Main topic: The Role of IOP in Glaucoma

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LEARNING OBJECTIVES

• Special Focus: A detailed description of the role of tonometry and other parameters influencing the results of IOP measurement. Pros and cons of all current approaches are discussed.

• What’s New: A comprehensive summary of the newest research findings around the role of the trabecular meshwork as well as the trabecular and uveoscleral outflow.

• Clinical Issues: A summary reviewing the relationship between sleep apnea and the occurrence of high IOP.

• Practical Tips: An in-depth expert discussion on how and when to apply the water-drinking-test and how to interpret results.

TARGET AUDIENCE

This educational activity is aimed at general ophthalmologists, glaucoma specialists and ophthalmology residents.

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Special Focus:
The Role of IOP – Tonometry and its Limitations

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Core Concepts
- Goldmann tonometry (GAT) is the most widely-used method of tonometry worldwide and is generally regarded as a ‘gold standard’ – but even under ideal conditions GAT has a reproducibility of ± 2.5 mmHg.
- Most tonometers in clinical practice are not out of calibration, a major cause of tonometry error. Ophthalmologists should know how to check calibration and have a protocol to do so regularly.
- Central Corneal Thickness (CCT) is a major confounder of GAT accuracy but ‘correction’ formulae and nomograms should not be used for individual patients.
- CCT should be measured in all patients, and can be used in the OHTS-EGPS predictive model to calculate risk of glaucoma onset among patients with ocular hypertension
- Glaucoma is unique among chronic diseases in that its primary risk (and likely causative factor) is measured only a few times a year in most patients.
- The importance of CCT in the management of glaucoma patients, particularly those with ocular hypertension, was underlined nearly fifty years later by the findings of the Ocular Hypertension Treatment Study (OHTS).

Measurements acquired during clinical care are always an estimate. We can never begin to approach the true underlying value of a physiological measurement without understanding and accounting for technical pitfalls as well as acquiring numerous measurements to average out the clinical noise in the data. The purpose of this brief review is to drive home the often under-appreciated limitations of current tonometry techniques with a special focus on central corneal thickness (CCT) and how best the clinician can acquire and use the highest quality data.

Goldmann Applanation Tonometry
Goldmann applanation tonometry (GAT) gained widespread and rapid acceptance after its introduction in the 1950s. The device was reasonably priced, and the technique was based on easily understood physical principles. GAT fits seamlessly into the workflow of the slit lamp examination and seems to provide accurate reproducible measurements. GAT arrives at an estimate of IOP based on the force needed to flatten the corneal apex to a given area. A flattened area with a diameter of 3.06 mm was chosen empirically to offset the surface tension of the tear film (which tends to draw the tonometer tip towards the eye) and both corneal and ocular rigidity (which resist applanation, independent of IOP).

That Goldmann tonometry is the “gold standard” and went largely unchallenged for 50 years, although Goldmann and Schmidt acknowledged several limitations in their design.1 In particular, they highlighted that their design assumptions were based on a CCT of 0.5 mm (500 µm) and that the accuracy of their device would vary if CCT deviated from this value.

In 1975, Ehlers cannulated 29 otherwise normal eyes undergoing cataract surgery and correlated corneal thickness with errors in GAT.2 He found that GAT most accurately reflected the true intracameral IOP when CCT was 520 µm and the deviations from this value resulted in an over or under estimation of IOP by as much as 7 mmHg per 100 µm. Subsequent cannulation experiments performed on many more patients with modern pressure transducers have confirmed Ehlers’ basic findings, but with distinct “correction” factors.3, 4 We now know that CCT varies far more among otherwise normal individuals than Goldmann conceived. Differences in CCT are seen between different racial and ethnic groups5 and are likely to lead to misclassification of patients as “normal tension glaucoma”6 and ocular hypertensives.7, 8

The Ocular Hypertension Treatment Study (OHTS)
The importance of CCT in the management of glaucoma patients, particularly those with ocular hypertension, was underlined nearly fifty years later by the findings of the Ocular Hypertension Treatment Study (OHTS). In the OHTS, patients were recruited who had untreated GAT measurements in one eye between 24 and 32 mmHg on two separate occasions (the fellow eye had to be between 21 and 32 mmHg) with no secondary cause of elevated IOP. The patients all had normal visual fields and optic nerves. CCT was measured in participants about 2 years after enrollment was completed. In a multivariate model of those baseline characteristics predictive of which subjects would go on to develop visual field or optic nerve changes attributable to glaucoma after five years, CCT proved to be the most potent.7 This finding was verified in the similar but separate cohort of the European Glaucoma Prevention Study (EGPS). The combined OHTS-EGPS Predictive Model9 can incorporate CCT into the risk assessment of individual patients. The interested reader should go to the OHTS website (http://ohts.wustl.edu/risk/index.html) for downloadable versions of the predictive model to use in direct patient care.

