and that estimated by Perkins or Draeger tonometer. At a true IOP of 10 mmHg, a 1 μm increase in corneal thickness increased the IOP by 0.0603 mmHg. Thus, the following formula was developed to correct the IOP for corneal thickness :

Corrected IOP [mmHg] = tonometric measurement of IOP [mmHg] + 0.0603(measered central corneal thickness [μm] − normal central corneal thickness [μm]).

The central corneal thickness of normal eyes varies considerably between studies. For example, the mean of 59 normal eyes reported by Herndon et al.[2] was 561(SD26) μm, while Hikishima et al.[13] reported a mean central corneal thickness of 525(33) μm in 130 normal eyes. Kremer et al.[14] found that the values repoprted for this parameter in normal eyes ranged from 507 to 564 μm and suggested that this great variation might be partly due to differences in the type of apparatus used. To correct the IOP data obtained in the present study, the normal central corneal thickness in the above formula was substituted by 559 μm, which was the mean value obtained in the 98 normal control eyes under the same conditions as were employed for measurement in the 57 NTG eyes.

The maximum IOP observed during follow-up was corrected using this formula. Eyes with a corrected IOP ≥ 20 mmHg were defined as having a high corrected IOP, while eyes a corrected IOP < 20 mmHg were defined as having a normal corrected IOP.

Measurement of IOP, corneal thickness, and corneal curvature

IOP was measured by Goldmann applanation tonometer (GAT).

Measurement of central corneal thickness was done using a Nidek UP-2000 ultrasonic pachymeter (Nidek Co. Ltd., Aichi, Japan)(ultrasound velocity, 1640 m/s). Local anesthetic was applied before measurement. Because it was reported that local anesthetic[15] can damage the corneal epithelium and endothelium and that this damage influences corneal thickness[16], all the data were measured within 1 minute after local anesthetic application. After repeating the test at least eight times, the average was calculated. All measurements were performed by the same operator. Many cases were under eye drop treatment for glaucoma. Some influences of topical glaucomatous drug on corneal configuration were studied. Herdon et al.[2] reported that eyes treated with dorzolamide hydrochloride had significantly increased corneal thickness compared with those eyes with not treated with dorzolamide. No cases in our study were treated with dorzolamide. The topical glaucomatous drugs by our patients were timolate maleate, carteolol hydrochloride, betaxolol hydrochloride, and isopropyl unoprostone. Airaksinen[17] studied the change in corneal thickness when timolate was applied for 6 months, and no remarkable change was found. The influence of the other types of eye drops on corneal thickness has been reported. The central corneal thickness change in 11 of our patients (11 eyes) treated with eye drops (timolate maleate, carteolol hydrochloride, betaxolol hydrochloride, isopropyl unoprostone) was examined for 1 month (Table 1). The results suggest that these topical glaucomatous drugs have no influence on the corneal thickness.

Table 1. Change in central corneal thickness after 1 month of medication

	Δ central corneal thickness (μm)
unoprostone (n=4)	−1±7
carteolol (n=1)	7
timolate (n=3)	4±11
betaxolol (n=3)	0±9

mean±SD

Measurement of corneal curvature was done using a Nidek ARK-2000 autokeratometer (Nidek Co. Ltd.), and was performed before the corneal thickness measurement. Patients with irregular astigmatism were excluded. Measurements of IOP and corneal thickness were obtained between 0900 and 1700 hours at the outpatients department of our hospital.

RESULTS

Measurements of the central corneal thickness and the radius of corneal curvature obtained in the 57 NTG eyes were statistically similar to those obtained in the 98 normal control eyes (Table 2).

