NEW CONCEPTS IN GLAUCOMA CARE & TREATMENT

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INTRODUCTORY REMARKS

The 15th Annual Scientific Meeting of the Optometric Glaucoma Society (OGS), held Nov. 15 and 16, 2016, in Anaheim, Calif., brought together some of the country’s top luminaries in the areas of glaucoma diagnosis, treatment, assessment, and management. These individuals shared groundbreaking research and the latest clinical knowledge about glaucoma—considered to be the top global eye burden by the World Health Organization.

Kicking things off in the President’s Lecture, Felipe A. Medeiros, MD, PhD, highlighted potential clinical applications for virtual reality devices. These devices, being tested in simulation laboratories, could one day assist clinicians in assessing patients at risk for glaucoma and in danger of falls and motor vehicle accidents due to visual field loss. Make no mistake: These cutting-edge tools are not your techie’s virtual reality.

Dr. Medeiros, in a separate lecture about glaucoma progression, unveiled an innovative metric developed by his research group to measure functional and structural vision loss in glaucoma patients. The RGC Index may offer clinicians a more cohesive picture of disease progression to better manage glaucoma.

In his talk on glaucoma pathogenesis, Derek S. Welsbie, MD, PhD, overviewed our current understanding about disease development and where our knowledge falls short. Profound genetic discoveries being made by his scientific team could lead to game-changing therapies that target specific gene mutations to actually prevent RGC axon degeneration and cell death.

The limitations of existing imaging methods to visualize the anterior segment have sparked the promise of real-time aqueous humor outflow imaging in the clinical setting. Alex A. Huang, MD, PhD, introduced a technique devised by his research group known as aqueous angiography, which provides a comprehensive, real-time view of the anterior chamber. The goal is to help surgeons customize minimally invasive glaucoma surgery (MIGS) for improved surgical outcomes.

And George A. Cioffi, MD, offered clinicians indispensable strategies for fielding queries from concerned patients about topics ranging from drop instillation to more serious issues such as: Will I go blind?

I hope you find the enclosed information useful, knowing that research on glaucoma happening today will be translated to the clinical realm to help clinicians take aim at this progressive and potentially devastating disease.

This supplement, developed by Review of Optometry, was made possible with generous support from Bausch + Lomb.

Please visit the OGS website (www.optometricglaucomasociety.org) and consider signing up for our free, quarterly e-journal to keep up with the group’s latest happenings and developments in glaucoma treatment and management.

Murray Fingeret, OD
Past President, Optometric Glaucoma Society
Editor, Proceedings of the Thirteenth Annual Scientific Meeting of the Optometric Glaucoma Society
More Than a Video Game: Virtual Reality and Its Uses in Glaucoma
Felipe A. Medeiros, MD, PhD

Though the term “virtual reality” often brings to mind images of video gamers wearing high-tech goggles, immersed in an interactive, three-dimensional world created by software developers, virtual reality (VR) devices hold a great deal of promise for applications in the clinical ophthalmic realm.

In fact, discoveries by our research group at the Visual Performance Laboratory are helping to pave the way for using virtual reality strategies to assess visual function and the visual field (VF) at earlier stages of glaucoma. These developing technologies may improve upon or offer alternatives to existing methods of disease assessment such as standard automated perimetry (SAP) exams, which are burdened by a host of clinical and logistical obstacles explained below.

SAP exams are the mainstream for determining functional glaucomatous loss and progressive damage. However, SAP—which typically involves the projection of a white stimulus onto a white background to determine threshold values via software algorithms—is limited by factors including the dependency on patient cooperation and highly trained technicians, subjectivity of findings, a tendency to produce false-positive and false-negative patient responses, a lack of portability, the need for an experienced, highly trained operator, and its use is limited by cumbersome set-up and equipment (e.g., wet-gel-based electrodes) and a relatively low signal-to-noise ratio.5-6

Using state-of-the-art EEG technology and VR goggles, my research group recently developed a portable brain-computer interface (BCI) that acquires and translates brain signals in tandem with an internet-of-things (IoT) device that collects and exchanges the information. The system is capable of objectively measuring visual function loss in glaucoma.

A Portable Brain-Computer Interface to Assess Glaucoma Damage

Our portable platform to assess functional loss, the nGoggle, is housed in a head-mounted display coupled with a dry-electrode, wireless EEG system. Designed to capture natural-response signals known as steady-state visual evoked potentials (ssVEPs) in response to visual stimuli sent by the EEG, the device can collect and convey information to the cloud via wireless or Bluetooth capabilities.7

We have compared the diagnostic performance of the nGoggle and SAP in detecting eyes with glaucomatous neuropathy in recent investigations. A pilot study including 54 eyes of glaucoma patients and 28 eyes of healthy individuals revealed that the nGoggle performed at least as well if not better than SAP in detecting eyes with glaucoma, with the potential advantages of objective assessment and portability.8

Future clinical applications for the nGoggle could include home-based testing for functional loss. This would enable the acquisition of many more tests over time, potentially improving detection of progression compared to what is possible with standard perimetry today. However, the feasibility of such an application would require further investigations.

Assessing Postural Responses in Glaucoma Patients

Falls are an important cause of morbidity in the older population, and studies reveal that glaucoma patients have an increased likelihood of falling. In fact, glaucoma patients are three times more likely to suffer a fall compared with healthy subjects.9 At our laboratory, we have investigated the use of VR-based tests that might improve our ability to predict which glaucomatous patients are at a higher risk for falling.

One assessment strategy involves the use of immersive dynamic visual stimuli presented on a VR headset (e.g., the Oculus Rift) to induce postural responses in glaucoma patients. So, for example, the system might elicit the sensation of rotation or of being in a tunnel. Specialized software then measures the degree of force of the patient’s movement.

This approach has enabled us to assess patient postural responses to dynamic visual stimulation in a manner that more...
closely represents real-world visual responses to everyday tasks. We found that a VR-based test was better able to predict risk of falls than SAP.10

**Determining Glaucoma Patients’ Risk of Motor Vehicle Accidents**

The impact of glaucoma on driving impairment has been another area of interest for our research group. Realizing that SAP, which presents a white stimulus on a white background and aims to minimize distractions, likely would not account for the real-world scene complexity and distractions inherent in a task such as driving, we determined from previous studies that SAP was only weakly predictive of motor vehicle accident risk among glaucoma patients.11

Given this fact, we instituted a driving simulator to assess various factors associated with driving ability in glaucoma patients and to help develop functional tests to better evaluate task performance.

The simulator, which consists of a cut-out section of a Ford Fusion sitting in front of large, panoramic screens, provides realistic driving experiences for patients. It enables us to investigate a variety of driving scenarios and tasks using hundreds of parameters, such as speed, reaction time, lane positioning, violations, ability to divide attention, collisions, etc.

