C. Nucci et al. (Eds.)
Progress in Brain Research, Vol. 173
ISSN 0079-6123

CHAPTER 3

Intraocular pressure and central corneal thickness

Gianluca Manni[1,2,*], Francesco Oddone[2], Vincenzo Parisi[2], Adriana Tosto[1] and Marco Centofanti[1,2]

[1]*Biopathology Department, University of Tor Vergata, Rome, Italy*
[2]*G.B. Bietti Eye Foundation — IRCCS, Rome, Italy*

Abstract: From the results of the Ocular Hypertension Treatment Study emerged the conclusion that ocular hypertensive subjects with thinner central corneal thickness (CCT) are at increased risk of developing glaucoma. Although possible underlying biases that could have led to this conclusion are still under investigation, there is an increasing interest in the scientific community to understand the potential mechanisms of this increased risk profile. It has been proposed that interindividual differences in CCT might be purely responsible for inaccuracies of the tonometric readings with potential underestimation of the true IOP in subjects with thinner CCT although it is becoming progressively clearer that the true IOP is unpredictable with linear correction formulas for CCT, and it is likely that other material properties of the cornea contribute, together with CCT, to the tonometric artifact. Recently, it has become possible to measure the biomechanical properties of the cornea in vivo and it has been suggested that differences in corneal biomechanics may be the expression of interindividual structural differences of the ocular tissues (including lamina cribrosa), with potential consequences on the interindividual susceptibility to the glaucomatous damage under the same IOP level. A possible underlying biological risk related to thinner CCTs, independent of the influence on tonometric reading, has been proposed and largely studied after the results of the OHTS were published. Besides the understanding of the mechanism underlying the role of CCT as a risk factor for the development of glaucoma, it is important to understand how the information about CCT should be integrated in the clinical management of both ocular hypertension (OHT) and glaucoma and whether other ocular properties should be measured to better understand the individual risk profile.

Keywords: corneal thickness; corneal biomechanics; tonometry; glaucoma; ocular hypertension; risk factor

Main text

Intraocular pressure (IOP) is an important risk factor for the development of glaucoma from OHT (Gordon et al., 2002) as well as for the progression of an already established glaucoma (Leske et al., 1999; Anderson et al., 2003). The results of the Ocular Hypertension Treatment Study (OHTS) published in 2002 brought to the attention of the scientific and clinical communities the importance of central corneal thickness (CCT) in the clinical management of OHT (Gordon et al., 2002).

Indeed, CCT proved to be the most potent predictor of which OHT subjects would develop glaucoma in a multivariate model of baseline characteristics. Specifically, OHT subjects with thinner corneas were found to be at increased risk of developing glaucoma compared to subjects

*Corresponding author. Tel./Fax: +39-(0)6-20902968;
E-mail: glmanni@inwind.it

DOI: 10.1016/S0079-6123(08)01103-5

with thicker corneas, and this was found to be independent of IOP. This result was subsequently confirmed by the European Glaucoma Prevention Study (EGPS) (Miglior et al., 2007; Pfeiffer et al., 2007) and the merged OHTS–EGPS risk model established CCT as a major element of the glaucoma risk (Gordon et al., 2002; Miglior et al., 2007; Pfeiffer et al., 2007). Ever since these results were published, there have been questions regarding whether the influence of CCT on the risk of developing glaucoma could be solely attributable to the accuracy of IOP measurement or whether other explanations might be advanced, claiming a role for CCT as a truly independent expression of risk. In these studies, IOP was measured by Goldmann applanation tonometry (GAT), originally introduced by Goldmann and Schmidt in the late 1950s (Goldmann and Schmidt, 1957) and still recognized as the gold standard to measure IOP, due to its accurate and reproducible measurements. Nonetheless, potential sources of measurement inaccuracy have been pointed out by Goldmann and Schmidt in their first papers published regarding the device and the technique (Goldmann and Schmidt, 1957). Specifically, they acknowledged that the tonometer was calibrated under the assumption of an average CCT of 500 µm, and that lack of measurement accuracy could be expected in the presence of deviations from this value. This assumption was based upon the principle that the resistance of the central cornea to flattening at a specific applanation area would have been neutralized by the capillary attraction of the tear film present on the corneal surface, under the Imbert–Fick law which states that the internal pressure of a fluid-filled sphere is directly proportional to the force required to applanate a fixed, external area of the sphere, provided that the encapsulating surface is a perfectly elastic, dry, spherical, and infinitely thin membrane. Thus, at the set applanation area of 3.06 mm diameter, it has been calculated that the force needed to flatten the central corneal surface would not influence the measurement unless the corneal resistance to flattening was outside the range that could be counterbalanced by capillary attraction.