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 ap-
pear 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.

Implications for clinical practice
Confronted with the evidence that CCT is an important ocular parameter and the recommendation that it 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 is not straightforward – there is wide disagreement among investigators as to whether there is any 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, many believed that CCT’s impact would be primarily through its effect as a confounder of GAT measurements.8 Attempts to model and adjust the impact would be primarily through its effect as a confounder of GAT measurements. Therefore, clinicians using CCT data would need to be ‘corrected’ upwards, those below ‘corrected’ downwards. In attempting to correct GAT measurements acquired in an individual patient using a fixed, linear correction nomogram, the ophthalmologist can thus be wrong both in the magnitude of the adjustment and also in its direction. A thick cornea gives rise to a greater probability of an IOP being overestimated (or in the case of a thin cornea, of IOP being underestimated) but the extent of measurement error in individual patients cannot be determined from CCT alone. No generalized ‘correction nomogram’ can ever adequately adjust IOP without knowing much more about the individual cornea being applanated. To add yet another layer of complexity, as actual IOP increases, both the cornea and sclera become stiffer – thus the relationship between GAT, CCT and “true” IOP varies across a range of IOPs in the same patient.

Practical Considerations – Tonometer Calibration
The terms ‘accuracy’ and ‘precision’ are often used interchangeably, but they are not the same. In the context of our discussion, ‘accuracy’ refers to a tonometer’s ability to reflect the ‘true’ intracameral IOP measurement, whereas ‘precision’ reflects how repeatable those measurements are. Both inaccuracy and imprecision will cause measured IOP to deviate from ‘true’ IOP, and it is the clinician’s task to recognize and account for both. With a modern ultrasonic pachymeter, CCT can be measured with great precision and accuracy. Goldmann tonometers, on the other hand, have mediocre precision (± 2.5 mmHg under ideal conditions in a controlled clinical trial) and most Goldmann tonometers in clinical use fall far from even this ideal –most tonometers develop calibration errors greater than ± 2.5 mmHg after just a few months of use.16 Goldmann tonometers represent a 60 year old mechanical technology (Figure 1) largely unchanged from the original design introduced in 1957. Why do Goldman tonometers go out of calibration? In addition to obvious things like being dropped or otherwise abused, the fluids used to clean the tonometer tip can leak into the mechanics of the device and cause corrosion or loss of lubricant. If a tonometer is mounted to a slit lamp that is itself not completely level, the device will not work as designed.

Very few clinicians check the calibration of Goldmann tonometers they use to make potentially life-changing clinical decisions.17 Indeed, few ophthalmologists or their staff know how to perform the calibration process, nor do they have protocols in place to assure this is done on a regular basis. In this context, applying very precise CCT measurements to poorly-calibrated and imprecise GAT measurements to arrive at a ‘more accurate’ estimate of IOP does not make a lot of sense.

CCT – Tonometry artifact, or something more?
The results of studies like OHTS beg the question whether CCT’s powerful influence on glaucoma risk arises because of how we measure IOP and is attributable solely to CCT’s impact on tonometry, or to something else. Might there be a biological link between aspects of the front of the eye that can be measured, such as CCT or biomechanical properties of the cornea and the structure/deforability/physiology of the lamina cribrosa and peri-papillary sclera that might underlie susceptibility to the glaucomatous optic neuropathy?
Whether CCT’s influence on glaucoma risk has an underlying biological component is a fascinating issue, one that is under active investigation by clinicians, biomedical engineers and molecular geneticists. Using confocal scanning laser ophthalmoscopy to measure the movement of the lamina cribrosa after induced changes in IOP, increased movement of the lamina has been found in subjects with thinner corneas or lower corneal hysteresis, thus linking the compliance of the optic nerve head to measurements made at the ocular surface.