Using data from motor vehicle collisions obtained from DMV records, our work has shown that simulator parameters have performed better in predicting real-world motor vehicle collisions in glaucoma patients than SAP.12

Based on our findings with the simulator, we developed a portable test, known as the Performance Centered Portable Test, or PERCEPT, to evaluate visual performance on a tablet device. The exam, combining spatial, temporal, and contrast components, requires glaucoma subjects to execute demanding visual tasks at low contrast.

In a recent study, we found that PERCEPT results compared favorably with those of SAP and the useful field of view (UFOV) test—which assesses how vision impairment impacts daily activities—to predict history of motor vehicle crashes in glaucoma patients.13,14

**Wayfinding**

Another area of our research is focused on how glaucoma patients navigate through an environment and whether visual impairment affects that process. We developed a virtual world to study wayfinding—the action of determining and following a path from origin to destination (e.g., walking through a building, driving through a city, etc.). Successful wayfinding depends on accurate representations of the spatial environment, and peripheral vision is important for establishing such representation as part of a “cognitive map.”

In one study, our team set up a “cave”—a group of large displays enveloping subjects, who in this case wore 3D glasses and stood inside of a virtual world. We used different scenarios to assess subjects’ wayfinding abilities. For example, a subject might have been told to walk through a “room” to a visible target where multiple objects were incorporated. Later, the subject may have been asked to find the location of the previously seen target, which was now hidden.

We found that variations between glaucoma subjects and controls were significantly greater in rooms that included multiple spatial cues.15 Due to VF loss impacting peripheral vision, individuals with glaucoma lacked allocentric navigation abilities, or
the means to orient themselves according to other objects. They also had difficulty coalescing visual information across multiple gazes and took longer to build a cohesive cognitive map of the spatial environment. These findings may have significant implications for assessing how glaucoma affects daily activities along with the creation of safe environments for patients, and the development of assistive devices and technologies.

As we are better able to assess individuals at risk of glaucoma and progression, and the clinical and real-world obstacles that glaucoma patients face due to VF loss, we will be able to diagnose and monitor patients at an earlier stage and develop technologies to help patients deal with the disease. VR devices are playing a pivotal role in the research today that will make more accurate assessment and assistive technologies a reality for our patients in the future.

Felipe A. Medeiros, MD, PhD, is a professor of ophthalmology and the Ben and Wanda Hildyard Chair for Diseases of the Eye at the UC San Diego School of Medicine. He is also the medical director and director of Virtual Function Research at the Hamilton Glaucoma Center, UC San Diego Department of Ophthalmology.


Patient Care

Questions Glaucoma Patients Ask

George A. Cioffi, MD

As the eye care field gains more knowledge about glaucoma diagnosis, treatment, management, and prognosis, patients are showing up in the clinician’s office with an ever-growing list of questions they want answered, in order to better understand how this progressive disease will affect their lives.

These questions run the gamut and usually start with more serious medical concerns such as: Is there a cure, how successful is surgery, and will I have to take drops forever?

During the course of their routine care, patients will often want to know whether generic medications are equivalent to brand name medications or even why pharmacies don’t fill the eye drop bottles to the top. More recently, advancements in the glaucoma surgical device market and an evolving political landscape have prompted patients to ask: What’s MIGS? and Will you prescribe medical marijuana?

Amid the long list of queries patients raise, one question continues to rise to the top: Will I go blind?

Addressing this perilous question for patients requires a careful and thoughtful approach on the part of clinicians, a wealth of patient information about the patient and visual field (VF) measurements taken over time, and a thorough understanding of the parameters and limitations of various testing strategies.

Clinicians must also arm themselves with current research on life expectancy and glaucoma progression rates, understand the realities of medication adherence, and be aware of statistics on the probability of blindness. For example, along with current life expectancy rates, a patient’s treatment and quality-of-life expectations can also help the clinician address the question of probability of blindness. For example, though the rates are relatively low, we know that people do still go blind from glaucoma.

Role of Age and Life Expectancy

Along with current life expectancy rates, a patient’s treatment and quality-of-life expectations can also help the clinician address the question of probability of blindness. For example, these questions run the gamut and usually start with more serious medical concerns such as: Is there a cure, how successful is surgery, and will I have to take drops forever?

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an 83-year-old patient who is resistant to taking drugs, is adamant about not having surgery, and who points out that both of his parents died at 62 years of age likely will be more inclined to just be monitored than a 53-year-old patient who is a busy accountant at the height of her career who is struggling to see numbers on a spreadsheet.

As life expectancy rates continue to rise, the age range of patients walking into the exam room has broadened. It is now extremely common to see patients in their 90s, and we have to consider this longer life span when deciding upon a strategy for long-term treatment and management. Two former cases demonstrate this point.

“Mrs. X,” a 72-year-old retired attorney, came in for a second opinion about whether she had glaucoma. Her IOPs were minimally elevated (23 OD, 20 OS) and visual acuity was 20/20 OU. She had erosion of the inferior rim in the right eye and moderately advanced optic nerve damage, but her central corneal thickness was normal, and she had no family history of glaucoma. Her referring physician wanted to know: “Should she be treated?”

At 72 years old, we knew Mrs. X might live 12 to 16 years longer, based on current life expectancy rates.3 Given that fact, we needed to get her IOP down significantly. We decided to treat Mrs. X aggressively, and we explained our course of action and rationale to the patient.

Another patient, “Ms. Verna,” was diagnosed with glaucoma 29 years previous to seeing me. Prior to medication instillation, her IOP was in the mid-20s. Once her referring physician placed her on a prostaglandin and a beta-blocker, Ms. Verna’s IOPs dropped to 14 mmHg and 16 mmHg. VA was 20/30 and 20/40, and the patient exhibited advanced optic nerve damage and dual arcuate scotomas. At the time of her visit to my office, the patient’s IOP was back up to 23 mmHg, and the referring physician wanted to know if it was necessary to get the pressures down.

At the current rate of progression, the patient was at a high risk of going bilaterally blind, so we placed her on a tempered course of long-term medication. Fast forward to three months shy of Ms. Verna’s 100th birthday—the last time I saw the patient at my former facility—and Ms. Verna was tolerating her medication well, with no need for surgery or more aggressive therapy.

Am I Getting Worse?

Glaucoma patients who are being monitored over time frequently want to find out: Am I getting worse? Just as the question about probability of blindness has its perils for clinicians, the question of whether disease is intensifying is also a clinical minefield.

The question is directly related to the patient’s probability, and rate, of progression and is best answered by taking a balanced approach to interpreting the results of various measurement techniques. It is often helpful to “take a step back” and consider all relevant factors concerning the assessments being employed.