The problem of the inaccuracy of IOP measurement was confirmed by studies where IOP was measured both by cannulation of the anterior chamber, likely obtaining the true IOP value, and by GAT. Ehlers et al. (1975) found that the most accurate GAT reading is given in eyes with CCT around 520 µm, and that for every 100 µm deviation from this value, a miss estimation by as much as 7 mmHg could be expected when IOP was measured by GAT. An extreme case was published by Johnson et al. (1978), reporting a patient with a CCT of 900 µm and a GAT IOP of 35 mmHg. After cannulation of the anterior chamber the true IOP was reported to be 11 mmHg, clearly showing that large variations of CCT may result in large inaccuracies of GAT readings.

Today, as the scientific literature has been enriched by epidemiological data of CCT from different populations (Foster et al., 1998, 2003; La Rosa et al., 2001), it is clear that CCT may vary considerably interindividually and depending on ethnic origin. In the OHTS, CCT was found to be thinner in African American participants (mean 529.8 µm) compared to Caucasians (mean 545 µm), and overall approximately 25% of the cohort showed a CCT greater than 600 µm (Aghaian et al., 2004). Considering these data, it is possible to hypothesize that many patients with normal IOP and thicker CCT in both the OHTS and the EGPS might have been misclassified at baseline as ocular hypertensive on the basis of inaccurate GAT IOP estimates, while the counterpart of this selection bias would have been an underestimation of the true IOP in patients with thinner CCT. Thus, the problem of including patients in the trial on the basis of GAT IOP estimates might have led to the enrolment of normal subjects with thicker CCTs who would have never developed glaucoma, and to the underestimation of the true IOP in OHT subjects with thin CCT, leading to an overall overestimation of the role of CCT as risk factor for the development of glaucoma.

Another consideration that could be advanced is that if OHT subjects with thinner CCT are more likely to progress to glaucoma, one would expect that the glaucoma population has an overall thinner CCT compared to the normal population, but this is not supported from epidemiological

data that show similar CCTs in normal subjects and glaucoma patients.

Moreover, considering CCT as a true risk factor for the development of glaucoma from OHT, it could be reasonable to expect an influence of CCT on the risk of progression in patients with an already established glaucoma. Data from the Early Manifest Glaucoma Trial (EMGT) (Leske et al., 1999) do not support this hypothesis. The EMGT was designed to evaluate the effectiveness of reducing IOP in early, previously untreated open-angle glaucoma patients and, as in the OHTS, CCT was measured after enrolment. Unlike the OHTS, the study design of the EMGT was probably more reliable in differentiating the influence of CCT on tonometry artifacts from a possible underlying biological risk related to a thinner CCT: in the EMGT, enrolled subjects were randomly assigned to the treatment or to the observation arm regardless of baseline IOP, and all treated patients received exactly the same treatment (argon laser trabeculoplasty and topical Betaxol) independently from entry IOP level. The results of the EMGT showed that CCT was not a significant predictor for glaucoma progression at 5 years, despite the claim that the sample size of the study, smaller than the OHTS, may have been too small and thus without the statistical power to detect an influence of CCT on the risk of progression; in addition, the followup may have been too short, and the range of IOPs and CCTs too narrow to detect an effect (Brandt, 2007).