CCT is among the most highly-heritable aspect of ocular structure. The findings that hint at a link between the thickness and material properties of the cornea with similar properties of the various ocular coats, including the lamina, suggest that CCT-controlling genes might be some of the genes involved in glaucoma pathophysiology. Investigators have identified a number candidate genes linked to CCT. Thus far these candidate genes appear to be linked most closely to keratoconus and their relationship to open-angle glaucoma risk remains to be proven.

The Bigger Picture

Among chronic diseases, glaucoma is remarkable in that its primary risk factor, IOP, is measured only rarely and mostly randomly, perhaps just a few times a year in most patients. This state of affairs has been unchanged for well over a century. During that same period, the measurement of blood sugar for the management of diabetes has evolved from random, crude measurements of urinary and blood glucose to fasting blood sugar, glucose tolerance tests, glycosylated hemoglobin and affordable computerized portable glucometers that allow patients to adjust therapy in real time. If diabetes management were still in the era of random blood sugar measurements, improving the accuracy of these measurements would not improve the care of diabetic patients. Similarly, focusing on improving the accuracy of an inherently flawed and random measurement is unlikely to improve the care of our patients. The water-drinking test described elsewhere in this monograph is the closest we have yet to a practical, “glucose tolerance test analog” for glaucoma. We need techniques for the continuous, real-time monitoring of IOP. A tonometric “Holter Monitor” for the eye that records IOP for a few weeks with a precision of ± 3 mmHg would be far more useful for patient care than a new tonometer unaffected by corneal parameters with a precision ± 0.1 mmHg but still used to acquire random measurements. Such technology is coming but is not yet practical for widespread deployment.

In summary, ophthalmologists should view current techniques of tonometry (and the way we use them) with skepticism. Measuring CCT doesn’t improve the accuracy of GAT, but one can take far better care of patients by using CCT in our now well-established risk models. Simply categorizing corneas as ‘thin, average or thick’ helps the clinician better understand IOP-related risk, just as recognizing that optic discs come as ‘small, medium and large’ helps the clinician better interpret disc appearance. Measuring CCT leads to the discontinuation of therapy in many over-treated ocular hypertensives and escalation of therapy in patients with thin corneas in whom control is clearly inadequate. Ultimately, incorporating the measurement of CCT into the glaucoma exam and avoiding a rigid IOP-centric approach to glaucoma management allows the astute clinician to better target and titrate the treatment of glaucoma.

References
The glaucomas are a leading cause of blindness globally, and their prevalence is increasing as the population ages. Primary open-angle glaucoma (POAG) is the most common form of the disease, although in some regions of Asia angle closure glaucoma (ACG) is more prevalent. POAG is predominantly composed of high-tension glaucoma (HTG), where intraocular pressure (IOP) is “raised” (IOP >21 mmHg). Normal-tension glaucoma (NTG), which is another important subgroup of POAG, is an optic neuropathy similar to HTG, in which IOP levels are within the statistically normal range (IOP ≤21 mmHg). Lowering IOP reduces the risk of disease.
progression’ and controlling IOP with topical eye drops continues to be the most common first line therapy, for both high- and normal-tension glaucoma. The most commonly prescribed drugs act on either the ciliary process epithelia to reduce aqueous humor production (beta-adrenergic receptor antagonists) or the ciliary muscle cells to increase uveoscleral outflow (prostaglandin analogs that bind to and activate prostaglandin F (FP) receptors). The goal of treatment for all forms of glaucoma is the preservation of visual function.

IOP elevation results from increased outflow resistance in the tissues of the outflow pathways: the trabecular outflow tract (trabecular meshwork or TM) and the uveoscleral pathway. In normal eyes, IOP builds up, in response to the inflow of aqueous humor, to the level sufficient to drive fluid across that resistance at the same rate it is produced by the ciliary body; this is the steady-state IOP. In the study of aqueous humor dynamics an important distinction to make is between aqueous outflow rate (measured in µl/min) and outflow facility (measured as µl/min/mmHg), which refers to hydraulic conductivity, the reciprocal of resistance. In most glaucomatous eyes, the resistance is unusually high, elevating IOP. Flow from the anterior chamber across the TM into Schlemm’s canal is pressure dependent, but drainage through the uveoscleral pathway is essentially independent of pressure at IOP levels greater than 7 to 10 mmHg. In young humans (and young monkeys) the percent flow through each pathway may be close to 50%; with age, TM outflow predominates as uveoscleral outflow declines. Resistance to outflow is thought to be greatest in the juxta-canalicular (JCT) region and inner wall of Schlemm’s canal (SC) (Figure 1) and is directly affected by contraction and relaxation of the ciliary muscle (CM) and TM. Contraction of the CM increases intercellular spaces in the TM, increasing the amount of fluid drained through that pathway. When the CM relaxes, the TM flow pathways become narrower and more resistive while the spaces between the muscle bundles are expanded and uveoscleral outflow is increased. Contractility of the TM also modulates outflow. In perfused anterior eye segments, substances that contract trabecular cells decrease outflow facility, whereas substances that induce relaxation widen intertrabecular flow spaces, increasing outflow facility. Studies of the structural and functional biology of outflow through the TM / SC indicate that many biological pathways intersect and interact to regulate IOP including cholinergic, adrenergic, prostaglandin, cytoskeletal, extracellular matrix (ECM) synthesis and degradation and cell junctional mechanisms.