Two trials that looked at rates of glaucoma progression offer valuable lessons in approaching a patient’s progression. These trials teach us that perception of patient progression is dependent on how the clinician looks at the data.

The first trial, the Ocular Hypertension Treatment Study (OHTS), which demonstrated probability of progression from OHT to primary open-angle glaucoma (POAG), randomized 1,636 patients between 40 and 80 years of age with no evidence of ocular damage, to either observation or treatment.4 Throughout the follow-up period, the patients’ cumulative probability of developing POAG was significantly lower in the medication group than in the observation group (p<0.0001). At 60 months, the cumulative probability of developing POAG was 4.4% in the treatment group compared with 9.5% in the observation group (p<0.0001). This study demonstrated that control of OHT is an important factor in slowing disease progression. Over roughly five years, patients were shown to have about a 2%-per-year risk of progressing onto glaucoma.

Another trial, the Early Manifest Glaucoma Trial (EMGT), demonstrated the benefit of treatment in patients with early-stage glaucoma.5 In this study, 255 patients with early glaucoma, VF defects, and a mean IOP of 20 mmHg were enrolled. Researchers observed a difference in the rates of progression between the treated and untreated patients over a six-year follow-up period, which increased over time. The median time to progression was 48 months in the untreated group compared with 66 months in the treated group. At 48 months, 49% of untreated patients showed evidence of disease progression compared with 30% of treated patients (p=0.004).

| 72 years retired lawyer |
| 2nd opinion for possible glaucoma |
| VA 20/20 OU; IOP 23 OD, 20 OS |
| FH negative for glaucoma |
| Should she be treated? Will she go blind? |

**FIGURE 2. TO TREAT OR NOT TO TREAT?**

This 72-year-old female referral had erosion of the inferior rim in the right eye and moderately advanced optic nerve damage, but her central corneal thickness was normal, and she had no family history of glaucoma. We decided to treat aggressively.
Looking at the results of both studies, clinicians may wonder about the discrepancy between a 2% rate of progression in OHTS and what turned out to be a 12% rate in the untreated group in EMGT. The key to understanding this difference is found in the unique parameters of each trial. In OHTS, researchers retested patients’ VFs twice, leading to a very specific diagnosis. Conversely, in the EMGT, a segment of early manifest glaucoma patients were not treated (the trial had to be conducted abroad for this reason), so this data was very sensitive to change. One study leaned on the direction of specificity, the other in the direction of sensitivity. These are not flaws; the researchers chose to measure the VFs differently.

Taking this important consideration a step further, clinicians must critically examine the measurement strategies they are employing to gauge progression. For example, one study pointed out that the Humphrey Visual Field Analyzer (Carl Zeiss Meditec), which offers Guided Progression Analysis (GPA) software to differentiate statistically significant VF loss progression from random variability, uses progression criteria based on EMGT, which we know was highly sensitive to change.6 Several other software programs on the market also use these criteria. So we, as clinicians, must understand that there will be some tradeoff between sensitivity and specificity for selected assessments.

As well, we should not dismiss older technologies, such as the Progressor (marketed by Medisoft), which offer glaucoma trend analyses through linear regression of VF sensitivity to gain additional perspective.7,8

The bottom line is that we need a wide swath of information from which to draw clues, along with the wisdom and perspective to put this intelligence into context to be able to adequately answer the question: Am I getting worse?

What Are My Options for Therapy?

When patients seek to know their therapeutic options, most clinicians will first explain to them the therapeutic triad that prevails in the glaucoma treatment realm, i.e., medication application, typically topical IOP-lowering medications; laser procedures such as selective laser trabeculoplasty (SLT); and filtration surgery.

As with many therapies, all three approaches carry with them advantages and drawbacks. When it comes to medication application, we depend on the patient to comply with our instructions, despite the fact that the patient is often not a reliable delivery system. For example, an 85-year-old arthritic woman with a 5-degree VF who has trouble getting a drop into her eyes is not going to be a reliable delivery system. With laser surgery, a recent study revealed that SLT mean success rates at six months to one year post-surgery were 55% to 82%—which are favorable, but far from optimal.9 And though results can be dramatically positive for patients who undergo filtration surgery, the procedure carries a small risk of serious side effects such as bleeding, infection, swelling, scarring, retinal detachment, droopy eyelid, double vision, loss of vision, or loss of the eye.10

Lowering IOP remains the only proven therapeutic intervention for glaucomatous optic neuropathy, thus making IOP reduction the first-line treatment for most OAG patients.11 However, the lack of successful sustained-release drug delivery systems in the marketplace make it ever important to critically look at obstacles associated with medication compliance. One study on patterns of glaucoma medication adherence revealed disturbingly low rates of patients who take their prescriptions as directed.12 So we know most patients are not taking their medications as prescribed.

Another study looking at barriers to glaucoma management uncovered the following factors affecting medication adherence, among others: issues with the doctor-patient relationship and a lack of doctor involvement (35.1%), patient education gaps (19.4%), patient dependency on caregivers (14.9%), and patient frustration with disease (10.4%).13

Several programs are now available to address the issue of medication compliance. One is the Will Eye Hospital Glaucoma App, designed to educate patients and caregivers about glaucoma and help with disease management through a medication reminder feature and calendar for tracking appointments.14 In addition, the eyeGuide offers tailored educational content and testimonials from patients who share how they were able to overcome barriers to improve medication adherence.15

As we contemplate therapies for our glaucoma patients, it behooves us to educate all patients, upon diagnosis, about the need to lower IOP and, therefore, take medication as prescribed. Patients must understand that the right therapy can be
Indications and Usage
ISTALOL® (timolol maleate ophthalmic solution) is a non-selective beta-adrenergic receptor blocking agent indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Preservative-free TIMOPTIC® (timolol maleate ophthalmic solution) in OCUDOSE® (dispenser) is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. It may be used when a patient is sensitive to the preservative in TIMOPTIC (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

Important Safety Information for Istalol® and Timoptic® in Ocudose®

- Both ISTALOL® (timolol maleate ophthalmic solution) and TIMOPTIC® (timolol maleate ophthalmic solution) in OCUDOSE® (dispenser) are contraindicated in patients with: bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock; hypersensitivity to any component of the product.

- The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. Severe respiratory reactions and cardiac reaction, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate.

- Patients with a history of atopy or severe anaphylactic reactions to a variety of allergens may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

- Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

- Beta-adrenergic blocking agents may mask signs and symptoms of acute hypoglycemia or certain clinical signs of hyperthyroidism. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving either insulin or oral hypoglycemic agents, or patients suspected of developing thyrotoxicosis, should be managed carefully, with caution.