A possible underlying biological risk related to thinner CCTs, independent of the influence on tonometric reading, has been proposed and largely studied after the results of the OHTS were published. These studies arise from the hypothesis of a possible correlation between thickness and related biomechanical properties of the central cornea and similar properties of other ocular structures, specifically the lamina cribrosa, able to influence the risk of developing glaucoma or the progression of the disease. Leske et al. (2003) investigated the correlations between CCT and ONH topography changes in response to IOP reduction in POAG patients, under the hypothesis that thinner CCTs might be associated with greater changes of the ONH topography, due to a more compliant lamina cribrosa. They reported that patients with thinner corneas show significantly greater shallowing of the cup, a surrogate marker for lamina cribrosa displacement, and compliance in response to IOP reduction. This finding may support the hypothesis of an increased risk of developing glaucomatous ONH changes secondary to a damage of the retinal ganglion cell axons at the level of the lamina in eyes with thinner CCTs, and laminas more prone to be displaced in response to IOP changes. Nonetheless, changes of the ONH topography were not confirmed by Nicolela et al. (2006) for relatively moderate IOP changes of the order of 5 mmHg. Moreover, it must also be considered that the stage of the ONH glaucomatous damage and the duration of the disease may also influence the degree of compliance of the lamina in response to IOP changes, so that for more advanced and long-standing damages less compliance of the lamina might be expected.

While several studies have been published trying to build mathematical models that would result in formulas to help the correction of GAT readings for CCT in the clinical practice (Ehlers et al., 1975; Orssengo and Pye, 1999), it appears progressively clearer that the true IOP is likely unpredictable with linear correction formulas for CCT, while it is likely that other material properties of the cornea might contribute, together with CCT, to the tonometric artifact. Using a biomechanical model of the cornea, the simulation results indicated that differences in corneal biomechanics across individuals may have greater impact on IOP measurement errors than CCT, and that if the material properties of the cornea were kept constant, variations in CCT would have the potential to produce errors of magnitudes of 2–3 mmHg from true IOP, while variations in biomechanical properties may result in IOP measurement errors up to 17 mmHg (Liu and Roberts, 2005; Brandt, 2007). In other words, it is likely that two eyes with the same true IOP and CCT but different corneal biomechanics (e.g. stiffness) give different GAT readings, and this is likely to represent one of the main reasons for which no linear correction formula is applicable if only CCT is introduced in the model to adjust the GAT reading.

Only recently, it has become possible to measure the biomechanical properties of the cornea in vivo and the role of corneal biomechanics has been the subject of a recent review by Kotecha (2007). This review pointed out that the importance of corneal biomechanics to the glaucoma clinician primarily rests with its effects on IOP measurement, although it is not possible to completely exclude the fact that corneal biomechanics may give an indication of the structural integrity of the optic nerve head. The Ocular Response Analyzer (ORA; Reichert Corporation; Depew, USA) has been recently developed by Reichert: this instrument is able to measure the corneal response to a rapid jet of air. The jet of air generates a corneal indentation consisting of an initial inward applanation and a second outward applanation when the cornea reverts to its steady shape. The instrument is able to quantify the force required to flatten the cornea during the first and second applanation separately. It has been found that the second applanation occurs at a lower IOP than the first, and the difference between the two pressures is called corneal hysteresis (CH). CH is believed to be a measure of corneal biomechanics and may contribute, together with CCT, to explain the corneal behavior during applanation tonometry. It has been observed that CH is reduced in eyes with keratoconus (Shah et al., 2007), Fuch's endothelial dystrophy (Luce, 2005), and congenital glaucoma (Kirwan et al., 2006), especially if Haab's striae are present. A marked decrease of CH following laser in situ keratomileusis has also been reported (Kirwan and O'Keefe, 2007; Ortiz et al., 2007). Since CH is not independent from CCT, and from the level of true IOP, further studies are required to elucidate the role of this property during applanation tonometry.

