Corneal hysteresis measured with the Ocular Response Analyzer® in normal and glaucomatous eyes

Olivia Abitbol,[1,2,3] Jihène Bouden,[2,3] Serge Doan,[2,3] Thanh Hoang-Xuan[2,3] and Damien Gatinel[2,3]

[1]Glaucoma Institute, Saint-Joseph Foundation, Paris, France
[2]Department of Ophthalmology, Bichat Claude-Bernard Hospital, Paris, France
[3]Department of Ophthalmology, Rothschild Foundation, Paris, France

ABSTRACT.

Purpose: To identify differences in corneal hysteresis (CH) and central corneal thickness (CCT) between healthy and glaucomatous patients.

Methods: Retrospective observational study. One hundred and thirty-three eyes of 75 healthy and 58 glaucomatous patients were included. CH was measured in each patient using Ocular Response Analyzer. CCT was determined by ultrasonic pachymetry. For each patient, one eye was randomly selected. We used a Student *t*-test to search for significant differences between the different groups (p < 0.05).

Results: In healthy and glaucomatous eyes, mean CH values were 10.46 ± 1.6 and 8.77 ± 1.4 mm Hg, respectively. Mean CCT values were 560.2 ± 36.3 and 535.3 ± 42.7 μm, respectively. CH and CCT were significantly lower in glaucomatous eyes than in normal eyes, (p < 0.05).

Discussion: In our series, CH was lower in glaucomatous than in normal eyes. The relationship between glaucoma, IOP, and ocular structures may not be confined to the consideration of CCT. A low CH value could be responsible for under-estimation of IOP. CH could also be a risk factor for glaucoma, independent of IOP. Further studies are needed to support these hypotheses.

Conclusion: In our investigation, CCT and CH were significantly lower in glaucomatous eyes than in healthy eyes.

Key words: central corneal thickness – corneal biomechanics – glaucoma – hysteresis

Introduction

Elevated intraocular pressure (IOP) is an important risk factor for glaucoma; the reduction of IOP in subjects with ocular hypertension (OHT) has been proven to reduce the incidence of conversion to glaucoma (Gordon et al. 2002).

The Goldmann applanation tonometer (GAT), which is frequently used to measure IOP, operates on the basis of the Imbert–Fick law ($W = P \times A$), where W is the force to applanate, P is IOP, and A is the area applanated. This law assumes that the cornea is an infinitely thin, perfectly flexible membrane. This assumption is flawed, however, because the cornea is not perfectly thin and infinitely flexible, and nor are all corneas similar in their elastic and mechanical characteristics. Therefore, the force required to applanate the cornea depends not only on IOP, but also on corneal rigidity, which itself depends on corneal thickness, curvature, hydration, composition and viscoelastic properties. Other components also play a role in the accurate measurement of IOP, including the subject's race and refractive surgery status (laser *in situ* keratomileusis [LASIK], photorefractive keratectomy [PKR]), and the presence of corneal pathology (keratoconus, Fuchs' dystrophy, scars). The influence of central corneal thickness (CCT) on IOP values measured with GAT has been demonstrated (Ehlers et al. 1975; Whitacre et al. 1993; Wolfs et al. 1997) and is now taken into account in the interpretation of IOP measurements. Several studies have already shown a significant correlation between a thin CCT and the severity of glaucomatous neuropathy (Herndon et al. 2004; Jonas et al. 2005; Congdon et al. 2006; Kniestedt et al. 2006; Papadia et al. 2007). Moreover, according to the Ocular Hypertension Treatment

Study (OHTS), a thin CCT may be an independent risk factor for the development and progression of glaucoma in patients with OHT (Gordon et al. 2002).

Until recently, corneal biomechanical properties could not be measured *in vivo*. The Ocular Response Analyzer® (ORA) (Reichert Ophthalmic Instruments, Inc., Buffalo, NY, USA) is a new, non-invasive device that analyses corneal biomechanical properties simply and rapidly (Luce 2005). The ORA allows IOP measurements and can estimate corneal hysteresis (CH) and rigidity.

Elasticity refers to how a material deforms in response to an external stress. The stress–strain relationship can be plotted graphically; an elastic material is one that regains its original form in a completely reversible displacement direction along the stress–strain pathway when the imposed stress is removed. Hysteresis refers to the energy lost during the stress–strain cycle. Viscous materials flow when an external shear stress is applied, but, unlike materials with elastic properties, they do not regain their original shape when the stress is removed. Collagen is viscoelastic and therefore exhibits hysteresis (Kotecha 2007).

The ORA uses a quick calibrated air puff that causes the cornea to move inward, past applanation and into a state of slight concavity. The cornea then recovers its normal configuration, passing through a second applanation state. An electro-optic detector system indirectly evaluates the corneal curvature in the central 3 mm during the 20 milliseconds of measurements and detects the two applanation moments when there is a spike of luminous intensity. Thus, the device measures two applanation pressures, P1 and P2, and then provides:

(1) the mean of the two measured pressures (P1 and P2) to give an IOP measurement correlated to IOP measured with GAT (IOPG), and
(2) the difference between the two pressures (P1 and P2) to give a measurement of CH.