- In patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta adrenergic receptor blocking agents because these agents impair the ability of the heart to respond to beta-adrenergically mediated reflex stimuli.

- The most frequently reported adverse reactions have been burning and stinging upon instillation. This was seen in 38% of patients treated with ISTALOL and in approximately one in eight patients treated with TIMOPTIC in OCUDOSE. Additional reactions reported with ISTALOL at a frequency of 4 to 10% include: blurred vision, cataract, conjunctival injection, headache, hypertension, infection, itching and decreased visual acuity.

Please see Brief Summary of Prescribing Information for ISTALOL and TIMOPTIC in OCUDOSE on the following pages.


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be used with caution in patients with cerebrovascular insufficiency. If signs or the immediate objective of treatment is to reopen the angle. This may require constricting the pupil. Timolol maleate has little or no effect on the pupil. Istalol should not be used alone in the treatment of angle-closure glaucoma. has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor 5.6 Masking of Hypoglycemic Symptoms in Patients with Diabetes with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-Mellitus: of the heart to respond to beta-adrenergically mediated reflex stimuli. This may 7.3 Catecholamine-Depleting Drugs: should, in general, not receive beta-blocking agents, including Istalol. 7.6 Clonidine: is recommended when a beta blocker is administered to patients receiving DRUG INTERACTIONS 6.2 Postmarketing Experience oral and Istalol® should be observed for potential symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Ibuprofen (100 mg/day). (50,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose; in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women Istalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 6.3 Nursing Mothers: Timolol has been detected in human milk following oral and systemic drug administration. Because of the potential for serious adverse reactions from Istalol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. 7.5 Pregnancy Istalol® (timolol maleate ophthalmic solution) 0.5% Initial U.S. Approval: 1978 STERILE INDICATIONS AND USAGE Timolol (timolol maleate solution) 0.5% is a non-selective beta-adrenergic receptor blocking agent indicated in the treatment of elevated intracocular pressure (IOP) in patients with open angle or narrow angle glaucoma. CONTRAINDICATIONS 4.1 Asthma, COPD: Istalol is contraindicated in patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease (see WARNSORS AND PRECAUTIONS, 5.2). 4.2 Cardiovascular: Fenofibrate may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition may further reduce cardiac output and cause hypotension in patients without a history of cardiac failure. Concomitant use of beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Istalol should be discontinued (see CONTRAINDICATIONS, 4.2). 4.3 Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, or moderate to severe bronchospastic, bronchitic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma in which Istalol is contraindicated) should avoid beta-blocking agents including Istalol. 4.4 Increased Reactivity to Allergens: While taking beta-blockers, patients with a history of allergy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to therapeutic, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions. 5.5 Potency of Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness associated with certain myasthenic symptoms (e.g., ptosis, pharyngeal, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in patients with myasthenia gravis or myopathies. 5.6 Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus: In the clinical trials, the incidence of hypoglycemic symptoms with Istalol was similar to placebo in diabetic patients. In patients with diabetes mellitus, beta-adrenergic blocking agents may mask the signs and symptoms of 5.7 Masking of Thyroiditis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia of hyperthyroidism. Patients suspected of developing Graves’s disease should be managed carefully to avoid withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm. 5.8 Contamination of Topical Ophthalmic Products After Use There have been reports of bacterial contamination with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concomitant corneal disease or a dioptric of the corneal epithelial surface (see PATIENT COUNSELING INFORMATION). 5.9 Impairment of Beta-adrenergically Mediated Reflexes During Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the role of general anesthetics in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced severe hypertension during anesthesia. Difficulty in reestablishing and maintaining the blood pressure has also been reported for these reasons, in patients undergoing elective surgery, some investigators recommend gradual withdrawal of beta-adrenergic receptor blocking agents. If necessary during surgery, the effects of beta-adrenergic blocking agents may be antagonized by sufficient doses of adrenergic agents. 5.10 Angle-Closure Glaucoma: in patients with acute or chronic angle closure glaucoma the immediate objective of treatment is to reopen the angle. This may require constricting the pupil. Timolol maleate has little or no effect on the pupil. Istalol should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Ibuprofen (100 mg/day). 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Because of the potential for serious adverse reactions from Istalol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. 6.4 Pediatric Use: Safety and effectiveness in pediatric patients have not been established. 6.5 Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients. OVERDOSAGE There have been reports of inadvertent overdosage with Istalol resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as clonidine, headaches, shortness of breath, bradycardia, bronnchospasm, and cardiac arrest. An in vitro histologic study, using “ 6.6 Tachycardia: overdose of Istalol® is usually treated by standard supportive and symptomatic therapy. The value of hypertensive therapy remains to be determined. 8.3 Nursing Mothers: Istalol contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lanset may be administered 15 minutes following Istalol administration. Re Oily Distributed by: Bausch & Lomb, a division of Valeant Pharmaceuticals North America LLC Bridgewater, N.J. 08807-1201 Under License From: SERV Planmedica Co., Ltd Poole, England Baulkamp, Switzerland Istalol is a trademark of Bausch & Lomb Incorporated or its affiliates. © Bausch & Lomb Incorporated Based on 940150 ISTALOL USA:17 Revised 02/2016
BRIEF SUMMARY OF PRESCRIBING INFORMATION
This is a summary of the prescribing information. For complete prescribing information, see Prescriber’s Information section. Refer to Prescriber’s Information for additional information needed to use TIMOPTIC® (timolol maleate ophthalmic solution) safely and effectively. See full prescribing information for TIMOPTIC in OCUDOSE, PRECAUTIONS category C, and CONTRAINDICATIONS for additional information.

TIMOPTIC* 0.25% AND 0.5% (TIMOLOL MALEATE OPHTHALMIC SOLUTION) IN OCUDOSE* (DISPOSER)

INDICATIONS AND USAGE
Preservative-free TIMOPTIC in OCUDOSE is indicated for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

PRECAUTIONS
Preservative-free TIMOPTIC in OCUDOSE may be used when a preservative is to be avoided for any reason. See Precautions category C and CONTRAINDICATIONS for additional information.

WARNINGs
As with any topically administered ophthalmic drug, this drug is absorbed systemically.

In patients with a history of cardiac failure, use with caution.

In patients undergoing anesthetic procedures (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease, TIMOPTIC may be used with caution after reevaluation of the patient's cardiac status.

In patients with angle-closure glaucoma, the immediate use of TIMOPTIC may be contraindicated due to the risk of acute angle closure.

In patients with congestive heart failure, continued depression of the myocardium may occur due to TIMOPTIC use. In patients with mitral stenosis, TIMOPTIC use is contraindicated due to the risk of pulmonary edema.