Other parameters such as corneal resistance factor (CRF) and a corneal constant factor (CCF) have been developed from the ORA measurement and both are believed to be relatively unaffected by the IOP level despite being positively associated with CCT (Kotecha, 2007). However, further studies are required to clearly understand which biomechanical properties are represented by these parameters and how they may influence applanation tonometry.

It has also been suggested that differences in corneal biomechanics may be the expression of interindividual structural differences of the ocular tissues (including lamina cribrosa), with potential consequences on the interindividual susceptibility to the glaucomatous damage under the same IOP level. A retrospective chart review by Congdon et al. (2006) has recently reported that low values of CH are associated with visual field progression, despite larger and longer studies are required to determine the role of CH in determining the glaucoma susceptibility.

The evidence of the influence of CCT on the GAT reading stimulated the development of new technologies to measure IOP independently from CCT, and among the new tonometers, the dynamic contour tonometer (DCT; Swiss MicrotechnologyAG, Port, Switzerland) has been proposed to reduce the corneal effect and to improve the accuracy of IOP assessment.

DCT is a new digital nonapplanation contact tonometer with a concave surface of the tonometer tip that matches the contour of the cornea, creating an equilibrium between capillary force, rigidity force, appositional force, and force exerted on the cornea by IOP. A piezoelectric sensor integrated into the contoured surface of the tip measures IOP once the corneal contour is perfectly matched. In a clinical observational study on 176 eyes, Kamppeter and Jonas (2005) observed a lower dependence of DCT–IOP on CCT than applanation tonometry, and this result is in agreement with several reports performed on mixed populations of healthy and glaucomatous eyes (Martinez de la Casa et al., 2006; Francis et al., 2007; Medeiros et al., 2007; Ceruti et al., 2008; Herdener et al., 2008). However, a significant correlation between CCT and DCT–IOP was reported by Grieshaber et al. (2007) in POAG patients. The authors hypothesized that in contrast to healthy subjects, patients with POAG have increased IOP, which is independent of CCT and, furthermore, the corneal rigidity in patients with glaucoma may be altered primarily or secondarily to topical drugs, possibly affecting IOP measurements, as some antiglaucomatous drugs may modulate the extracellular matrix (Ito et al., 2006; Brandt, 2007). Therefore, the potential

advantage of DCT relative to CCT independence may not hold true for patients with POAG.

The answer to the clinical questions of whether CCT measurement is useful in the clinical practice and how the pachimetric data should influence the clinical decision process in the management of glaucoma suspects, established glaucomas, or OHT is all but straightforward.

The evidence that CCT is a reliable indicator of risk for progression of OHT to glaucoma is consistent, as shown by the OHTS and EGPS results. The decision to treat a patient with OHT depends on an assessment of risk, and CCT is an important and necessary part of that determination while there is little evidence that CCT is useful in predicting progression of glaucoma as shown by the results of EMGT. Besides the hypothesis that CCT might influence the underlying biological risk to develop glaucoma, there is the universally acknowledged influence of CCT on IOP measurements, and the fact that IOP is an important parameter for diagnosing glaucoma and represents the only risk factor modifiable with therapy.

As previously discussed, a correction formula for CCT would be useful to improve the accuracy of GAT readings, but considering the variety and inconsistency of the published correction algorithms, the arbitrary selection of one algorithm carries the risk of introducing further errors rather than removing them.

Moreover, the accuracy in measuring true IOP might not be absolutely necessary in every stage of glaucoma management and the error induced in an individual case is likely to be constant, not impairing monitoring of IOP changes over time.

It is generally accepted and consistent in most reports in the literature that thicker corneas are associated with an overestimation of the true IOP and thinner corneas are associated with an underestimation of the true IOP although it is likely that for the majority of patients the inaccuracy would be small with little clinical impact.

On the basis of the scientific knowledge available so far, it is likely that a reasonable approach is, as proposed by James D. Brandt, to ''take care of patients simply by categorizing corneas as thin, average or thick, just as it is important to recognize that optic discs come in small, medium, and large, allowing the clinician to interpret the configurations accordingly'' (Brandt, 2007).