The IOP corrected for central corneal thickness was high in 12 NTG eyes (21.1%) and normal in 45 NTG eyes (78.9%). The eyes with a high corrected IOP had significantly thinner corneas and a significantly higher IOP compared to the eyes with a normal corrected IOP (Table 3) ($p<0.01$, Student's t-test)

Fifteen of 57 eyes (25%) developed DH and all had a normal corrected IOP. The incidence of DH was significantly different between the eyes with a high corrected IOP and those with a normal corrected IOP ($p<0.05$, χ^2-test) (Table 4). Tonometric and corrected IOP of the

Table 2. Central corneal thickness and radius of corneal curvature in NTG eyes and age-matched normal controls

	eyes	age	Central corneal thickness (μm)	Radius of corneal curvature (mm)
Normal tension glaucoma	57	67.1±7.8	559±35	7.66±0.22
Normal control	98	63.3±6.7	558±28	7.67±0.23

Mean±SD

Table 3. IOP and corneal configuration of the eyes with a high corrected IOP and those with a normal corrected IOP

	eyes	Intraocular pressure (mmHg)	Central corneal thickness (μm)	Radius of corneal curvature (mm)
high corrected IOP	12	18.2±1.1	522±21	7.53±0.20
normal corrected IOP	45	15.1±2.5	568±29	7.68±0.23

Mean±SD

Table 4. Incidence of DH in the eyes with high corrected IOP and those with normal corrected IOP

	Disc hemorrhage(+)	Disk hemorrhage(−)
the eyes with a high corrected IOP	0	12
the eyes with a normal corrected IOP	15	30

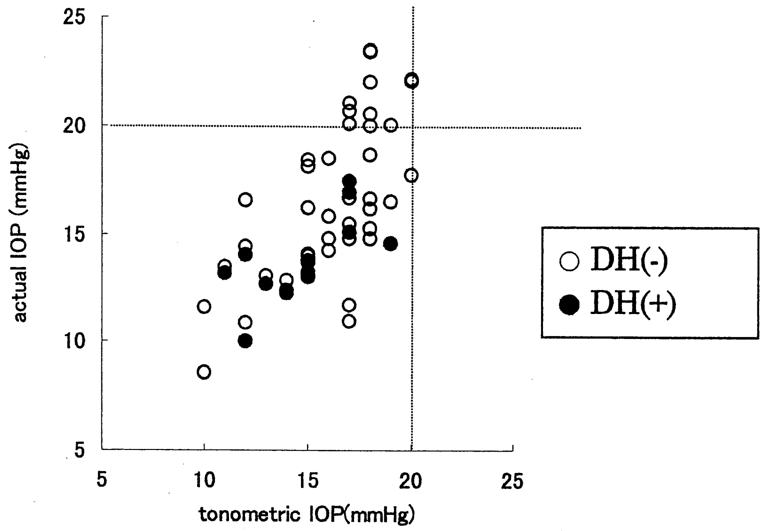

Fig. 1. Scattergram for tonometric and corrected IOP of eyes with normal tension glaucoma. The maximum IOP observed during follow-up was used as tonometric and corrected IOP. Disc hemorrhage (DH) did not develop in any eyes with high corrected IOP, but developed in 15 eyes with a normal corrected IOP.

case of NTG are shown in the scattergram (Fig. 1).

DISCUSSION

It has long been believed that IOP measurements obtained using a GAT are not likely to be affected by the corneal configuration. However, underestimation of IOP using such an apparatus following eximer laser photorefractive keratectmy for myopia has recently been reported[18,19]. These findings suggest that corneal configuration also has some influence on IOP measurements obtained using a GAT, which is besed on the Imbert-Fick principle. Assuming that the force pulling the tonometer tip towards the cornea by the surface tension of the precorneal tear film is S and that modulus of ocular rigidity is M, the relationship of the force acting on the tonometer tip (W) to the area of contact with the tear film (A) and the intraocular pressure (P) can be expressed by the following equation:

$W+S=P\times A+M$.

Goldmann proved that M was equal to S and that influence of M on W could thus be appropriately evaluated when the diameter of the tonometer tip was approximately to 3.00 mm[20]. However, as shown in Fig. 2, M is influenced by the corneal thickness and corneal curvature, as evidenced by the radial displacement characteristcs of thin shells[21]. Because S is proportional to the area of contact with the tear film[22] and is not influenced by the corneal configuration, M can not be compensated by S in GAT.

