Central corneal thickness, tonometry, and glaucoma risk — a guide for the perplexed

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ABSTRACT • RÉSUMÉ

The results of the Ocular Hypertension Treatment Study (OHTS) brought to the forefront the role of central corneal thickness (CCT) as a confounder of applanation tonometry, and established CCT as an independent predictive factor for the development of glaucoma. Ophthalmologists often wonder how to use CCT in daily practice. This article reviews the current CCT literature and provides some basic guidance to clinicians wishing to integrate CCT into their care of glaucoma patients.

Les résultats de l'étude sur le traitement de l'hypertension oculaire (ETHO) font ressortir le rôle de l'épaisseur du centre de la cornée (ÉCC) en tant que facteur de confusion en tonométrie par aplanation et établissent l'ÉCC comme facteur prédictif du développement du glaucome. Les ophtalmologistes se demandent souvent comment utiliser l'ÉCC dans leur pratique quotidienne. Cet article examine la littérature courante sur l'ÉCC et présente quelques conseils de base aux cliniciens qui souhaitent intégrer l'ÉCC dans le soin des patients atteints du glaucome.

> "I do not object to having a patient of mine subjected to examination with a mechanical tonometer, but expect very little from this test since digital tonometry by an expert is a much more accurate test…"
>
> Isador Schnabel (1842–1908) before the Vienna Ophthalmological Society, 1908

Ever since the recognition that certain forms of blindness were associated with a firm eye, ophthalmologists have been trying to measure intraocular pressure (IOP). The simultaneous explosion of ophthalmic knowledge and medical instrument-making in the 19th century led to mechanical tonometers of varied underlying principles and designs. These devices were met with almost uniform suspicion by the leaders of the day. More than a century later, it seems that perhaps their skepticism was well founded.

Goldmann applanation tonometry (GAT) rapidly gained widespread acceptance following its introduction in the 1950s. It was reasonably priced, based on easily understood physical principles, fit seamlessly into the workflow of the slit-lamp examination, and appeared to provide accurate, reproducible measurements. GAT's status as a "gold standard" went largely unchallenged for 50 years, even though Professor Goldmann himself drew attention to various potential sources of error for the device in his first description of his tonometer. In particular, Goldmann and Schmidt[1] acknowledged that their design assumptions were based on a central corneal thickness (CCT) of 500 μm and that the accuracy of their device would vary if CCT deviated from this value. Given the paucity of published data at the time, 500 μm seemed a reasonable assumption for the "average" patient. We now know that CCT varies greatly in the population, to a degree that affects the accuracy of GAT in daily practice.

In 1975, Ehlers et al.[2] cannulated 29 otherwise normal eyes undergoing cataract surgery and correlated corneal thickness with errors in GAT. They found that GAT most accurately reflected "true" intracameral IOP when CCT was 520 μm and that deviations from this value resulted in an over or underestimation of IOP by as much as 7 mm Hg per 100 μm. Subsequent cannulation experiments performed with modern pressure transducers have confirmed Ehlers et al.'s basic findings.[3,4] Numerous

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investigators have since demonstrated that CCT varies far more among otherwise normal individuals than Goldmann and Schmidt ever dreamed; differences in CCT are seen among different racial and ethnic groups[5–7] and may lead to misclassification of patients with normal tension glaucoma and ocular hypertension.[8,9]

The ocular hypertension treatment study

The importance of CCT in the management of glaucoma patients, particularly those with ocular hypertension, was brought to the forefront by findings from the Ocular Hypertension Treatment Study (OHTS).[10,11] Among the OHTS participants, African–American participants had thinner corneas than their Caucasian counterparts, and 25% of the overall OHTS cohort had CCT values above 600 μm.[7] If one uses Ehlers' correction of roughly 7 mm Hg/100 μm deviation from the nominal value of 520 μm, then as many as 50% of OHTS subjects had "corrected" IOP values upon entry of 21 mm Hg! Most dramatically, in a multivariate model of baseline characteristics found to be predictive of which OHTS subjects would develop glaucoma, CCT proved to be the most potent.[11] These findings have been confirmed independently in the European Glaucoma Prevention Study (EGPS),[12,13] and the merged OHTS/EGPS risk model features CCT as a major component of glaucoma risk.[14]