References

Aghaian, E., Choe, J.E., Lin, S. and Stamper, R.L. (2004) Central corneal thickness of Caucasians, Chinese, Hispanics, Filipinos, African Americans, and Japanese in a glaucoma clinic. Ophthalmology, 111(12): 2211–2219.

Anderson, D.R.Normal Tension Glaucoma Study. (2003) Collaborative normal tension glaucoma study. Curr. Opin. Ophthalmol., 14(2): 86–90.

Brandt, J.D. (2007) Central corneal thickness, tonometry, and glaucoma risk — a guide for the perplexed. Can. J. Ophthalmol., 42(4): 562–566.

Ceruti, P., Morbio, R., Marraffa, M. and Marchini, G. (2008) Comparison of Goldmann applanation tonometry and dynamic contour tonometry in healthy and glaucomatous eyes. Eye, 25(1):

Congdon, N.G., Broman, A.T., Bandeen-Roche, K., Grover, D. and Quigley, H.A. (2006) Central corneal thickness and corneal hysteresis associated with glaucoma damage. Am. J. Ophthalmol., 141: 868–875.

Ehlers, N., Bramsen, T. and Sperling, S. (1975) Applanation tonometry and central corneal thickness. Acta Ophthalmol. (Copenh.), 53: 34–43.

Foster, P.J., Baasanhu, J., Alsbirk, P.H., Munkhbayar, D., Uranchimeg, D. and Johnson, G.J. (1998) Central corneal thickness and intraocular pressure in a Mongolian population. Ophthalmology, 105: 969–973.

Foster, P.J., Machin, D., Wong, T.Y., Ng, T.P., Kirwan, J.F., Johnson, G.J., Khaw, P.T. and Seah, S.K. (2003) Determinants of intraocular pressure and its association with glaucomatous optic neuropathy in Chinese Singaporeans: the Tanjong Pagar Study. Invest. Ophthalmol. Vis. Sci., 44(3): 885–891.

Francis, B.A., Hsieh, A., Lai, M.Y., Chopra, V., Pena, F., Azen, S. and Varma, R.Los Angeles Latino Eye Study Group. (2007) Effects of corneal thickness, corneal curvature, and intraocular pressure level on Goldmann applanation tonometry and dynamic contour tonometry. Ophthalmology, 114(1): 20–26.

Goldmann, H. and Schmidt, T. (1957) Applanation tonometry. Ophthalmologica, 134(4): 221–242.

Gordon, M.O., Beiser, J.A., Brandt, J.D., Heuer, D.K., Higginbotham, E.J., Johnson, C.A., Keltner, J.L., Miller, J.P., Parrish II, R.K., Wilson, M.R. and Kass, M.A. (2002) The ocular hypertension treatment study: baseline factors that predict the onset of primary open-angle glaucomaArch. Ophthalmol., 120: 714–720. discussion 829–830

Grieshaber, M.C., Schoetzau, A., Zawinka, C., Flammer, J. and Orgul, S. (2007) Effect of central corneal thickness on dynamic contour tonometry and Goldmann applanation tonometry in primary open-angle glaucoma. Arch. Ophthalmol., 125(6): 740–744.

Herdener, S., Hafizovic, D., Pache, M., Lautebach, S. and Funk, J. (2008) Is the PASCAL-tonometer suitable for measuring intraocular pressure in clinical routine? Long- and short-term reproducibility of dynamic contour tonometry. Eur. J. Ophthalmol., 18(1): 39–43.

Ito, T., Ohguro, H., Mamiya, K., Ohguro, I. and Nakazawa, M. (2006) Effects of antiglaucoma drops on MMP and TIMP balance in conjunctival and subconjunctival tissue. Invest. Ophthalmol. Vis. Sci., 47(3): 823–830.

Johnson, M., Kass, M.A., Moses, R.A. and Grodzki, W.J. (1978) Increased corneal thickness simulating elevated intraocular pressure. Arch. Ophthalmol., 96: 664–665.

