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## LEARNING OBJECTIVES

### Special Focus

A comprehensive overview on tonometry and its limitations, including accuracy of measurement, influencing parameters and future monitoring devices.

### What's New

A review of natural outflow pathways (trabecular, uveoscleral and subconjunctival) and how these can be managed by current medical and surgical interventions.

### Clinical Issues

A summary defining the relationship between glaucoma and obstructive sleep apnea syndrome (OSAS) and describing measures of OSAS treatment.

### Practical Tips

A practical approach to identify IOP- and non-IOP-dependant factors of progression such as monitoring IOP fluctuation and peak IOP with the WDT.

## TARGET AUDIENCE

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

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## MAIN TOPIC:

# “The role of IOP in Glaucoma”

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## Special Focus:

# Tonometry in the 21st Century – New Technologies, New Challenges

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### Core Concepts

Glaucoma is unique among chronic diseases in that its primary risk factor and therapeutic target (IOP) is measured only a few times a year in most patients.

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 (precision) of only  $\pm 2.5$  mmHg.

Central Corneal Thickness (CCT) is a major confounder of GAT accuracy but ‘correction’ formulae and nomograms should not be used to ‘correct’ GAT measurements for individual patients, even when available in electronic health records.

The material properties of the cornea play an important role in GAT error and likely dwarf the influence of CCT. Corneal Hysteresis (CH) can only be measured by the Ocular Response Analyzer (ORA) but a compelling body of data suggest low CH is a powerful risk factor for glaucoma and progression

Home tonometry is emerging as another tool in the management of glaucoma

Implantable or wearable devices that measure IOP continuously will supplant our office-based ‘snapshots’ of IOP. How we analyze the coming deluge of IOP data from these devices will be a crucial challenge in the coming decades.

### 1. Introduction

Measurements acquired during clinical care are always an estimate.<sup>1</sup> Without acquiring numerous measurements to average out clinical noise while also understanding and accounting for technical limitations, we can never begin to approach the true underlying value of a

physiological measurement. Nowhere is this more relevant than in the measurement of intraocular pressure (IOP) in the care of patients with glaucoma. Among chronic diseases, glaucoma is remarkable in that its primary risk factor and therapeutic target, IOP, is measured only rarely and randomly, perhaps just a few times a year in most patients. Although this remains true in 2020, we’re now seeing progress with home tonometry, short-term continuous IOP monitoring and even implantable devices, all of which portend a paradigm shift in how we understand and manage glaucoma.

The purpose of this brief review is to update the reader on how tonometry continues to evolve, focusing on the often under-appreciated limitations of current techniques, how the material properties of the eye (and especially the cornea) may provide clues to glaucoma pathophysiology and finally, how home tonometry and continuous tonometry will change how we care for glaucoma patients

### 2. Goldmann Applanation Tonometry

Goldmann applanation tonometry (GAT) rapidly gained widespread acceptance after its introduction in the 1950s. The device was reasonably priced, and the technique was based on easily understood physical principles. GAT fit seamlessly into the workflow of the slit lamp examination and appeared 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). Goldmann tonometry’s

status as a “gold standard” went largely unchallenged for 50 years, even though Goldmann and Schmidt acknowledged several limitations to their device.<sup>2</sup> In particular, they acknowledged that their design assumptions were based on a CCT of 0.5 mm (500  $\mu$ m) 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.<sup>3</sup> He found that GAT most accurately reflected the true intracameral IOP when CCT was 520  $\mu$ m and that deviations from this value resulted in an over or under estimation of IOP by as much as 7 mmHg per 100  $\mu$ m. Subsequent cannulation experiments performed on many more patients with modern pressure transducers have confirmed Ehlers’ basic findings. We now know that CCT varies far more among otherwise normal individuals than Professor Goldmann ever dreamed. Differences in CCT are seen among different racial and ethnic groups<sup>4</sup> and likely lead to misclassification of patients with normal tension glaucoma<sup>5</sup> and ocular hypertension.<sup>4,6</sup>

The importance of CCT in the management of glaucoma patients, particularly those with ocular hypertension, was brought to the forefront in 2002 by the findings of the Ocular Hypertension Treatment Study (OHTS). In the OHTS, 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.<sup>6</sup> The interested reader should go to the OHTS website (<http://ohts.wustl.edu/risk/index.html>) for versions of the predictive model to use in direct patient care.

The OHTS results and subsequent confirmatory studies suggest that many patients are mis-classified in terms of glaucoma risk based on 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 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.

A number of so-called ‘correction nomograms’ employ data acquired by cannulation during cataract surgery and attempt to ‘correct’ GAT measurements based on CCT. In the linear regression analyses generated by such 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. 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 magnitude and direction of the adjustment. 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. 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.

No generalized ‘correction nomogram’ can ever adequately adjust IOP without knowing much more about the individual cornea being applanated. This was driven home recently by Wachtl and colleagues<sup>7</sup> who used the Pascal Dynamic Contour Tonometer (DCT) as the reference standard believed to be closest to the “true” IOP short of cannulating an eye (see below); they compared DCT to conventional GAT and to “adjusted” GAT measurements

at various stages of glaucoma. They found that GAT measurements become increasingly discordant from DCT measurements as glaucoma advances, especially in older patients with thinner corneas. Application of published “correction” nomograms to the GAT data worsened this discordance and resulted in more unpredictable errors.

Remember that the definitions of ‘accuracy’ and ‘precision’ are different, though the terms are often used interchangeably. In the present context, ‘accuracy’ reflects how closely tonometer measurements reflect the ‘true’ IOP (e.g., what you would measure were you to cannulate the eye with a manometer), whereas ‘precision’ refers to the consistency and repeatability of the measurements. CCT can be measured with micron level precision, whereas even in the best of hands GAT has a variance of  $\pm 2.5$  mmHg. Attempts to ‘correct’ an imprecise measurement (GAT) with a precise measurement (pachymetry) cannot and does not lead to a more ‘accurate’ IOP estimate. Clinicians should avoid using these correction nomograms in the care of individual patients, even though pachymeter and electronic health record vendors make it easy to do the math with a button or mouse click.<sup>8</sup>

### 3. Material properties

The OHTS CCT findings ignited interest in studying the eye from an engineering perspective. Might the material properties of ocular structures provide clues to how evolution has designed eyes to protect ganglion cell axons at the optic nerve head? Relevant to our discussion is how the material properties of the cornea influence tonometry techniques. The cornea is a far more complex structure than a piece of plastic or steel in which thickness has a straightforward linear relationship with stiffness. The cornea is a living viscoelastic biological structure that responds dynamically to deformation, whether by the tip of a tonometer or an air puff. Mathematical models<sup>9</sup> have repeatedly demonstrated that the influence of CCT on GAT measurements is but a small component of GAT error – factors such as ocular rigidity, viscoelastic properties hydration state and age all interact with CCT. To add further complexity, material prop-

erties change with different ‘true’ IOP. If we could measure material properties, might we gain a more accurate estimate of IOP in our patients?