Recent studies with endothelial nitric oxide synthase (eNOS) knockout mice demonstrate that nitric oxide (NO) serves a biochemical / molecular signaling role in increasing TM (conventional, pressure-dependent) outflow facility; that NO-mediated facility can be manipulated both genetically and pharmacologically and that the NO-mediated facility increase may be triggered by mechanical distension of the TM (Fig-
Figure 3. Schematic drawing of the cribri-form elastic-like plexus (CP) connected to the inner wall endothelium (E) of Schlemm’s canal by connecting fibrils (CF). The outer tendons of the CM, insert into the CP so that muscle contraction can influence the aqueous humor pathways through the cribri-form region and the giant vacuoles of the endothelium(both black) into Schlemm’s canal. Arrow indicates footlike connection between endothelial and subendothelial trabecular cell. With permission from Gabelt BT and Kaufman PL. Changes in aqueous humor dynamics with age and glaucoma, Progress in Retinal and Eye Research 24 (2005) 612–637.

Figure 4. Light micrographs of trabecular meshwork (TM) and Schlemm’s canal (SC) in monkey eyes treated with 300 µM intracameral H-7 (B) or vehicle (A). The JCT and intercellular spaces are extended following H-7 (arrow in B). Inner wall endothelial cells in H-7-treated eyes are thinner than in controls. SC is dilated in H-7 treated eyes. Inner uveal TM (b) is not significantly affected. Bars are 50 µm. With permission from: Overby, D.R., Stamer, W.D., Johnson, M, The Changing Paradigm of Outflow Resistance Generation: Towards Synergistic Models of the JCT and Inner Wall Endothelium, Exp Eye Res. 2009 April; 88(4):656–670. Panels originally published in “H-7 effects on the structure and fluid conductance of monkey trabecular meshwork”. Sabanay I, Gabelt BT, Tian B, Kaufman PL, Geiger B. Arch Ophthalmol. 2000 Jul; 118(7):955–62.

outflow facility and IOP. The active role of TM contraction and relaxation in the regulation of IOP results from the aggregate of the actomyosin contractility/cytoskeleton/cell–cell and cell–matrix adhesion responses of the individual TM/JCT/SC cells. The cytoskeleton and contractility mechanisms may be the efferent “implementation” arm of the reflexive and regulatory mechanism, governing the final facility. The eNOS/NO system may be a signal/transduction system noted above, modulated differently by sensors in the CM tendons, the CM apex, the scleral spur and the TM (Figure 3). Taken together the evidence supports the TM being a responsive self-aware, self-regulating tissue/orGAN. It may well be possible to manipulate both the afferent and efferent mechanisms that influence the TM cytoskeleton, making it an attractive target for therapeutics aimed at enhancing outflow. Relaxing TM, JCT and SC inner wall cells leads to a tissue configuration that may be a geometrically and biomechanically critical event and a fundamental endogenous control mechanism for outflow resistance. Several classes of compounds act on the TM to disrupt the actin cytoskeleton, altering cell shape, contractility and adhesions, and reducing outflow resistance through the relaxation and expansion of the TM (Figure 4). Rho kinase modulation of aqueous outflow is a therapeutic approach in development by a number of groups, but there are other ways to target manipulation of TM architecture for glaucoma therapeutic purposes. The broad-spectrum protein kinase inhibitor H-7 blocks cellular actomyosin-driven contractility, via inhibition of myosin light chain kinase, rho kinase, or both; overexpression of non-muscle caldesmon un couples actin from myosin; cytochalasins (fungal metabolites) and latrunculins (sea sponge metabolites), inhibit actin polymerization by different mechanisms (Figure 5); all are potent ocular hypotensive agents and increase trabecular meshwork outflow facility in eyes of nonhuman primates. Derivatives of some of these agents are in human clinical trials and are expected to be complementary with prostaglandins.