In patients with a history of atopy or a history of bronchospastic disease, TIMOPTIC use is contraindicated due to the risk of bronchospastic reaction.

In patients with a history of a previous reaction to a beta-adrenergic blocking agent, TIMOPTIC use is contraindicated due to the risk of anaphylactic reaction.

Other Contraindications
The concomitant use of beta-adrenergic blocking drugs and antiarrhythmic drugs, especially disopyramide, should be avoided (see PRECAUTIONS category C).

Nursing Mothers
Preservative-free TIMOPTIC in OCUDOSE is available in concentrations of 0.25 and 0.5 percent. The usual starting dose is one drop of 0.25 percent preservative-free TIMOPTIC in OCUDOSE in the affected eye(s). The dose may be changed to one drop of 0.5 percent solution in the affected eye(s) administered twice a day. Additional dosages may be appropriate (see PRECAUTIONS category C). The solution from one individual unit is to be used immediately after opening for administration to one eye. The remaining contents of the individual unit are to be discarded immediately after administration (see PRECAUTIONS category C).

Overdosage
Overdosage has been reported with Tablets BLOCADREN (timolol maleate tablets). A 30-year-old female ingested 650 mg of BLOCADREN (maximum recommended oral daily dose is 60 mg) and experienced second and third degree heart block. She recovered without treatment after approximately two days without further cardiac complications. (See PRECAUTIONS category C.)

Dosages above one drop of 0.5 percent TIMOPTIC (timolol maleate ophthalmic solution) should not be administered if the patient shows any signs of anaphylactic reaction.

The patient should be observed for signs and symptoms of overdose, and furthermore, the patient's condition should be assessed and reevaluated periodically until the signs and symptoms of overdose subside.

Dosage and Administration
Preservative-free TIMOPTIC in OCUDOSE is a sterile solution that does not contain a preservative.

The solution from one individual unit is to be used immediately after opening for administration to one eye. Since identity cannot be guaranteed after the individual unit is opened, the remaining contents should be discarded immediately after administration.

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Dosage and Administration
Preservative-free TIMOPTIC in OCUDOSE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Timolol maleate has been detected in human breast milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS
The most frequently reported adverse experiences have been burning and stinging upon installation (approximately once in eight patients).

The following additional adverse experiences have been reported less frequently with ocular administration of this drug:

Cardiovascular: Angina pectoris, atrioventricular block, cardiac failure, decreased heart rate, electrocardiographic changes, heart block, myocardial failure, palpitation, pulse changes, tachycardia, vein distention.

CNS: Dizziness, drowsiness, headache, malaise.

Dermatologic: Itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, General, and Brief Summary).

GU: Urethral stricture.

Hematologic: Anemia, leukopenia.

Musculoskeletal: Arthralgia;

Nervous System/Psychiatric: Drowsiness, headache, malaise, nervousness, weakness, dizziness.

Ocular: Allergic ocular reactions, blepharitis, keratitis, lacrimal pain, photophobia (e.g., increased ocular sensitivity, tearing, and burning), and dry eyes; pruritus, decreased corneal sensitivity; opthalmic edema.

Respiratory: Bronchospasm (predominantly in patients with pre-existing bronchospastic diseases), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.

Skin: Allergic reactions.

Urinary: Dysuria, frequency.

Other: Viral infections.

The following additional adverse effects have been reported in clinical experience with oral timolol maleate or other oral beta blocking agents, and may be considered potential effects of ophthalmic timolol maleate:

Allergic: Erythematous rash, fever, conjunctival hyperemia, conjunctival swelling, blepharitis, keratitis, lacrimal pain, photophobia (e.g., increased ocular sensitivity, tearing, and burning), and dry eyes; pruritus, decreased corneal sensitivity; opthalmic edema.

Cardiovascular: Angina pectoris, atrioventricular block, cardiac failure, decreased heart rate, electrocardiographic changes, heart block, myocardial failure, palpitation, pulse changes, tachycardia, vein distention.

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rendered ineffective if not applied properly. Beyond education, we must consider and turn to technological tools and reminders to aid in patient compliance.

Will You Prescribe Medical Marijuana?

Depending on which state you practice in, patients may approach you about prescribing medical marijuana. A total of 28 states had legalized the use of medical marijuana as of this writing. I practice in New York and periodically get this question. When this happens, I refer to a physician’s statement from the American Glaucoma Society (AGS).

The AGS acknowledges in the statement that marijuana can lower IOP, but it takes issue with the drug’s short duration of action, suboptimal delivery options, lack of evidence showing any resulting alteration of glaucoma’s long-term course, and psychotropic side effect profile that prevents a patient who is using the drug from driving, operating heavy machinery, and functioning at maximum mental capacity. The AGS concludes that these factors “preclude recommending this drug in any form for the treatment of glaucoma at the present time.”

As research and technology advance our knowledge about glaucoma, clinicians must field a growing number of questions from glaucoma patients about their diagnosis, treatment options, management strategies, and prognosis. It is incumbent upon eye care specialists to stay abreast of the latest developments in the field, and continue to gain knowledge and perspective about this chronic and progressive disease in order to answer patients’ questions appropriately and sensitively. Doing so will ultimately build patient trust and elevate the doctor-patient relationship.

George A. Cioffi, MD, is the Edward S. Harkness Chairman and Ophthalmologist-in-Chief of the Department of Ophthalmology at NewYork-Presbyterian Hospital/Columbia University Medical Center; he currently holds the Jean and Richard Deems Professorship at Columbia University.

Scientific Discoveries

Pathogenesis of Glaucoma

Derek S. Welsbie, MD, PhD

The importance of understanding the cellular pathways responsible for the development of glaucoma cannot be understated. Our advancing knowledge of the signaling cascades that mediate axon degeneration and cell death could identify novel drug targets that might complement the current glaucoma treatment strategy of lowering intraocular pressure (IOP).

This critical mission comes at a time when worldwide rates of glaucoma continue to rise. Previous estimates put the number of suspected cases in the world at around 70 million, with that number expected to increase to 111.8 million in 2040. Moreover, the World Health Organization ranks glaucoma as the leading cause of irreversible blindness and visual impairment worldwide.

The increasing prevalence of glaucoma is complicated by the fact that symptoms of glaucoma may be few and subtle. It is estimated that more than 4 million Americans have glaucoma, with only half of those individuals aware that they have the disease. Elevated IOP—the one modifiable risk factor that responds to medical and surgical intervention—is only experienced by 50% of primary open-angle glaucoma (POAG) patients in certain populations, glaucoma can go undiagnosed for years.

Fortunately, we continue to make tempered strides in understanding glaucoma’s pathogenesis and have shifted the way we view and define this disease. While elevated eye pressure (greater than 21 mmHg) used to be an integral part of the definition, we now understand glaucoma to be a disease of the optic nerve head that damages the axons of retinal ganglion cells (RGCs).