### 4. The Ocular Response Analyzer (ORA) and Corneal Hysteresis (CH)

The Ocular Response Analyzer (Figure 1; Reichert Instruments, Depew, NY USA) is a modern non-contact tonometer (NCT) designed to not only measure IOP but also to measure and account for variability in corneal biomechanical properties in individual eyes. Like other NCTs, a pulse of compressed air flattens the corneal apex and electro-optical sensors measure the physical behavior of the cornea. Unlike conventional NCTs, the ORA measures both the inward and outward movement of the cornea. The cornea is not a purely elastic but rather a visco-elastic structure – it deforms and then returns to its original shape at different velocities. In other words, it does not behave like a spring but rather as a viscous damping system (e.g., a hydraulic shock absorber). This behavior, termed hysteresis, is a well-studied physical property of biological structures such as joints and blood vessels. The ORA is the first clinical device to measure corneal hysteresis (CH) in the living eye.<sup>10</sup> In longitudinal studies, low CH values appear to be a significant risk factor for the development of glaucoma<sup>11</sup> and are associated with visual field progression.<sup>12</sup> Linking corneal measurements to the optic nerve, CH appears related to behavior of the lamina cribrosa over time.<sup>13</sup>

The ORA software combines CH and corneal response factor (CRF; a measure of the cornea’s elastic response) to derive a corneal-corrected IOP (IOPcc). A recent longitudinal study demonstrated that IOPcc was more predictive of rates of visual field loss obtained by GAT or rebound tonometry.<sup>14</sup>

### 5. CATS™ Prism

If a clinician cannot afford to purchase an ORA, might there be a way to account for material properties in individual patients using existing technology? GAT has employed a flat appplanation surface for over 50 years. McCafferty and colleagues used finite element



Figure 1: Ocular Response Analyzer (ORA; Reichert Instruments, Depew, NY USA), Image courtesy of Reichert.

modeling to modify the applanating surface of a Goldmann prism in order to minimize errors due to corneal stiffness, curvature and tear film.<sup>15</sup> Their models predicted this approach would reduce GAT error by 50%. A randomized clinical trial recently demonstrated that the correcting applanation tonometry surface (CATS) tonometer prism (CATS Tonometer LLC, Tucson AZ, USA) significantly reduced the influence of both CCT and CH on IOP estimates acquired by GAT, simply by replacing the standard flat prism with the CATS prism (Figure 2).<sup>16</sup>

## 6. Dynamic Contour Tonometry

Dynamic contour tonometry (Pascal DCT; Ziemer Ophthalmic Systems AG, Port, Switzerland) employs a contoured tip with an embedded piezoelectric sensor; it measures IOP directly via hydrostatic coupling.<sup>17</sup> IOP estimates acquired by DCT compare favorably to cannulated IOP in vivo, and appear to be mostly unaffected by CCT or prior corneal surgery. DCT is more repeatable and reproducible than GAT and ORA.<sup>18</sup> The device is challenging to

use in clinic with any but the most cooperative patients<sup>19</sup> and has not gained widespread adoption. It remains a useful research tool.

## 7. Rebound (iCare™) Tonometry

First described by its inventor Kontiola in 1996,<sup>20</sup> rebound tonometry uses a solenoid to accelerate a magnetized probe onto the cornea at a fixed velocity; the same solenoid then detects the corneal impact and rebounding velocity of the probe.<sup>21</sup> Clinical trials of the commercialized devices (iCare Finland Oy, Vantaa, Finland) support sufficient correlation with GAT for clinical use. This portable device does not require topical anesthesia and is well tolerated by young children and uncooperative patients. The device generally over-estimates the IOP when compared to Goldman tonometry, especially at higher IOPs<sup>22</sup> and this effect is amplified at increased CCTs.<sup>23</sup>

The iCare tonometer has seen widespread adoption as a screening tool; it is particularly useful in young children.<sup>24,25</sup> An Ophthalmic Technology

Assessment by the American Academy of Ophthalmology suggested that rebound tonometry was sufficiently accurate to avoid the need for general anesthesia in many children.<sup>26</sup> Rebound tonometry lends itself nicely to home tonometry, and a device to do so (the iCare™ ONE) has been commercialized. The device appears to have reasonable comparability to both GAT and rebound measurements by a physician.<sup>27</sup>

## 8. 24 Hour Continuous IOP Measurement

To better understand glaucoma and guide its treatment, we need something analogous to the continuous, ambulatory monitoring of blood pressure and electrocardiogram that our internal medicine colleagues have employed for years. Progress towards that vision of glaucoma management is accelerating.

The Triggerfish® contact lens sensor (Sensimed AG, Lausanne Switzerland) provides 24-hour measurements of corneal curvature presumed to be related to changes in IOP. The device appears to provide reproducible results and is generally well tolerated, even with overnight use while sleeping.<sup>28</sup>

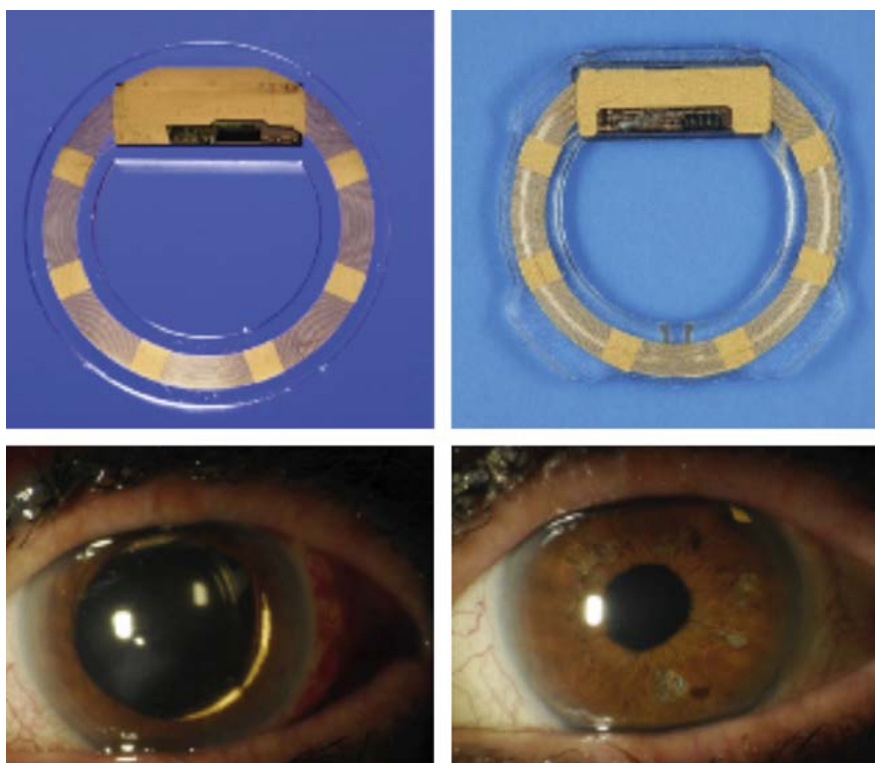
In contrast to an external, temporary, contact lens approach, the EyeMate IO (Implandata Ophthalmic Products GmbH, Hannover Germany) is designed to be implanted into the ciliary sulcus during cataract surgery and remain inside the eye permanently (Figure 3). The device can be wirelessly interrogated by an external probe. Twelve month results in a cohort of 22 patients were recently published; the device performed reliably through that first year without serious adverse events.<sup>29</sup>