Shiose & Kawase[23] studied the relationship between IOP and glaucomatous visual field abnormalities in 13,000 eyes and found that the incidence of glaucomatous visual field increased in proportion to the IOP at values of 15 mmHg or higher, but remained constant (at 1.2-1.6%) when the IOP was below 15 mmHg. This suggests that other factors may play a major role in the etiology of glaucomatous visual field abnormality at a low IOP. Levene[12] documented two pathological types of NTG : one was characterized by an IOP at the upper limit of normal and pressure-sensitive visual field defects with progression controllable by normalization of the IOP, whereas the other type was characterized by a multifactorial etiology and pressure-indifferent visual field defects, with progression not being controlled by normalization of the IOP. He reported that NTG was of the latter type in most patients diagnosed as having this condition. In addition to IOP, impaired perfusion of the optic disc has been inplicated in the etiology of NTG ; drugs which increase peripheral blood flow as well as those which reduce IOP may have some efficacy for this condition[24,25]. Even patients whose IOP has been suffciently

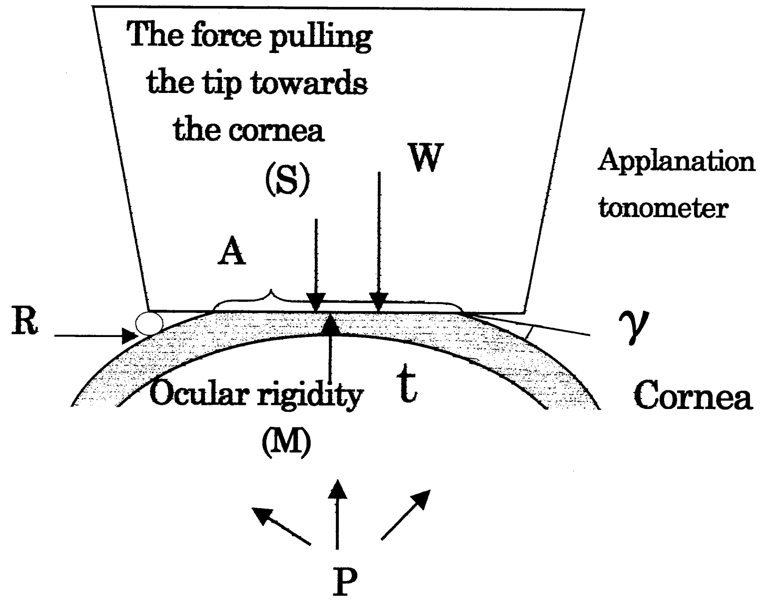

Fig. 2. ①Rigidity of cornea deformed by tonometer tip is influenced by force for radial displacement. Theoretical results of radial displacement of thin shell can be expressed by following equation[21].

$$\mu=\frac{(1-\upsilon)r^2P}{2tE}=\frac{(1-\upsilon)P}{2E}\times\left(\frac{r^2}{t}\right)$$

(μ : radial displacement, t : thickness of membrane, r : radius of corneal curvature, P : internal pressure, υ : Poisson's ratio of membrane, E : elastic constant.)

②S ; force pulling tonometer tip and cornea by surface tension of precorneal tear film can be expressed as follows[22].

$S=\alpha/R\sin\gamma$

(R : Radius of curvature of tear film spanning tonometer tip and cornea, α : Surface tension of precorneal tear film, γ : Half-angle formed by the intersection of tonometer and cornea)

From these equations, it was theoretically proven that ocular rigidity influenced by corneal thickness and corneal curvature was not equal to surface tension of the tear film.