Site of RGC Injury

A key insight to understanding glaucoma’s pathogenesis relates to the initial site of RGC injury. One hypothesis, in particular, suggests that this injury occurs at the optic nerve head, specifically at the lamina cribrosa—the fenestrated connective tissue through which RGC axons exit the eye. Research leans in this direction based on the finding of characteristic visual field (VF) defects that respect the horizontal midline and the anatomic pattern of axon movement.

Experimental evidence for this hypothesis came in the 1970s...
Glaucomatous eyes experiencing hoop stress, i.e., laminar remodeling along with elevated IOP, exhibit an apparent tautening of the lamina, as shown in this diagram.

When researchers Harry Quigley and Doug Anderson injected a radioactive tracer into the vitreous of primates to label RGCs and study axonal transport after short-term IOP elevation, they showed that the tracer became concentrated at the optic nerve head, specifically at the lamina cribrosa.

Thirty years later, in 2007, Gareth Howell and Simon John at Jackson Labs confirmed the hypothesis using a variety of genetic axon labeling techniques in a mouse model of pigmentary glaucoma. Importantly, the initial axon damage at the lamina cribrosa sets off a cascade of axon dysfunction and degeneration, and, eventually, cell death. Given that RGCs are responsible for processing and transmitting visual information, patients with glaucoma progressively lose vision.

**Lamina Cribrosa’s Complex Role in Glaucoma**

Given the importance of the optic nerve head as a site of RGC axon injury, it is essential to understand the lamina cribrosa’s larger role in glaucoma and response to increased intraocular pressure.

Using a technique called 3D histomorphometry, Claude Burgoyne and J. Crawford Downs have quantified the movement of the optic nerve head in a primate model of experimental glaucoma. After raising eye pressure for a period of time, they have enucleated and fixed eyes before serially sectioning, staining, and imaging the optic nerve head. The team has shown that in early glaucoma, the lamina cribrosa thickens, the peripapillary sclera bows posteriorly, and laminar insertion actively remodels to a more posterior position. Later in the disease, the lamina begins to thin. All of these changes are responsible for the characteristic “cupping” seen in glaucoma patients.

These findings are consistent with those of optical coherence tomography (OCT) demonstrating similar laminar changes. OCT imaging also has shown that areas of the optic disc with more laminar displacement (and presumably remodeling) correlate with the location of disc hemorrhages. One hypothesis for this scenario is that remodeling of the laminar beams (where capillaries run inside rather than between the beams as axons do) might disrupt the blood vessels, leading to small hemorrhages. This would explain why patient disc hemorrhages can be found in glaucoma (i.e., because of the associated laminar changes) and not other optic neuropathies.

The cause of laminar remodeling is likely a change in the net forces experienced by the lamina cribrosa (related to the translaminar pressure gradient and may be influenced by biomechanical properties of the lamina and peripapillary sclera.

Further complicating this complex interplay of forces is the fact that, when IOP is elevated, it can cause the peripapillary sclera to move outwards, which serves to taunt the lamina cribrosa. Finally, in some eyes, the remodeling may be related more to low retrolaminar pressures than elevated intraocular pressure. These varying scenarios underscore why elevated IOP is not found in all glaucoma patients.

Though we have learned a great deal about the physiology of glaucoma, we have yet to cement our understanding about the mechanism by which laminar remodeling damages RGC axons—threadlike segments of the nerve cell conducting impulses from the cell body to other cells. We know the composition of the laminar beam includes axons, blood vessels, and astrocytes—star-shaped glial cells—between them, as well as connective tissue. Several hypotheses suggest that deformation of the lamina cribrosa may do one or more of the following: mechanically damage or compromise blood flow to the axons, lead to toxic gene expression by neighboring glial cells, and/or interfere with axonal transport.

**Cell Energy Mismatch & Mitophagy Offer Additional Clues**

Offering additional clues to glaucoma pathogenesis are the RGC axon cell makeup and process of mitophagy in disease pathophysiology.

RGC axons make up nearly 90% of the cell by volume, placing a large energy demand on the cell. This is compounded by the fact that myelination, an energetically-efficient method of conducting action potentials, occurs distal to the lamina cribrosa.

Furthermore, because capillaries are embedded in the laminar beams and surrounded by collagen, astrocytes charged with nourishing RGCs do not have direct access to the capillaries, unlike other regions of the brain. This high demand/law supply may explain why axons are damaged here in glaucoma.

Evidence specifically linking mitochondria to the disease process comes in two forms. First, experimental research has determined that mitochondria localize (primarily or secondarily) to the lamina cribrosa and that the optic nerve head is a key site of mitochondrial turnover (called mitophagy). Secondly, one of the few genes linked to rare familial cases of glaucoma—OPTN (i.e., optineurin)—has been shown to be a mitophagy receptor.

These facts, taken together, bolster the idea that the process of mitophagy—which plays an integral part in keeping cells healthy by promoting turnover of mitochondria and preventing accumulation of dysfunctional mitochondria that can lead...
to cellular degeneration—combined with glaucoma’s unique pathophysiology may be creating a confluence of conditions promoting glaucoma pathogenesis.

Moving Forward: Looking to Genetics

While details about the cause of axon degeneration and cell death in glaucoma are yet to be elucidated, neuronal models are providing new information.

For example, experimental studies in mice have shown that axonal damage in sciatic nerves leads to distal and proximal degeneration.\(^5\) Distal, or Wallerian, degeneration, was recently found to use an active genetic program, mediated by a gene called SARM1, to injure axons.\(^6\) Recent studies have found that, when both copies of SARM1 were disrupted, distal axonal degeneration was lessened despite axon injury. Investigators are now assessing whether inhibiting SARM1 might protect RGC axons in glaucoma, and, consequently, prevent resulting cell death.\(^6\)

Our research group has been interested in understanding how RGC axon injury signals trigger cell death. To find genes responsible (and potential drug targets), we established a screening platform using mouse RGCs. By harnessing RNA interference to individually turn off thousands of transcript-level genes in injured RGC axons, we are measuring this disarming effect on RGC survival.

Our work has already identified the protein dynein light chain kinase (DLK) as a key mediator of RGC cell death. In rodent models of optic neuropathy, including glaucoma, inhibiting DLK has been shown to be robustly protective to RGCs. Other groups have independently validated these findings and further revealed that DLK inhibition has not only translated to a protective effect for RGC cells, the cells have actually survived—a key feature of any future neuroprotective strategy.

These steps forward in our understanding about DLK and SARM1 offer the potential for future drug targets to defend against, and even prevent, axon degeneration and cell death. In the future, these neuroprotective strategies could be combined with IOP-lowering therapies to better treat glaucoma patients.