Implanted IOP sensors would seem particularly useful in eyes with the Boston Keratoprosthesis in which no conventional technique of tonometry is reliable. A preliminary series of 12 such eyes demonstrated that the EyeMate-IO could identify postoperative IOP spikes and longitudinal increase of IOP over time and correlated well with clinical (tactile) estimates of IOP.<sup>30</sup>

As technology and miniaturization progress in coming years, implanted sensors will play a growing role in our



Figure 2: Correcting applanation tonometry surface tonometer prism (CATS™; Reichert Instruments, Depew, NY), Image courtesy of Reichert.



The left panel shows the first-generation EYEMATE-IO sensor design with a uniform thickness of 0.9mm and sharp edges, which caused mechanical problems during the first series of implantations.<sup>15</sup> The second-generation design used in this study is shown in the right panel. It is significantly thinner at 0.5mm with rounded edges tapered to 0.1mm and features 4 haptics to prevent unwanted motion in the sulcus.

The left panel shows the correct positioning of the EYEMATE-IO sensor in an eye with medically induced mydriasis 1 week after surgery (patient DE\_01\_001). In maximal dilation, the inner edge of the sensor is visible. The right panel shows the same patient 3 months after surgery. The sensor ring is only visible through an iridectomy placed during a previous trabeculectomy several years before sensor implantation. There are mild defects to the pigment layer of the iris that were first seen directly after surgery and did not change over the course of the study.

Figure 3: "Telemetric Measurement of Intraocular Pressure via an Implantable Pressure Sensor – 12-month results from the ARGOS-02 Study".<sup>29</sup>

management of glaucoma. It is easy to predict the integration of IOP sensors into intraocular lenses or glaucoma drainage devices quite soon. The challenge will come as we begin to deal with the deluge of data generated by these devices. What aspect of this data will prove most useful and predictive in clinical management? Average IOP over hours, days or weeks? IOP variability? If so, on what time scale? What about the other side of the pressure equation affecting the optic nerve head, intracranial pressure?<sup>31</sup>

As we move from managing glaucoma using random, snapshot measurements of IOP to a future in which our computers or electronic health records can ingest massive IOP data from individual patients, software-based analytics will become a key enabling technology to help us in our clinics and offices. It will be a challenging but exciting transition.

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## What's New:

# Natural and created outflow pathways in medical and surgical glaucoma treatment: trabecular, uveoscleral and subconjunctival

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### Core Concepts

Medical therapy – new drugs

Drug delivery

Conventional and unconventional outflow

Lymphatic and distal conventional outflow

Gene and stem cell therapy

Laser treatment

MIGS devices

## 1. Introduction

Enhancing outflow, through trabecular, uveoscleral and subconjunctival pathways, is a mainstay in glaucoma management. Treatment options include: medications, typically eye drops, to help fluid drain more effectively or lessen fluid production; laser surgery; minimally invasive glaucoma surgery (MIGS); and conventional surgery.

## 2. Medical therapy

Trabecular meshwork/Schlemm's canal inner wall (TM/SCIW) cellular relaxation/contractility and cell-extracellular matrix (ECM)/cell-cell adhesion junction formation/degradation may be the efferent arms<sup>1</sup> of an IOP-regulating mechano-sensitivity reflex. Intraocular pressure (IOP), shear stress, various hormones and cytokines may be the afferent arms; endothelial nitric oxide synthase (eNOS) – NO may be a signaling arm.<sup>2</sup> Carreon and Johnstone have provided excellent descriptions of the movements of the system at the macro level.<sup>3,4</sup>

Two new drug classes have become commercially available in the last few years: rho kinase inhibitors and nitric oxide donors, both facilitating aqueous humor outflow via the trabecular meshwork – Schlemm's canal – distal conventional outflow pathway.<sup>5,6</sup>

Actomyosin contractility can be inhibited by the Rho kinase (RK) and myosin light-chain kinase (MLCK) pathways. Preventing phosphorylation and activation of the myosin light chain leads to degeneration of focal contacts (actin microfilaments and vinculin-rich cell-ECM junctions) and ultimately to expansion of the juxtacanalicular connective tissue JCT and dilation of SC but without SCIW breaks, thereby facilitating outflow. At present, two such agents entered the commercial market (ripasudil<sup>5</sup>, Glanatec®, Kowa, netarsudil<sup>6</sup> Rhopressa® Aerie). Netarsudil also has a norepinephrine transporter inhibitor component, that reduces aqueous humor formation and is hypothesized to reduce episcleral venous pressure. (Figure 1)

Nitric oxide (NO) is a signaling molecule that stimulates soluble guanylyl cyclase (sGC) activity and cyclic guanosine monophosphate (cGMP) formation.<sup>2</sup> Acting via cGMP as a 2nd mediator, NO relaxes vascular endothelial cells and vascular smooth muscle at least in part by inhibiting various aspects of the rho cascade. Compounds that contain a nitric oxide-donating moiety dilate Schlemm's canal (SC), relax the TM and increase outflow facility after intracameral injection in non-human primates.<sup>1</sup> cGMP itself injected into the anterior chamber also increases outflow facility. Latanoprostene bunod (Vyzulta®, Bausch & Lomb), a single molecule with a PGF<sub>2α</sub> backbone and an NO-donating moiety,

lowers IOP in ocular hypertensive and POAG human subjects.<sup>7</sup> It is commercially available in different markets. A similar drug in development, NCX 470 (NicOx), is composed of the prostamide bimatoprost, structurally related to PGF<sub>2α</sub> with an NO-donating moiety 6-(nitrooxy) hexanoic acid.<sup>8</sup> NicOx recently completed enrollment for an adaptive design cohort for the NCX 470 multicenter Mont Blanc Phase 3 clinical trial. Since NO inhibits the rho cascade, additivity between RKI and NO-donating compounds is uncertain.

Fixed-dose combination products continue to be developed. A number of options are available involving complementary mechanisms of action: aqueous formation inhibitors, conventional outflow enhancers, uveoscleral outflow enhancers. Novel products include combinatorial molecules - one molecule, two effects (e.g. Latanoprostene bunod (Vyzulta®, Bausch & Lomb)<sup>7</sup>; and combination products - two molecules, two effects, one or more effects for each molecule (e.g. Rocklatan®, latanoprost and netarsudil, Aerie)<sup>6</sup>. Development of the adenosine A1 agonist trabodenoson (Inotek) was paused because of weak response in the first phase 3 trial.