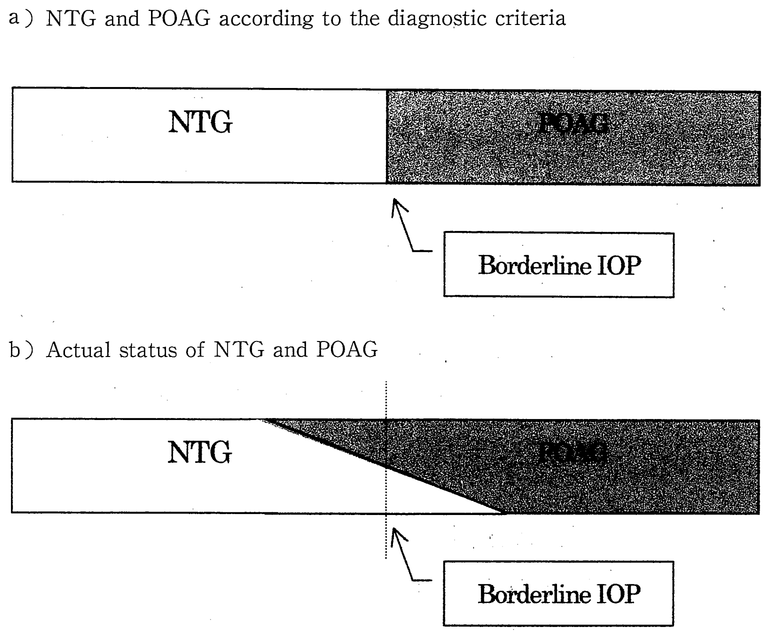

Fig. 3. a) According to diagnostic criteria, IOP is only parameter that distinguishes NTG from POAG.
b) There seems to be a heterogeneous group of patients around the IOP judged as dividing NTG from POAG with characteristics of both NTG and POAG. Some patients diagnosed as NTG who have characteristics of POAG may have had IOP underestimated because the influence of corneal configuration on tonometric measurements.

reduced by filtration surgery occasionally show further progression of glaucomatous changes. So typing of NTG by its dependence on IOP is also helpful for determining the optimum therapeutic approach. In the present study, the NTG eyes with a high corrected IOP had clinical features more similar to those of POAG than those of NTG in terms of the incidence of DH. As shown in Fig. 3, some cased of NTG with diagnosis based on IOP values may have various clinical and pathophysiological features of POAG. Though dependence of progression on IOP is not observed in all patients with POAG[26], many patients with NTG who have some POAG characteristics are found among the IOP-sensitive type of NTG (as described by Levene), which also includes patients with underestimation of IOP due to the effect corneal configuration.

It has been suggested that DH indicates an ischemic disc caused by impaired blood supply to the optic disc[27] or else the condition is secondary to microangiopathy[28]. DH is more prevalent in patients with NTG than in those with POAG[29,30,31]. The incidence of DH reported by Gloster[29] was 19.4% for NTG compared with 9.2% for POAG, while the corresponding values reported by Kitazawa et al.[30] were 20.5% and 4.1%. Kitazawa also reported that DH tended to recur in NTG, however some eyes remained free of it throughout the entire course, as was observed in the eyes with a high corrected IOP which had features of POAG in the present study.

The etiology of NTG remains controversial. Some investigators have previously suggested that NTG patients have had their IOP underestimated by tonometry due to the influence of corneal configuration. This suggestion was not confirmed by the present study, which showed no significant differences between NTG eyes and normal eyes with respect to the corneal thickness or the radius of the corneal curvature. However, some cases of NTG may have IOP underestimation and may actually have a high IOP. Ehlers' formula was used in the present study to correct IOP measurements for corneal thickness. It has not gained very wide acceptance and its reliability remains to be verified. In any case, tonometric measurement of IOP should be corrected for corneal configuration. Though the corrected IOP using this formula may not be true IOP, correction of IOP data using the formula in this study helped to clarify the clinical features of this subtype of NTG.

It should be noted that at least some patients diagnosed as NTG may suffer from IOP underestimation and may actually have a high IOP. For eyes with a high corrected IOP, the target IOP can be set appropriately. For eyes with a normal corrected IOP, effort should be concentrated on detecting other etiologic factors.

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