Dr. Weliebe is assistant professor of ophthalmology at the University of California San Diego, Department of Ophthalmology.

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Assessment Strategies: Glaucoma Progression: What’s New and What’s Best

Felipe A. Medeiros, MD, PhD

A n accurate and swift diagnosis of glaucoma is the first priority when it comes to getting a handle on this chronic and progressive disease—ranked as the top global eye disease burden by the World Health Organization, with rising incidence rates worldwide.\(^14\)

Once the clinician confirms the patient has glaucoma or is at risk for developing the disease, the next critical step is determining the rate of disease progression. Doing so is no easy task for clinicians due to inherent discrepancies within and between the two primary technologies available to assess functional and structural glaucomatous loss and damage. Advancements in these respective technologies, described below, have only brought us so far, leaving the clinician to navigate the often-conflicting findings yielded by the current methods of measurement.

This is not a matter to take lightly, given that the clinician’s conclusions about disease progression will fundamentally impact treatment and management decisions, as well as the ability to bring the disease under control.

Fortunately, researchers are developing tools to reconcile
the challenges present in today’s technologies to offer the clinician an effective workaround. As a result, the clinician will be able to reap the benefits of existing measurement methods without being stymied by their limitations in helping to classify a patient’s glaucoma status.

State of Technology for Determining Progression

Though the two prevailing methods of assessing functional and structural glaucomatous damage have advanced over the years, there is still room for improvement.

The widely used method of performing perimetry—detecting a small target superimposed on a uniform background at different locations within the field of view—has not changed substantially since visual fields (VFs) were introduced 150 years ago. However, the 1970s saw the introduction of standard automated perimetry (SAP) with software that enabled perimetry to map VFs. This automated version of manual perimetry offered greater sensitivity and reproducibility than its predecessor.

In the realm of assessing structural glaucomatous loss and damage, the advent of optical coherence tomography (OCT)—a noninvasive imaging technique that provides high-resolution, cross-sectional images of the retina, retinal nerve fiber layer (RNFL), and optic nerve head—has revolutionized the clinical eye practice by providing unprecedented access to this region of the eye. A 2013 review pointed to a confluence of evidence suggesting that the RNFL remained the dominant parameter for glaucoma diagnosis and detection of progression. More recently, a new generation of OCT, spectral-domain (SD)-OCT, offers additional benefits over its precursor for glaucoma assessment, including increased axial resolution, faster scanning speeds, and improved reproducibility.

And yet, shortcomings persist with both SAP and OCT for determining glaucoma progression. SAP’s challenges include: the dependency on interpreter training and subjectivity, a tendency to produce false-positive and false-negative patient responses, a lack of portability, the need for sometimes expensive perimeter devices, the limited ability to collect data over time, and relatively late detection of VF defects—given that substantial losses of retinal ganglion cells (RGCs) often have to occur before statistically significant defects are detectable. In the case of OCT, the clinician frequently struggles to discriminate glaucomatous structural damage from measurement variability and age-related structural loss when assessing structural changes.

Measurement Variability

In light of these ongoing challenges for clinicians, it goes without saying that a comprehensive approach to determining glaucoma progression requires longitudinal follow-up of glaucoma patients using various measurement assessments. This strategy provides the best diagnostic evidence to confirm presence or worsening of disease over time.

But while the use of both structural and functional methods may enhance the ability to detect change over time, it can sometimes lead to confusing results. For example, when analyzing longitudinal data, clinicians must realize that SAP and OCT will often show considerable disagreement in the assessment of progression, as the two methods’ performance in detecting change varies according to the stage of the disease. In early stages of glaucoma, OCT is generally better than SAP at identifying progressive disease. Conversely, in eyes with moderate or late glaucoma, SAP tends to perform better than OCT in detecting further progression.

As such, it is important to consider why and when these disagreements occur and be able to reconcile the information. Two recent investigations addressed this topic.

In the first study, we were interested in determining whether SAP or OCT would show the first signs of glaucoma in a group of 373 cases of suspect eyes. All eyes had VFs at baseline and an average follow-up of 4.6 ± 1.0 years (average 8.8 tests) via SAP SITA Standard and OCT. We extracted information about test-retest variability from this cohort and used computer simulations to reconstruct real-world trajectories of functional and structural change over time. We found that, for the same level of specificity, OCT detected true progression in eyes suspected of having glaucoma on average five years earlier than SAP.

In the second study, we assessed over time 462 eyes with glaucomatous damage and a wide range of disease severities at baseline. The eyes were followed for 3.6 ± 0.9 years, taking an average of eight tests from OCT and SAP 24-2. Progression was defined as a statistically significant change on OCT RNFL thickness, or SAP mean sensitivity that was faster than age-related change. A group of healthy eyes also was followed over

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**FIGURE 1. CUMULATIVE PROBABILITY OF DETECTING PROGRESSION**

In one study including 373 cases of patients suspected of having glaucoma that were followed up at 4.6 ± 1.0 years, OCT RNFL was found to detect progression approximately five years earlier than VFs.
RNFL loss when evaluating glaucoma progression with OCT. Therefore, it is crucial to properly take into account age-related RNFL loss in glaucomatous eyes if the rate of change was a statistically significant confounder in the assessment of glaucoma progression, given that healthy eyes will eventually show some degree of structural change over time.

In a study on 70 healthy eyes followed over time, the lower limit of 95% confidence limits was demonstrated to have a 0.85μm per year change in RNFL thickness, despite being classified as healthy. This research demonstrated that age-related RNFL loss can be an important confounder in the assessment of glaucoma progression, given that healthy eyes will eventually show some degree of structural change over time.

We found that SAP and OCT tests rarely agreed on progression. OCT and SAP revealed progression concomitantly in only 95% of the healthy eyes.

The Age-Related Structural Loss Conundrum

Adding to the discord of the SAP and OCT measurements is the issue of age-related RNFL loss—another confounder in the assessment of progression. Almost all healthy eyes follow a long enough period of time will eventually show some degree of structural change. One study in particular demonstrates this fact.

We followed roughly 70 healthy eyes over time and analyzed different criteria to take into account age-related RNFL loss. It was determined that large numbers of healthy eyes could be shown as progressing according to the criteria employed.

Therefore, it is crucial to properly take into account age-related RNFL loss when evaluating glaucoma progression with OCT and SAP.

Comparing Functional and Structural Change Discrepancies

It is essential to assess the rate of change to properly manage glaucoma. However, the unique designs of structural and functional tests can lead to rate disparities that potentially confuse clinicians.