Prostaglandin analogs (PGAs) currently in development target the prostaglandin EP2 and EP4 receptors. EP2 and EP4 agonists dose-dependently decrease cell stiffness. TM and SC from glaucomatous eyes are stiffer than age-matched normal controls, making EP2 and EP4 agonists attractive candidates for IOP lowering via decreasing cell stiffness and enhancing of outflow through the conventional drainage pathway. Omidenepag isopropyl (OMDI) (DE-117/ STN10117, Santen Pharmaceuticals) is an EP2 receptor agonist. Phase 3 clinical trials started in the US

## Molecular Structures

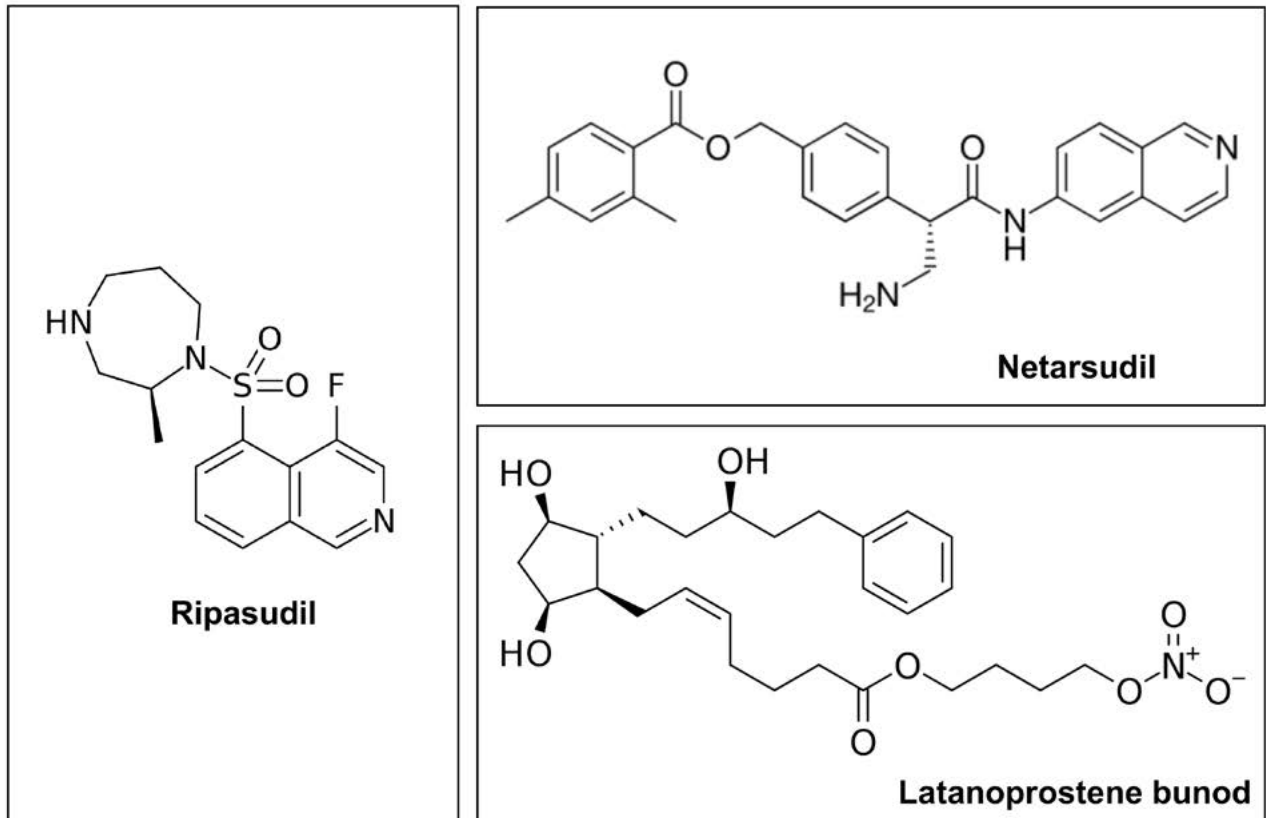
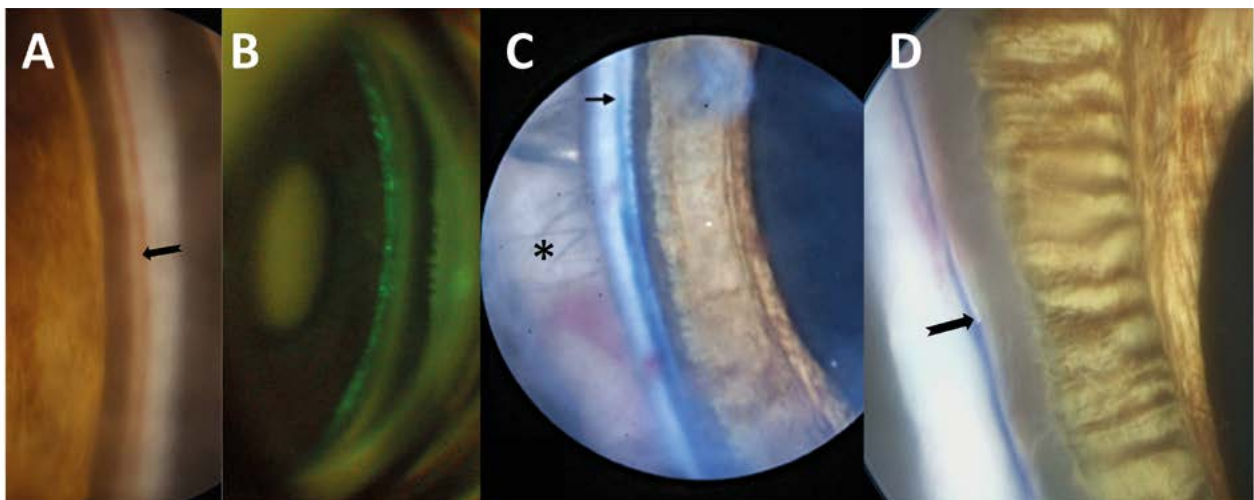


Figure 1

## Targeting Schlemm's Canal: Catheterization and Trypan Blue Injection



Drug / viral vector gene delivery via injection into the anterior chamber (A, B) or catheterization of Schlemm's Canal in live monkeys (C, D).  
A: Monkey anterior chamber angle. Arrow points to blood-filled Schlemm's canal.

B: Monkey chamber angle after intracameral administration of scAAV.GFP vector, day 641 post injection. Green fluorescence from trabecular meshwork. No inflammation, IOP normal.