The OHTS and EGPS results suggest that many patients are being misclassified in terms of glaucoma risk on the basis of erroneous IOP estimates by GAT. Clearly, many individuals with elevated GAT measurements but no other findings suggestive of glaucoma probably have normal "true" IOPs and do not need treatment or even increased glaucoma surveillance. CCT measurements in patients with diagnosed glaucoma also appear useful: following the OHTS publications, numerous investigators have explored the role of CCT in patients with existing glaucoma, and they have generally found CCT to have a significant impact in these patients as well.[15–22]

CCT differences among racial groups

Several investigators recently provided further evidence that African–American subjects, as a group, tend to have thinner corneas than their Caucasian counterparts. Nemesure et al.,[23] following a CCT survey of participants in the Barbados Eye Survey, reported that black participants had thinner corneas (mean thickness 529.8 μm) than white participants (545 μm). No relation between IOP and CCT was found in this population-based survey. Shimmyo and colleagues[24] performed a retrospective biometric review of patients at a large refractive surgery center, also finding that African–American patients had thinner corneas than Caucasian patients seeking refractive surgery; there was no difference in CCT among Caucasian, Asian, and Hispanic patients in their population. This is in contrast to the findings of the population-based Los Angeles Latino Eye Study,[25] which found CCTs in Hispanic patients to be intermediate between values reported for African–American and Caucasian populations.

CCT — tonometry artifact, or something more?

The results of the OHTS and other studies raise the question of whether CCT's influence on glaucoma risk is attributable solely to its known impact on tonometry or to something else. Perhaps there is a biological link between aspects of the front of the eye that can be measured, such as the thickness or material properties of the cornea (e.g., corneal hysteresis), and the structure, deformability, or physiology of the lamina cribrosa and peripapillary sclera.

The OHTS and other studies that demonstrate a link between CCT and either glaucoma risk or disease severity are unable to separate tonometry effect from underlying biological risk. In the OHTS, initial eligibility was based primarily on GAT; in the OHTS and in retrospective chart reviews of CCT and glaucoma it is impossible to account for physician behavior in treatment decisions driven by GAT results.

In contrast to the OHTS, which studied patients initially enrolled *without* glaucoma damage, the Early Manifest Glaucoma Trial (EMGT)[26] studied subjects *with* glaucomatous damage documented at enrollment. Like the OHTS, the EMGT measured CCT in all participants shortly after enrollment had been completed. Two fundamental differences between the OHTS and EMGT, at least from the standpoint of differentiating tonometry artifact from an underlying biological link related to CCT, are that the EMGT randomly assigned patients to treatment vs. observation without regard to entry IOP, and all subjects in the treatment arm received the same treatment: laser trabeculoplasty and betaxalol. This design minimized the influence of tonometry artifact on physician behavior.

In a publication analyzing baseline risk factors for progression of glaucoma at 5 years among EMGT participants, Leske et al.[27] reported that CCT was *not* a significant predictor of progression. However, the EMGT was a relatively small sample (at least compared with the OHTS) and may not have had the statistical power to find such a relation. The EMGT investigators have published few details on the range and distribution of CCTs measured in their racially homogeneous population; it is quite possible it was far narrower than what was found in the OHTS. If there is an effect of CCT on progression

rates in established disease, the EMGT might be too small, the follow-up too short, and the range of IOPs and CCTs too narrow to detect an effect.