Recent studies indicate that TM outflow is also affected by TGF-β and consequent downstream mediators that have effects on the ECM, including connective tissue growth factor (CTGF), bone morphogenic protein (BMP), gremlin and the Smad-signaling pathway. TGF-β2 has been implicated in the pathogenesis of POAG, based on elevated levels in the aqueous humor of glaucoma patients and its ability to induce ECM remodeling (collagen formation, ECM synthesis, tissue stiffening) in the TM, which leads to an increase of aqueous humor outflow resistance. In perfused human cultured anterior eye segments TGF-β2 increases ECM deposition in the TM and elevates IOP. CTGF is a TGF-β2 target gene with high constitutive TM expression. Treatment of human TM cells with recombinant CTGF causes distinct changes in gene expression indicating that CTGF is a mediator of the effects of TGF-β2 on ECM synthesis in human TM cells. Actin stress fibers and contractility are
Figure 5. Pathways targeting actomyosin contractility to enhance aqueous humor outflow through the TM. MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase; MLC, myosin light chain. With permission from Gabelt BT and Kaufman PL. Changes in aqueous humor dynamics with age and glaucoma, Progress in Retinal and Eye Research 24 (2005) 612–637.

also induced by CTGF in cultured TM cells.10,11 The BMP, gremlin and Smad-signaling pathway also plays a role in TGF-β2 induced ECM synthesis in the TM.14 TGF-β2 and BMP4 act in concert to maintain a balance between ECM deposition and degradation.15 The BMP antagonist gremlin inhibits BMP-4 activity in cultured TM cells and increases outflow resistance in a perfusion cultured human eye anterior segment model.12 Gremlin employs canonical TGF-β2/Smad signaling to induce ECM genes and proteins in cultured human TM cells. Gremlin also induces both TGF-β2 and CTGF, which can act downstream to mediate ECM changes in TM cells.13

Secreted frizzled-related protein 1 (sFRP-1), an antagonist of the Wnt signaling pathway, is differentially expressed in glaucomatous human TM cells compared with normal human TM cells.11 Addition of recombinant sFRP-1 to ex vivo perfusion-cultured human eyes decreases outflow facility. Intra-vitreal injection of an adenoviral vector encoding sFRP1 in mice produces a titer-dependent increase in IOP. These data indicate that Wnt signaling plays a role in regulating IOP, that increased expression of sFRP1 in the TM appears to be associated with elevated IOP and that inhibiting Wnt signaling is a viable strategy for developing a model of experimental glaucoma.15

Adenosine agonists Adenosine A1 and A2a receptor agonists are in development as IOP-lowering therapies. In bovine organ-cultured anterior segments, the adenosine A1 agonist cyclohexyladenosine produces an outflow facility increase associated with MMP activation in the TM outflow pathway. In a Phase 1/2 single ocula dose clinical trial, the selective adenosine A1 agonist INO-8875 significantly reduced IOP in glaucoma patients, reportedly by increasing outflow of aqueous humor through the trabecular meshwork. An adenosine A2a receptor agonist (OPA-6566) is also thought to lower intraocular pressure by enhancing aqueous humor outflow via the trabecular meshwork.

Novel therapeutic targets will continue to be in demand, as glaucoma is a lifelong condition requiring a multi-faceted, additive approach to medical treatment. Over time, most glaucoma patients will be prescribed multiple topical drops, of varying classes/mechanisms, to control their IOP. Understanding how the outflow system functions is critical for determining how to effectively and efficiently manipulate elements of the system to therapeutic effect.

References


Clinical Issues:
What is the importance of Glaucoma and Obstructive Sleep Apnea Syndrome?