C: Microcatheter in Schlemm's canal (arrow) showing trypan blue in Schlemm's canal after injection via catheter. \*, aqueous veins carrying trypan blue-tinged aqueous humor from the canal

D: Microcatheter in Schlemm's canal (arrow pointing to catheter tip), showing trypan blue in Schlemm's canal after injection via catheter.

Figure 2



in September 2018.<sup>9</sup> The product was launched in November 2018 in Japan. OMDI received marketing approval in Korea in December 2019. Sepetaprost (DE-126/STN10126, Santen Pharmaceuticals), is an FP- and EP3 receptor dual agonist. Targeting EP3 receptors in the TM and ciliary muscle may facilitate outflow of aqueous humor through the TM pathway (although this seems counter-intuitive to the EP3 TM-stiffening effects described above) in addition to the uveoscleral pathway, for an additive effect to lower IOP.

## 2.1 Novel therapeutic strategies

### *Gene and stem cell therapy*

Gene therapy centered on enhancing aqueous outflow or inhibiting aqueous inflow (i.e., aqueous formation), by up- or down-regulating a normal physiological mechanism, rather than replacing a defective gene, is in development. Gene constructs can be delivered intracamerally, intravitreally, or directly into Schlemm's canal. (Figure 2)

Stem cell strategies for the TM/SCIW are attractive for the same reason as gene therapy: the potential to provide patients with one-time long-term solutions. Stem cell approaches aim to replace or regenerate lost tissue in the conventional outflow pathways, restoring normal function.

### *Drug delivery – intracameral, supraciliary and suprachoroidal*

Durysta<sup>®</sup>, (Allergan), a bimatoprost intracameral biodegradable implant injected transcorneally via a 30-gauge needle, coming to rest in the inferior chamber angle, releases the drug at a constant rate as it slowly degrades and eventually disappears. It reduces IOP at least as much as topical bimatoprost for at least several months. It is now approved and on the market in the USA. Allergan has five ongoing Phase III studies with Durysta to support further potential FDA label enhancement and rest of the world approvals. The implant is designed to reduce IOP for 4 to 6 months, though some patients experienced sustained IOP lowering for longer than 6 months, without requiring additional treatment.

Interest is growing in targeted delivery to the suprachoroidal / supraciliary spaces. Modifying the properties of a drug formulation (e.g. using hydrogels or increasing viscosity) can result in diffuse or focal patterns of dispersion.<sup>10</sup> Greater drug exposure to anterior segment eye tissues can be achieved with supraciliary delivery, where a microneedle or a regular needle is used to penetrate just beyond the sclera, with the drug deposition occurring above the ciliary body.<sup>11</sup>

## 2.2 Drainage pathways

### *Lymphatic drainage*

The presence of lymphatic drainage channels coursing through the ciliary muscle in human, sheep and rodent eyes, was demonstrated using a variety of imaging techniques.<sup>12,13</sup> Mice treated with latanoprost had increased lymphatic drainage from the eye documented by using hyperspectral imaging at multiple times following topical application of latanoprost and intracameral injection of quantum dots as a tracer.<sup>13</sup> A recent study demonstrated that lymphatic drainage from the eye was significantly reduced in older eyes.<sup>13</sup> It may be that impaired lymphatic clearance of aqueous humor, proteins and antigens from the eye plays a role in age-related diseases of the eye such as glaucoma and inflammatory eye disease. This outflow pathway may be a new target for glaucoma therapeutics.

### *'Distal' Conventional Outflow Pathway*

The labyrinth of intrascleral vessels connecting Schlemm's canal and the episcleral veins was identified and beautifully shown by castings nearly 75 years ago<sup>14</sup>, but their complex anatomy and physiology was poorly understood. Virtually nothing was known about their putative pathophysiology, if any. Recent studies have shown that the collector channels emanating from the outer wall of Schlemm's canal may have contractile and perhaps sphincter-like properties<sup>15</sup>, and even more distal intrascleral venules may have a contractile apparatus, so that resistance in this pathway under some conditions may be higher than previously thought.<sup>16,17</sup> Recent advances and future develop-

ments in optical coherence tomographic (OCT) imaging and angiography<sup>18</sup> may help unravel their physiologic and pharmacologic properties and possible regulatory role for aqueous outflow.

### *Subconjunctival drainage*

Various shunting devices that completely bypass the sclera and drain aqueous humor from the anterior chamber to various iterations of subconjunctival or sub-Tenon's equatorially placed plates were introduced ~50 years ago, and are constantly evolving. Most recently, smaller shunt devices that drain to the perilimbal subconjunctival space have been introduced (DE-128 Glaucoma MicroShunt, Xen Gel Implant, Express Miniature Glaucoma Shunt, etc. {see below})

## 3. Non-medical strategies

### *3.1 Laser treatment*

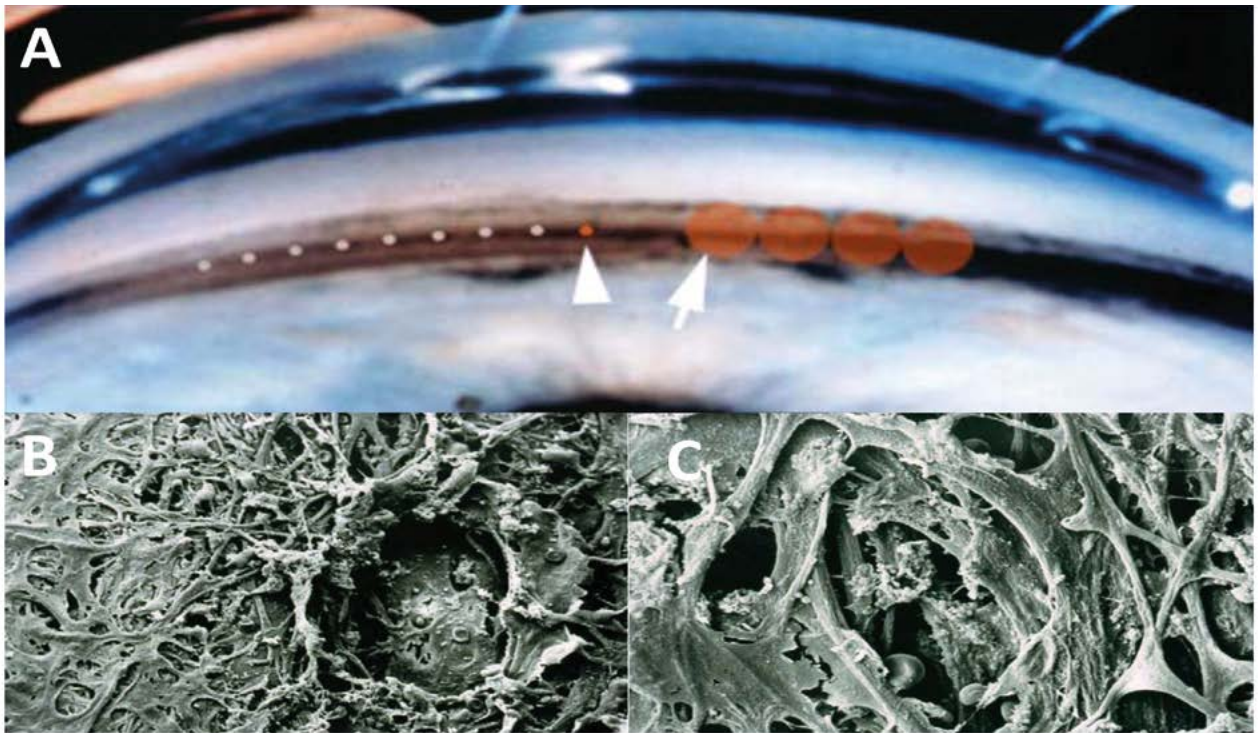
Laser therapy targets the trabecular meshwork / inner wall of Schlemm's canal. (Figure 3)