This new parameter is very important in any assessment of corneal biomechanical properties (Luce 2005).

We sought to identify differences in CH and CCT between normal and glaucomatous patients.

Materials and Methods

We conducted a retrospective study including patients referred to our hospital between December 2005 and May 2007. All procedures conformed to the tenets of the Declaration of Helsinki. Based on their ophthalmological status and history, two groups of patients were constituted.

Normal control subjects

Normal control subjects were patients with no remarkable medical or ocular history who sought refractive or cataract surgery. All patients underwent a full eye examination including review of medical history, slit-lamp biomicroscopy and dilated fundoscopic examination. The ORA was used to record the CH and IOPG in both eyes of each patient. Patients with familial or personal history of glaucoma, IOPG > 20 mmHg or abnormal cup : disc ratios were excluded from the study. All subjects underwent corneal topography (Orbscan®; Bausch & Lomb, Inc., Rochester, NY, USA) and subjects with previously undetected keratoconus or suspected forme fruste keratoconus were also excluded.

Glaucomatous patients

All glaucomatous patients had a confirmed white-on-white automated 24-2 or 30-2 Humphrey typically glaucomatous visual field defect. All patients also had a history of OHT and were therefore treated with antiglaucoma eyedrops. Patients with normal tension, pigmentary, inflammatory and aphakic glaucoma and patients who had undergone glaucoma surgery were excluded from the study. Patients with angle-closure glaucoma were also excluded, except for those with a combined mechanism.

Ocular Response Analyzer® measurements were performed in all patients during a medical ophthalmological examination carried out by trained physicians. All patients gave their oral consent to undergo ORA measurement. Unreliable measurements (atypical signals) were excluded. Four measures of the CH were saved and averaged at each examination. During the same examination, GAT IOP and ultrasonic CCT were measured in all patients.

In glaucoma subjects with glaucoma in only one eye, that eye was selected for statistical analysis. In all other subjects (glaucoma subjects with glaucoma in both eyes and control subjects), one eye was randomly selected for statistical analysis. All statistical tests were performed on computer (EXCEL; Microsoft Corp., Seattle, WA, USA). A Student's test (p < 0.05) was used to search for significant differences in CH and CCT between the groups.

Results

Table 1 summarizes baseline characteristics, CCT, CH and IOPG in normal and glaucoma patients. The study included a total of 133 eyes of 133 patients, of whom 75 subjects served as normal controls and 58 had glaucoma. Fifty-one patients (87.9%) had open-angle glaucoma and seven (12.1%) had angle-closure glaucoma with suspected combined mechanism. Mean CH values in healthy and glaucomatous eyes were, respectively, 10.46 ± 1.6 mmHg and 8.77 ± 1.4 mmHg. Mean CCT values were, respectively, 560.2 ± 36.3 μm and 535.3 ± 42.7 μm. Both CH and CCT were significantly lower in glaucomatous eyes than in normal eyes (p < 0.05). There was no statistically significant correlation between age and CH in the control group ($r = -0.149$, p > 0.05), nor in the glaucoma group ($r = -0.078$, p > 0.05). Moderate correlations were found between CCT and CH in both the control

Table 1. Baseline characteristics, central corneal thickness (CCT), corneal hysteresis (CH), and intraocular pressure measured with the ORA (IOPG) in normal ($n = 75$) and glaucoma ($n = 58$) subjects. Values are means $\pm$ standard deviation (SD).

	Normal subjects Mean $\pm$ SD (range)	Glaucoma subjects Mean $\pm$ SD (range)	t-test p-value
Age, years	61.44 ± 10.9 (45–85)	65.68 ± 13.9 (37–93)	0.06
CCT, μm	560.2 ± 36.3 (483–657)	535.34 ± 42.7 (435–654)	0.001
CH, mmHg	10.46 ± 1.6 (7.1–14.9)	8.77 ± 1.4 (5.0–11.3)	< 0.0001
IOPG, mmHg	15.9 ± 2.6 (10.3–19.9)	17.1 ± 5.1 (7.3–29.8)	0.09

($r = 0.543$, $p < 0.05$) and glaucoma groups ($r = 0.679$, $p < 0.05$). In the control group, we found no correlation between CH and IOPG ($r = 0.003$, $p > 0.05$). However, we found a statistically significant correlation between CH and IOPG in the glaucoma group ($r = -0.262$, $p < 0.05$).

Discussion

In this study, CH, like CCT, was significantly lower in glaucoma patients than in control subjects. Congdon et al. (2006) postulated that lower CH might be associated with a progressive field worsening. The relationship between glaucoma, IOP and ocular structures may therefore not be confined to the consideration of CCT.