CCT as a biological risk factor

Whether CCT's influence on glaucoma risk has an underlying biological component is a fascinating issue, one that is being actively investigated around the world. Mark Lesk and colleagues[28] at the University of Montréal used confocal scanning laser ophthalmoscopy to measure the movement of the lamina cribrosa after profound IOP lowering. They found that the lamina moved forward more in patients with thin corneas than in those with thick corneas, in contrast to the results of Nicolela et al.,[29] which showed no such relation. Recently, Nathan Congdon and colleagues[19] from Wilmer showed that corneal hysteresis (a measure of corneal "stiffness") was independently associated with glaucoma risk. Pakravan et al.[30] recently reported that CCT was linked to disc size, thicker corneas being associated with smaller optic discs. Finally, Toh and associates[31] in Australia recently showed that CCT is among the most highly heritable aspects of ocular structure. The preponderance of these findings hints at a link between both the thickness and material properties of the cornea and similar properties of the various ocular coats, including the lamina. The OHTS finding(s) and other studies have generated an enormous interest in the material properties of the ocular coats of the eye and the likelihood that they may underlie some aspects of the genetic susceptibility to glaucoma.

Implications for clinical practice

Confronted with the expanding evidence that CCT is an important ocular parameter that should be measured in clinical practice, most ophthalmologists acquire pachymetry measurements in their patients but then wonder what to do with the information. How to use CCT measurements in daily practice, however, is not as straightforward. There is wide disagreement among investigators as to whether there is an adequately validated correction algorithm; without a validated algorithm, the argument goes, clinicians cannot use the data. When the pachymetry protocol was added to the OHTS,[7] most of the investigators (myself included) believed that CCT's impact in the OHTS would be primarily through its effect as a confounder in GAT measurements. It is notable that attempts to model and adjust the OHTS IOP data using every published correction nomogram for GAT and CCT has so far failed to eliminate CCT as a predictive factor from the OHTS multivariate model.

Several engineering models of the cornea suggest that variations in the material properties of the cornea (i.e., viscoelastic properties or Young's modulus, an engineering term for inherent properties) can dwarf the effect of CCT on GAT measurements.[32,33] These models suggest that if the material properties of the cornea were constant, variations in CCT from mid-400 to mid-600 μm would explain only some ± SD 4 mm Hg in variance from true (directly measured) IOP. These same models suggest that variations in the material properties of the cornea (measured directly only ex vivo but thought to vary by several orders of magnitude) could explain ± 10 mm Hg in the variance from true IOP. For example, a lifelong 625 μm cornea might behave quite differently from one that was thickened by subclinical edema. In the latter case, a thicker, slightly edematous cornea may in fact measure *lower* by GAT than expected. Thus it is entirely possible that in correcting GAT by a fixed, linear correction nomogram, the ophthalmologist can be wrong both in the magnitude of the adjustment but also in its direction. Remember that in the linear regressions generated by cannulation experiments, just as many data points lie above the regression line as below: the data points above the line need to be "corrected" downwards, those below "corrected" upwards. For this reason no generalized correction nomogram can ever adequately adjust IOP without much more being known about the individual cornea being applanated. Again, depending on which nomogram is used, if GAT measurements are corrected only for CCT then they may be off by quite a bit (and even in the wrong direction!).

If there is one thing I have learned over the past few years of performing pachymetry on my patients it is that one can take far better 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 disc configurations accordingly. Measuring CCT leads to the discontinuation of therapy in many overtreated patients with ocular hypertension and escalation of therapy in patients with thin corneas in whom control is clearly inadequate. Ultimately, incorporating the measurement of CCT into the glaucoma examination allows the astute clinician to better target and titrate the treatment of glaucoma.

Diabetes — A useful analogy

If we in fact *could* adjust GAT measurements to improve their accuracy, would this represent a big advance? Among chronic diseases, glaucoma is remarkable in that its primary risk factor, IOP, is measured only rarely and mostly randomly, perhaps a few times a year in most patients. This state of affairs has been unchanged for well

over a century. The measurement of blood sugar for the management of diabetes, however, has evolved during that same period from random, crude measurements of urinary and blood glucose to fasting blood sugar, glucose tolerance tests, glycosylated hemoglobin, and affordable, computerized portable glucometers to adjust therapy in real time. If diabetes management were still in the era of random blood sugar measurements, would improving the accuracy of these measurements improve the care of diabetic patients? Not really. Similarly, focusing on improving the accuracy of an inherently flawed and random measurement is unlikely to improve the care of our patients. We need to focus our efforts on 24-h monitoring, self-monitoring, and a better understanding of the material properties of the eye as we move forward in the 21st century.

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