Selective laser trabeculoplasty (SLT) is currently preferred over argon laser trabeculoplasty (ALT). Due to the longer wave length, larger spot size, and localization of the damage to only pigmented cells, there is less tissue damage and scarring, and re-treatment is better-tolerated and more effective. SLT frees patients from having to use eye drops and its efficacy is comparable to the individual medical mainstays, e.g., timolol, latanoprost. Recent studies indicate that laser treatment is as effective as medication for first-line therapy in patients with glaucoma and ocular hypertension.<sup>19</sup>

### *3.2 Minimally Invasive Glaucoma Surgery (MIGS)*

Bypassing TM and SCIWE, i.e., establishing a conduit between the anterior chamber and the lumen of SC, bypassing TM/SCIWE resistance. A first principle is that such resistance is likely segmental, so that one 'hole' in the system does not remove the resistance over the entire circumference.<sup>20</sup> Examples are the Glaukos iStent (simple shunt), Ivantis Hydrus Microstent (also dilates / splints SC). (Figure 4)

## Laser Trabeculoplasty



**A:** Argon laser trabeculoplasty (ALT) spot size (left arrow) versus selective laser trabeculoplasty (SLT) spot size (right arrow). **B, C:** Scanning electron microscopy (SEM) after argon laser trabeculoplasty (B) reveals crater formation and disruption of the ropelike components of the trabecular meshwork. SEM after selective laser trabeculoplasty (C) shows intact trabecular meshwork beams.

Figure 3

## Artistic rendering of the main MIGS devices

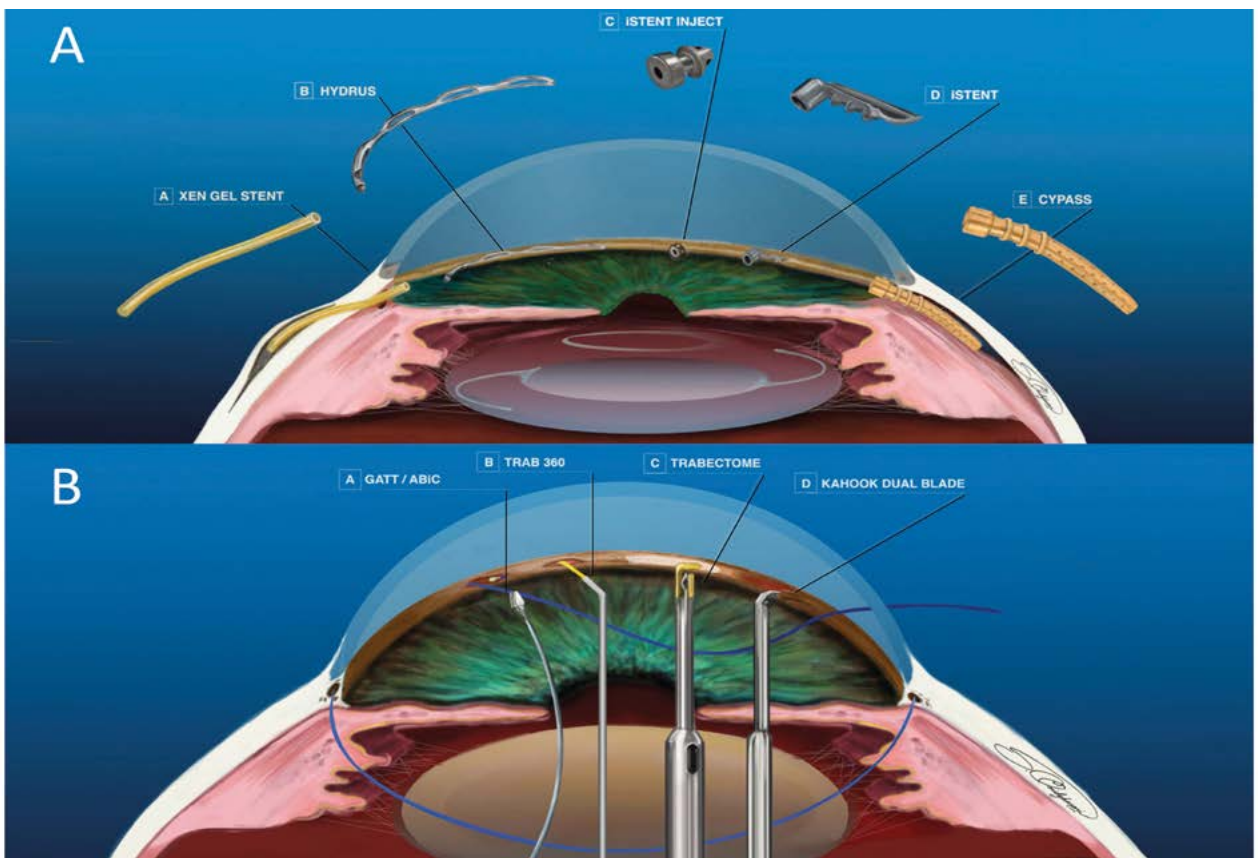


Figure 4

Catheterizing and dilating Schlemm's canal by injecting visco-elastic material, to dilate and 'revitalize' the canal (viscodilation) and enhance outflow (perhaps by establishing long-lasting micro-perforations/channels between SCIWE cells, allowing low-resistance flow pathways between the JCT and the SCI4), such as Ellex iTrack Microcatheter for ab-inter-no canaloplasty (ABiC), Sight Sciences Visco 360 Viscosurgical System.

Disrupting/ablating/removing the trabecular meshwork and SCIWE can be achieved by creating unimpeded access for aqueous flow from the anterior chamber to the lumen of Schlemm's canal.

Gonioscopy-assisted transluminal trabeculotomy (GATT) involves incising the SCIW and cannulating SC with a polypropylene suture or a microcatheter and passing it 360 degrees around SC, and then pulling the ends to disrupt the entire TM and SCIW. Ablation of the entire SCIW and TM can be performed over 360 degrees electrically (Trabectome, Neomedix), or manually/mechanically over a portion of the circumference (Kahook dual blade, New World Medical).