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- Relatively common, increasingly recognized but still under-diagnosed, Obstructive Sleep Apnea Syndrome (OSAS) sufferers experience apneic and hypopneic episodes during sleep.
- OSAS symptoms include daytime somnolence, daytime headaches, difficulty concentrating and memory problems.
- OSAS has been correlated with ocular diseases including glaucoma and it has been identified as a possible risk factor for glaucoma.
- OSAS may alter the blood flow to the optic nerve, thus decreasing perfusion pressure.
- The severity of OSAS was reported to be correlated with the extent of glaucomatous damage.
- When applying continuous positive airway pressure (CPAP) – the most common treatment for OSAS – normalized IOP and restored blood pressure have been observed.
- When taking a patient history it is important to inquire about snoring or daytime somnolence, as these symptoms are indicative of OSAS. Treatment of OSAS may positively impact on glaucoma status.

Relatively common, increasingly recognized but still under-diagnosed, Obstructive Sleep Apnea Syndrome (OSAS) sufferers experience repeated episodes of upper airway obstruction called apneic episodes, or decreases in airflow called hypopneas during sleep with varying severities. Both diagnosis and severity of OSAS can be made with formal polysomnography (PSG) or with a home sleep test. This analyzes nasal airflow, respiratory effort and oxygen saturation. These variables determine an apnea-hypopnea index (AHI) and respiratory disturbance index (RDI). OSAS is defined as >5 AHI/hour, with severity graded as mild, moderate or severe.

Symptoms of OSAS include daytime somnolence, daytime headaches, difficulty concentrating and memory problems. Factors predisposing to OSAS are obesity, male gender, upper airway abnormalities (palate shape), large tongue, large tonsils, a shorter lower than upper normalities (palate shape), large tongue, obesity, male gender, upper airway abnormalities.1 OSAS can alter the blood flow to the optic nerve, thus decreasing perfusion pressure.

- The severity of OSAS was reported to be correlated with the extent of glaucomatous damage.
- When applying continuous positive airway pressure (CPAP) – the most common treatment for OSAS – normalized IOP and restored blood pressure have been observed.
- When taking a patient history it is important to inquire about snoring or daytime somnolence, as these symptoms are indicative of OSAS. Treatment of OSAS may positively impact on glaucoma status.

Several studies observed a significant proportion of glaucoma patients (5.7 – 27%) suffer from OSAS.5-10 These studies ranged from 30 to over 200 patients and all patients had either a prospective PSG (i.e. after an ophthalmic exam and diagnosis of glaucoma) or were referred for ophthalmic examination directly after a positive PSG for OSAS in a consecutive manner.6-12 In 2007 Sergi and colleagues performed prospective PSG and ophthalmic examinations on 51 consecutive OSA patients (RDI≥10) and 40 age-matched controls, observing normal tension glaucoma (NTG) in 5.9% (3/51) versus 0% in the control group. In another study, 27 of 100 consecutive OSA patients who had a PSG within 2 days of ophthalmic examination (RDI≥15) were found to have glaucoma.9 Lin et al. diagnosed NTG in 12 of 209 patients (5.7%) consecutively diagnosed with OSAS by prospective PSG (RDI≥5).11 Two small studies respectively found OSAS in 3/6 NTG patients and 12/25 OAG patients, and in 5/9 NTG patients and 2/4 NTG suspects.13,14 In one study testing visually evoked potential (VEP) and pattern electroretinography (PERG), patients with OSAS had higher AH1 and IOP, and showed abnormal VEPs and PERGs compared with matched control patients.6

Episcleral venous pressure increases in the supine position.15 The intermittent hypoxic episodes of OSAS can increase sympathetic tone, resulting in the same physiologic response.12 OSAS may alter blood flow to the optic nerve head, decreasing ocular perfusion pressure. The severity of OSAS was reported to correlate with the extent of glaucomatous damage.7

Treatment with continuous positive airway pressure (CPAP) is the most common treatment for OSAS. Pepin
and colleagues showed that CPAP normalized IOP and restored blood pressure to a normal rhythm. CPAP in patients with OSAS and glaucoma may have a beneficial effect for the glaucoma as well as the OSAS.

It is important when taking a patient history to inquire about snoring and daytime somnolence. Often a patient's spouse or partner can elucidate if he or she snores or describe moments when he or she stops breathing for a few seconds then resumes snoring. These symptoms are possible indications for OSAS and these patients should consider a formal polysomnography. If diagnosed with OSAS, the patient should seriously consider CPAP treatment to aid glaucoma treatment as well as improve their systemic status.