Intraocular pressure is underestimated in patients with thin CCT (Ehlers et al. 1975). Similarly, a low CH value may be responsible for the underestimation of IOP when measured with GAT. Some epidemiological studies have found a systematic bias in IOP measurements in certain races. As Foster et al. (2000) were unable to identify any association between measurement error and corneal thickness, corneal curvature, anterior chamber depth or axial length, this bias may reflect differences in corneal biomechanics. These, in turn, may be explained by differences in the composition of ocular structures. Thus, the 'elastic responses' of eyes with the same CCT might differ.

According to Copt et al. (1999), overestimation of IOP in normal subjects who have thick corneas may lead to a misdiagnosis of OHT, and, if IOP were to be corrected for CCT, many patients with OHT might be reclassified as normal. We may also assume that correcting IOP values according to CH might change a patient's diagnosis. Indeed, we found a moderate, but significant, correlation between IOPG and CH in glaucoma patients. However, this correlation was not significant in healthy patients.

It is also possible that CCT and CH each correspond to risk factors for glaucoma, independent of IOP. Eyes with lower CH and/or thinner than normal CCT might exhibit structural weakness. Some researchers have already found a lower CCT in normal-tension glaucoma (NTG) eyes than in open-angle glaucoma eyes (Copt et al. 1999). Corneal hysteresis represents a dynamic resistance component of the cornea (Congdon et al. 2006). More elastic or distensible ocular structures may be associated with the progression of glaucomatous lesions and, according to this hypothesis, the biomechanical status of the cornea may reflect weakness of the lamina cribrosa. Indeed, Bochmann et al. (2008) compared CH measurements in glaucoma patients and patients with acquired pit of the optic nerve head (APON). The latter condition predominantly occurs in NTG and is associated with a higher risk of progressive optic disc changes (Ugurlu et al. 1998). They found that CH was significantly lower in APON than in glaucoma patients (Bochmann et al. 2008). This finding also suggests that a lower CH could be a marker for a possible susceptibility of the optic nerve to glaucomatous damage.

Given that chronic OHT is responsible for lesions on the optic nerve head, it may also lead to alterations in corneal structure, with subsequent reductions in CH and CCT. Indeed, Weizer et al. (2006) showed that CCT diminishes after a mean follow-up of 8 years, and this reduction was more pronounced in glaucomatous patients than in healthy subjects. However, the exact link between this reduction and glaucomatous lesions has not been explained. Other parameters, such as age, may also influence CCT values. Indeed, several studies have shown a reduction of CCT with age (Foster et al. 1998; Nemesure et al. 2003; Kotecha et al. 2006; Moreno-Montanes et al. 2008). According to Ortiz et al. (2007), CH also diminishes with age, which suggests that the elastic properties of the cornea alter with age. In our series, we found no correlation between CH and age in normal and glaucoma subjects. In agreement with our results, Kirwan et al. (2006) found that CH in children was similar to that reported in adults.

In our series, CH was lower in glaucomatous than in normal eyes and several hypotheses can be used to explain these results. However, because of our selection criteria, our groups were not matched for parameters other than age. Therefore, other factors may have affected the CH values in both groups. The majority of our glaucoma patients had been taking glaucoma medications, including prostaglandins, for a significant length of time. There is a chance that this may have affected their corneal biomechanical properties. Prospective studies should be carried out to confirm this hypothesis.

It is known that CH varies with CCT, such that a cornea with a thicker CCT will have a greater CH (Kotecha et al. 2006); this may suggest that the differences in CH between our groups may be partly explained by differences in IOP and CCT. In our series, mean IOPG was 15.9 mmHg in the normal group and 17.1 mmHg in the glaucoma group. The difference between the two groups was not statistically significant ($p = 0.09$). Plus, even though we found a moderate correlation between CH and IOPG in the glaucoma group, there was no correlation in the control group. Central corneal thickness was higher in the normal group than the glaucoma group and we found a correlation between CH and CCT in the normal and glaucoma groups. (Kirwan & O'Keefe (2007) also found a moderately strong correlation between CH and CCT.

Our analyses of CH and CCT were made at a single time-point; however, the values of both parameters can change with time. Therefore, it would be interesting to perform a prospective study with longer follow-up.

Conclusions

The present study simply compared corneal biomechanical findings in a glaucoma and a control group. Further prospective longitudinal studies are required to confirm these results and to analyse the usefulness of CH measurements in clinical practice in order to allow for better interpretation of IOP values and earlier administration of medical treatment.

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Correspondence:
Olivia Abitbol
Department of Ophthalmology
Glaucoma Institute
Saint-Joseph Foundation
185, rue Raymond Losserand - 75674
Paris cedex 14
France
Tel: + 33 144 123 039
Fax: + 33 144 123 285
Email: oliviaabitbol@free.fr