Completely bypassing the conventional and uveoscleral pathways; i.e., shunting aqueous from the anterior chamber directly to the subconjunctival space – Ex-PRESS Mini Glaucoma Shunt, ab externo, Alcon/Optonol; DE-128 Glaucoma MicroShunt, Santen/InnFocus, ab externo, recently notified of FDA acceptance of premarket approval (PMA) application; Xen Gel Implant, ab interno, Allergan; CyPass Microstent, Alcon, ab interno anterior chamber to supraciliary space shunt, recalled due to corneal endothelial cell loss.

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## Clinical Issues:

# The importance of Glaucoma and Obstructive Sleep Apnea Syndrome?

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### Core Concepts

Relatively common, increasingly recognized but still far under-diagnosed, Obstructive Sleep Apnea Syndrome (OSAS) sufferers experience apneic and hypopneic episodes during sleep.

OSAS symptoms include daytime fatigue, headaches, difficulty concentrating and memory problems.

OSAS has been correlated with glaucoma and is a risk factor for glaucoma progression, especially in normal-tension glaucoma (which is also underdiagnosed).

The severity of OSAS has been correlated with the extent of glaucomatous damage.

OSAS reduces ocular perfusion pressure (blood flow to the optic nerve), resulting in decreased oxygen supply (ischemia) and predisposes the eye to glaucomatous damage.

Continuous positive airway pressure (CPAP) - the most common treatment for OSAS - improves ocular blood flow and may stabilize glaucoma progression

OSAS and systemic hypertension are associated with each other and CPAP treatment can lead to improvement in control and lowering of elevated blood pressure.

Obstructive Sleep Apnea Syndrome (OSAS) is a widely prevalent condition in which upper airway resistance is increased during sleep, primarily in the supine position, during which the elastic tissue of the airway narrows or collapses, resulting in disordered breathing. Sufferers experience repeated episodes of upper airway obstruction (apneic episodes – cessation of breathing for 10 seconds or more) or decreases in airflow (hypopneas) during sleep with varying severities. Hypopneas are of shorter duration than apneas.

When the first paper connecting OSAS and glaucoma was published in 2002, it was estimated that 4% of men and 2% of women had OSAS. It was largely unknown and unrecognized. The numbers have currently increased as much as ten-fold, which is staggering. OSAS is associated with numerous ocular and systemic disorders, and it is important for not only ophthalmologists, but other physicians as well.<sup>1</sup>

Both diagnosis and severity of OSAS can be made with formal polysomnography (PSG) or with a home sleep test. If a home sleep test is positive, then an overnight continuous positive airway pressure (CPAP) titration should be performed to determine whether and what treatment is necessary. 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.<sup>2</sup>

Symptoms of OSAS include daytime somnolence, 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 jaw, snoring and enlarged neck thickness.<sup>3</sup> Alcohol and sedatives worsen the symptoms. Most patients with OSAS do not remember waking in the night during an apnea-hypopnea episode. OSAS can affect the pulmonary, cardiovascular and cerebrovascular systems (Table 1).<sup>4</sup> The Joint National Committee on the Prevention, Detection Evaluation, and Treatment of High Blood Pressure has identified OSAS as a treatable cause of secondary hypertension.<sup>2</sup>

OSAS has been correlated with an increasing of ocular conditions (Table 2).

Elevated intraocular pressure (IOP) is the most common known risk factor for the development and progression of glaucoma. Other risk factors include a family history of glaucoma, optic disc hemorrhages, and increased corneal deformability. However, the progression of glaucoma can still occur with an IOP within the normal range (normal-tension glaucoma, NTG), attributed currently in large part to factors affecting ocular perfusion, including low nocturnal blood pressure, IOP fluctuation, low intracranial pressure, Flammer syndrome, and OSAS.<sup>5</sup> Once regarded as rare, NTG is now known, just like OSAS, to be extremely common, comprising perhaps as many as 30-50% of glaucoma in Caucasians and up to 80 to 89% in Japan and Korea.<sup>6</sup>

The association of OSAS is greater in patients with NTG. The association of the two increases with age. OSAS is very common in NTG patients in eastern Asia, where obesity rates are much lower than in the West. In one study performed at the Mayo Clinic on 100 patients diagnosed with sleep apnea, 27 were found to have glaucoma.<sup>7</sup> A number of publications have shown that patients with OSAS may have not only glaucoma as defined by the presence of visual field damage, but early signs (pre-perimetric glaucoma) including thinning of the retinal nerve fiber layer and electrophysiologic (pattern electroretinography, visual evoked potentials) abnormalities.<sup>5</sup>

We recommend taking a sleep history on all glaucoma patients and ask about snoring. We check for floppy eye lid syndrome (Figure 1). We suggest that all patients with NTG undergo polysomnography as well as any patients who progress in spite of apparently well-controlled IOP (and we also recommend 24-hour blood pressure

measurements), and that all patients with OSAS and no previous eye examination undergo testing to rule out glaucoma. CPAP is important not only for glaucoma, but is associated with improvement of diabetic retinopathy and decreases all-cause mortality.

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**Table 1**  
**Systemic Associations of OSAS**

Hypertension
Stroke
Epilepsy
Atrial fibrillation
Impaired sympathetic tone
Cerebral and coronary vascular disease*
Congestive heart failure
Cognitive dysfunction
Endothelial dysfunction and coagulopathies
Oxidative and inflammatory stress
Excessive daytime sleepiness

**Table 2**  
**Ocular Associations of OSAS**

Non-arteritic ischemic optic neuropathy
Papilledema (idiopathic intracranial hypertension)
Glaucoma
Floppy eyelid syndrome
Blepharitis
Keratoconus
Retinal vascular tortuosity
Diabetic retinopathy (several recent reports)
Central serous chorioretinopathy
Ptosis
Papillary conjunctivitis
Filamentary keratitis



Figure 1: Figure Legend: Floppy Eyelid Syndrome

Easily inverted lid with papillary conjunctivitis. 90% of patients with FES have OSAS. 31.5% of OSAS pts had FES in one series. Caused by loss of elastin fibers with upregulation of elastolytic proteases in tarsal plates

## Practical Tips:

# IOP assessment with the water drinking test (WDT)

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### Core Concepts

It is essential to identify both IOP-dependent and non IOP-dependent factors to understand why progression takes place in glaucoma patients with apparently satisfactory IOP control as measured in clinics.

Current 24-hour ambulatory, continuous IOP monitoring devices are not cost-effective.

Surrogate measures such as inter-visit IOP variation or diurnal IOP curves, although helpful, are sometimes impractical.

Water drinking test (WDT) is a feasible, evidence-based alternative measure to determine IOP fluctuation and peak IOP clinically.

Peak WDT-induced IOP correlates well with peak diurnal IOP and may help to identify patients with significant IOP spikes and fluctuations.