References

Practical Tips:
IOP assessment with the water drinking test

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Core concepts
• To identify both IOP-dependant and non IOP dependant factors is essential to understand why progression takes place in patients.
• We are currently unable to monitor 24 hour IOP continuously.
• Surrogate measures such as inter-visit IOP variation or diurnal IOP curves, although helpful, are sometimes impractical.
• An alternative to determine IOP fluctuation and peak IOP is the water-drinking test (WDT), which is simple to perform and evidence based.
• Peak WDT-induced IOP correlates well with peak diurnal IOP and may help to identify patients with fluctuating IOP peaks outside or even within routine office hours.
• The WDT requires the patient to drink a set volume of water within a short time period (usually 5 minutes).
• Due the diuretic effect of the WDT, care should be taken in individuals with cardiovascular or renal co-morbidities.
• Because of its poor sensitivity, the WDT is no longer acceptable as a provocative test to diagnose glaucoma.
• The WDT is a low cost, low tech practical alternative for cumbersome assessments of diurnal variations and peak IOPs and can highlight the need for further intervention or re-evaluation of current treatment plans.

Well-designed clinical trials provide strong evidence that elevated intraocular pressure (IOP) is a risk factor for the development of glaucoma and for progression of established disease. For example, pooled data from the Ocular Hypertension Treatment Study (OHTS) and European Glaucoma Progression Study (EGPS) suggests that for every 1mmHg higher baseline IOP, there is a relative risk of 1.09 for glaucoma development.1 IOP reduction is a proven strategy to prevent progression from ocular hypertension (OHT) to glaucoma or to slow the rate of glaucoma progression. However, patients with glaucoma progression despite IOP reduction remain a significant challenge. To identify both IOP-dependent and non IOP-depen-
IOP-dependant factors are likely to include IOP fluctuation and peak IOP, both of which are associated with disease progression, both of which may be easily missed or underestimated with standard clinic based IOP measurements.²

We are currently unable to monitor 24 hour IOP continuously and surrogate measures such as inter-visit IOP variation or diurnal /circadian IOP curves, although helpful, are sometimes impractical. An alternative to determine IOP fluctuation and peak IOP, which is both evidence-based and simple to perform, is the water-drinking test (WDT).³ It is essentially a “stress-test” which may lead to elevated IOP in some eyes due to yet to be determined mechanisms, which may include increased episcleral venous pressure, choroidal thickening or sympathetic excitation. The peak WDT-induced IOP correlates well with peak diurnal IOP and may help to identify individuals with fluctuating IOP peaks outside or even within routine office hours.⁴

The WDT requires the patient to drink a volume of water in a short period, usually 5 minutes. Our preferred protocol is 10ml/kg body weight such that a 70 kg patient would drink 700mls; others have used a fixed volume such as 1 litre. Very occasionally, patients are intolerant of this volume of water but we find the addition of a small volume of fruit juice can help. Patients should be warned of the diuretic effect and care taken in individuals with congestive cardiac failure, renal impairment, hyponatraemia or significant cardiovascular disease. IOP is measured every 15 minutes for 1 hour after the water is imbibed (figure 1). A modified WDT, where IOP is measured only 15 mins and 30 mins after consumption, may be adequate in the setting of significant time constraints given peak IOP typically occurs within this time period.⁵

Results of a WDT can aid patient management in a number of ways:
- It facilitates discussion with the patient about reasons for progression
- It helps assess efficacy of current treatment
- It potentially allows treatment to be tailored if a high peak is identified. For example, prostaglandin analogues could be more suitable than beta-blockers for many patients or surgery more effective than medical treatment.

Because of poor sensitivity and specificity the WDT is no longer acceptable as a provocative test to diagnose glaucoma. However, it provides relevant information about the homeostatic mechanisms of in vivo aqueous dynamics for an eye and a patient: the extent of IOP increase and the speed with which it recovers. It is, therefore, a low cost, low tech, practical alternative for cumbersome assessments of diurnal variations and peak IOPs and can highlight the need for further intervention or re-evaluation of treatment plans. This is especially so in those who progress despite having achieved previously determined “target” pressures, as well as those with advanced glaucomatous damage.

References:
STATEMENT OF NEED AND PROGRAM DESCRIPTION
Recent months and years have seen significant advances in our understanding of glaucoma. Much has been learned, not only about damage mechanisms and pathogenesis, but also about diagnosis and management. Treatment options – both medical and surgical – continue to expand. This program will review this new knowledge with an emphasis on incorporating recent insights into day-to-day practice.

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