Kamppeter, B.A. and Jonas, J.B. (2005) Dynamic contour tonometry for intraocular pressure measurement. Am. J. Ophthalmol., 140(2): 318–320.

Kirwan, C. and O'Keefe, M. (2007) Corneal hysteresis using the Reichert ocular response analyser: findings pre- and post-LASIK and LASEK. Acta Ophthalmol. Scand., 21.

Kirwan, C., O'Keefe, M. and Lanigan, B. (2006) Corneal hysteresis and intraocular pressure measurement in children using the Reichert ocular response analyzer. Am. J. Ophthalmol., 142(6): 990–992.

Kotecha, A. (2007) What biomechanical properties of the cornea are relevant for the clinician? Surv. Ophthalmol., 52(Suppl 2): 109–114.

La Rosa, F.A., Gross, R.L. and Orengo, N.S. (2001) Central corneal thickness of Caucasians and African Americans in glaucomatous and nonglaucomatous populations. Arch. Ophthalmol., 119: 23–27.

Leske, M.C., Heijl, A., Hyman, L., Bengtsson, B., Dong, L. and Yang, Z. (1999) Early manifest glaucoma trial: design and baseline data. Ophthalmology, 106: 2144–2153.

Leske, M.C., Heijl, A., Hussein, M., Bengtsson, B., Hyman, L. and Komaroff, E.Early Manifest Glaucoma Trial Group. (2003) Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch. Ophthalmol., 121(1): 48–56.

Liu, J. and Roberts, C.J. (2005) Influence of corneal biomechanical properties on intraocular pressure measurement: quantitative analysis. J. Cataract Refract. Surg., 31: 146–155.

Luce, D.A. (2005) Determining *in vivo* biomechanical properties of the cornea with an ocular response analyzer. J. Cataract Refract. Surg., 31(1): 156–162.

Martinez de la Casa, J.M., Garcia Feijoo, J., Vico, E., Fernandez Vidal, A., Benitez del Castillo, J.M., Wasfi, M. and Garcia Sanchez, J. (2006) Effect of corneal thickness on dynamic contour, rebound, and Goldmann tonometry. Ophthalmology, 113(12): 2156–2162.

Medeiros, F.A., Sample, P.A. and Weinreb, R.N. (2007) Comparison of dynamic contour tonometry and Goldmann applanation tonometry in African American subjects. Ophthalmology, 114(4): 658–665.

Miglior, S., Pfeiffer, N., Torri, V., Zeyen, T., Cunha Vaz, J. and Adamsons, I. (2007) Predictive factors for open-angle glaucoma among patients with ocular hypertension in the European glaucoma prevention study. Ophthalmology, 114(1): 3–9.

Nicolela, M.T., Soares, A.S., Carrillo, M.M., Chauhan, B.C., LeBlanc, R.P. and Artes, P.H. (2006) Effect of moderate intraocular pression changes on topographic measurement with confocal scanning laser tomography in patients with glaucoma. Arch. Ophthalmol., 124(5): 633–640.

Orssengo, G.J. and Pye, D.C. (1999) Determination of the true intraocular pressure and modulus of elasticity of the human cornea in vivo. Bull. Mathematical Biol., 61: 551–572.

Ortiz, D., Piñero, D., Shabayek, M.H., Arnalich Montiel, F. and Alió, J.L. (2007) Corneal biomechanical properties in normal, post-laser in situ keratomileusis, and keratoconic eyes. J. Cataract Refract. Surg., 33(8): 1371–1375.

Pfeiffer, N., Torri, V., Miglior, S., Zeyen, T., Adamsons, I. and Cunha Vaz, J. (2007) Central corneal thickness in the European glaucoma prevention study. Ophthalmology, 114(3): 454–459.

Shah, S., Laiquzzaman, M., Bhojwani, R., Mantry, S. and Cunliffe, I. (2007) Assessment of the biomechanical properties of the cornea with the ocular response analyzer in normal and keratoconic eyes. Invest. Ophthalmol. Vis. Sci., 48(7): 3026–3031.