The WDT requires the patient to drink a given volume of water (a fixed volume of 800 ml, or 10 ml of water / kg body weight) in 5 minutes; IOP is measured at 15-minute intervals post water consumption.

WDT is a reliable test to identify peak IOP that correlates with peak circadian IOP and to estimate risk of progression in treated glaucoma patients

WDT response allows clinicians to evaluate the efficacy of current IOP lowering interventions for an individual patient and to tailor the treatment plan accordingly.

### 1 Introduction

Intra-ocular pressure (IOP) is the primary modifiable risk factor that has been linked to glaucoma onset and progression. Interestingly, individuals with low IOP also develop glaucomatous optic neuropathy, while some treated patients continue to progress despite having satisfactory IOP control. It has been postulated that

IOP independent factors such as altered optic nerve head microcirculation, oxidative stress, immune mechanisms, and increased trans-laminar stress from low cerebrospinal fluid pressures may play a role in progressive optic neuropathy.<sup>1,2</sup> However, inadequacies in IOP assessment has also been shown to contribute to this phenomenon.

Like other biological parameters, IOP is a continuous variable: it varies considerably during the circadian cycle and over time. Twenty-four-hour IOP profile studies have shown that two-thirds of patients experienced peak IOP outside regular clinic hours.<sup>3</sup> Diurnal and 24-hour IOP curves have been useful to determine peak IOP levels. Circadian variations can be best assessed by a non-invasive recording of ambulatory, continuous 24-hour IOP monitoring using a contact lens sensor or other telemetric devices.<sup>4</sup> But this is not always feasible or cost-effective in routine clinical practice. The water drinking test (WDT) has been shown to predict peak IOP reasonably reliably in an office setting.

The WDT is a provocative test that was initially developed to differentiate open-angle glaucoma from ocular hypertension patients. However, the WDT lacked the sensitivity and specificity needed to be a reliable screening test. In recent years WDT has attracted attention as an indirect tool to evaluate ocular outflow facility to estimate peak IOP.

### 2. How to perform WDT

Co-existing systemic diseases, especially cardiac failure or renal dysfunction, or history of urinary retention, are contraindications to this test. The patient is required to liquid fast for two hours before the WDT. After measuring the baseline IOP, the patient drinks a given volume of water (a fixed volume of 800 ml, or 10 ml of water /kg body weight) within 5 minutes. The IOP is measured at 15-minute intervals, documenting the maximum elevation, time taken to reach the peak IOP

and time taken to return to baseline IOP (Figure 1). Normal eyes handle the fluid challenge by increasing outflow, whereas a glaucomatous eye with increased outflow resistance respond to the fluid load with an increased IOP.

### 3. Mechanism of action

The exact mechanism explaining the IOP spike provoked by the WDT has not been established. Studies have suggested that increase in epi-scleral venous pressure, blood-aqueous osmotic pressure gradient, choroidal expansion, and autonomic nerve stimulation may lead to the IOP changes post WDT.<sup>5-7</sup>

### 4. Application

WDT plays an important role in the management of glaucoma patients who show functional and/or structural signs of progression despite an apparently well-controlled IOP in the clinic.

#### 1. To identify IOP peaks that correlate with circadian peaks

Peak IOP value is identified as a better predictor of glaucoma progression than average IOP or IOP fluctuation.<sup>3</sup> WDT has shown good correlation and agreement with physiological IOP peaks in circadian cycle.<sup>8</sup> Susanna et al investigated the WDT response in patients with bilateral disease with symmetrical baseline IOP and found that eyes with higher IOP peak have worse visual field damage than their fellow eye.<sup>9</sup>

#### 2. Risk assessment for progression

The WDT peak has been reported to be a strong predictor of progression in treated open angle glaucoma patients, where clinic-based IOP measurements failed to show such significant association.<sup>10,11</sup> A prospective study found that average peak IOP and percentage of IOP variation during WDT is significantly higher in patients with visual field progression compared with patients who did not progress.<sup>12</sup>

### 3. To detect Impaired trabecular outflow facility

Pseudoexfoliation glaucoma patients showed significant IOP elevation with WDT as compared to with those with pseudoexfoliation syndrome alone, indicating impairment in the drainage system with decreased facility of outflow.<sup>13</sup> Primary angle closure patients showed rapid IOP recovery following WDT after peripheral iridectomy, reflecting an improved outflow facility.<sup>14</sup>

### 4. Evaluation of efficacy of treatment

WDT has been proven its value to evaluate the efficacy of IOP lowering interventions. Brubaker suggested using the WDT as an indirect measurement of the outflow facility to compare the IOP responses of glaucomatous eyes with different drugs.<sup>15</sup> Patients with open-angle glaucoma treated with selective laser trabeculoplasty have demonstrated significantly reduced peak IOPs and fluctuation in IOP in response to the WDT.<sup>16</sup> Subjects who had undergone filtering surgery showed a stable WDT- IOP profile as compared with those on ocular hypotensive drops.<sup>17</sup>

In summary, WDT is an inexpensive, feasible clinical test that is useful to evaluate IOP dependent factors that contribute to glaucoma progression. WDT response allows clinicians to evaluate the efficacy of current IOP lowering treatment and to tailor management accordingly.

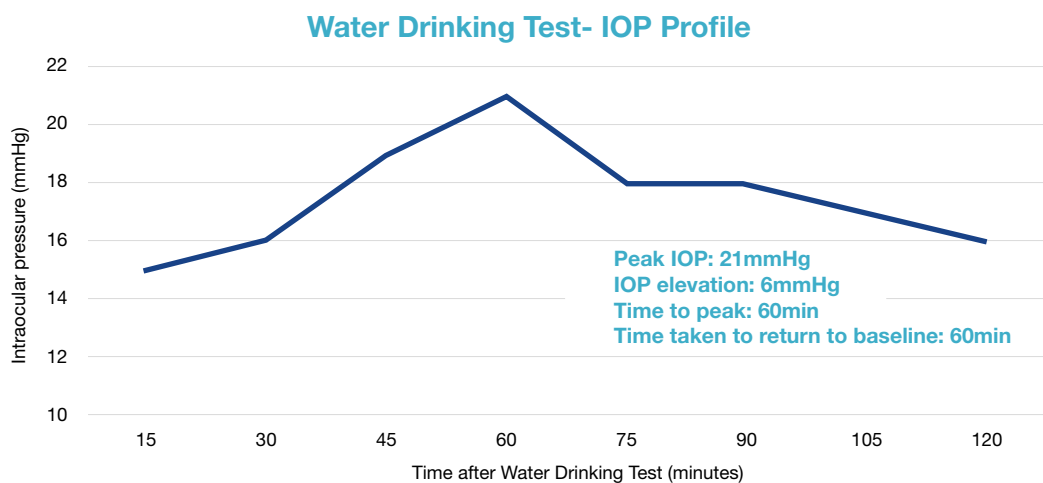


Figure 1

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#### 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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