Note that SAP measurements are designed to assess visual function through changes in mean deviation, and are represented by decibels—a logarithmic scale. Conversely, OCT measurements are intended to assess structural damage, and are often expressed in microns of RNFL thickness—linear units. These dissimilar values of measurement make it challenging to compare rates of structural and functional change in clinical practice.

For example, in one early-glaucoma case, SAP revealed some progression superiorly, but with a shallow slope of change, given to us as -0.1 dB per year. This would represent nearly 1 dB in 10 years—very slow change. However, OCT findings for the same patient revealed a significant rate of RNFL thickness loss of about 2μm per year. This would represent 20μm in 10 years, indicating a fast rate of progression. So, the VF and OCT results strongly disagreed about the velocity of change.

As another example, in an eye with advanced glaucoma with clear VF loss and a rapid slope of about 3% per year, OCT results showed no progression over time, with a flat slope given to as -0.25μm per year. So the VFs suggested a 30% loss of function in 10 years, while the OCT indicated that the patient would only experience about 2.5μm of structural deficit in that time. These findings reveal, again, a major inconsistency in information produced by the two assessment strategies.

The question of how to rectify these seemingly contradictory results is paramount to our ability to correctly evaluate rates of change. Simple logic suggests that OCT is better at visualizing early stages of the disease, and VFs are more effective later on. Yet, this insight still leaves clinicians to determine at what point in disease they must emphasize one method over the other. To spare clinicians from having to navigate this confusing task, our research group has developed a new tool that may help.

RGC Index: Resolving the Functional/Structural Paradox

Expanding on earlier experimental glaucoma research in monkeys conducted by Ron Harweth’s group, we strove to combine a measurement of functional and structural loss that could better assess the rate of change and be used throughout the disease continuum.

Toward that end, we developed the RGC Index to integrate functional and structural measurements into a single index. Using empirical formulas to estimate ganglion cell counts from VF and OCT findings, we developed a single index that combined the two assessment strategies’ information and weighted it by disease severity to account for the associated differences in performance. The index leans toward OCT in early glaucoma and toward VFs in later stages of the disease.

We evaluated the ability of the RGC index to diagnose, stage, and detect glaucoma progression, and found that it performed better than isolated indices from OCT and SAP. In eyes with progressive optic neuropathy but normal VFs, it performed effectively for ROC curve areas, at 0.88. It was determined that large numbers of healthy eyes could be shown as progressing according to the criteria employed.
The site of aqueous humor outflow (AHO) resistance is located in the juxtaocular tissue, where the trabecular meshwork (TM) and Schlemm’s canal interface. Aqueous humor leaves the eye by passive flow via two avenues: the TM and the uveoscleral pathway. The TM, tissue made of cells embedded in an extracellular matrix (ECM) of molecules providing structural and biochemical support to surrounding cells, acts like a filter for the majority of the aqueous humor before it passes through Schlemm’s canal and enters the episcleral venous system. At the same time, the uveoscleral pathway is a gateway for what some studies have estimated to be between 5% and 15% of AHO as it flows from the anterior chamber into the ciliary muscle, and supraciliary and suprachoroidal spaces, exiting the eye into or through the sclera.

The natural process of aging can lead to the breakdown and loss of TM cells, resulting in some dysfunction in the outflow system. However, in glaucomatous eyes, researchers also have observed an increase in ECM thickness compared with healthy, age-matched eyes. As a result, studies have shown that AHO impairment can be accelerated in open-angle glaucoma. And since many therapeutic strategies target aspects of the outflow system to lower IOP but all have various drawbacks, this would be especially important for selecting the optimal therapeutic solution for a given patient and customizing that for the individual's needs.
been some degree of effectiveness.10

safety over standard glaucoma surgeries, the tradeoff has
surgeries reduce the incidence of complications and increase
of microscopic-sized equipment and tiny incisions. While the
surgical procedures such as minimally invasive glaucoma
provides a picture of gross anterior chamber angle structures
for improvement.

chronic and progressive disease, but each with opportunities
all serving a useful purpose in collecting clues about this
former system (as described below), none are without fl aws,
major obstacle for many glaucoma patients.9 As well, new
IOP. However studies show that medication adherence is a
solution based on the unique disease characteristics.
For example, many glaucoma medications and others on
the horizon are designed to increase outflow in order to lower
IOP. However studies show that medication adherence is a
major obstacle for many glaucoma patients.9 As well, new
surgical procedures such as minimally invasive glaucoma
surgery (MIGS) aim to improve aqueous drainage by way
of microscopic-sized equipment and tiny incisions. While the
surgeries reduce the incidence of complications and increase
safety over standard glaucoma surgeries, the tradeoff has
been some degree of effectiveness.10

Though several imaging tools exist to evaluate aspects of
the AHO system (as described below), none are without flaws,
leaving clinicians with gaps in their awareness about structural
status of the outflow system. A new imaging technique our
research group has developed, aqueous angiography, may
play a pivotal role in highlighting the path of aqueous humor
flowing out of the eye. Such information could help clinicians
create personalized patient plans for surgery, particularly
when it comes to newer procedures such as MIGS.

Assessing Aqueous Humor Obstruction

Until now, four main imaging approaches have been
available to clinically assess angle structures in glaucoma—
all serving a useful purpose in collecting clues about this
chronic and progressive disease, but each with opportunities
for improvement.

The first and most familiar, gonioscopy, is considered the
gold standard for diagnosing and managing glaucoma. It
provides a picture of gross anterior chamber angle structures
and alerts the clinician to the angle width (open, narrow, or
closed) by way of a special contact lens prism placed on the
surface of the eye.

Another widespread imaging modality, ultrasound, provides
images of the TM and Schlemm’s canal, as do the increasingly
popular optical coherence tomography (OCT) and spectral-
domain OCT imaging techniques.

More recently, researchers have offered up the possibility
of multiphoton microscopy, which provides three-dimensional
images of the outflow apparatus and information on function.11
This method operates without the need for a pinhole, yielding
higher resolution than single-photon (confocal) microscopy.10

Though all of these imaging techniques add value (or poten-
tial value in the case of multiphoton microscopy) in the clinical
realm of glaucoma, each suffers from its own constraints.

For example, gonioscopy cannot provide fine detail at a
level, and is hampered by interpreter subjectivity, a lack
of standards to determine occludability of narrow angles, and
variability due to exam techniques and illumination. In the case
of ultrasound and OCT, both necessitate expensive equipment,
are technique dependent, and do not provide cellular-level
information. And multiphoton microscopy uses a costly titanium
sapphire laser and lacks a commercial imaging device for wide-
spread clinical use.11

These issues, compounded with the increasing popularity
of MIGS and its variable results, call for an alternative way
to image AHO.12 14 This new method would assist surgeons in
visualizing the patient’s outflow system and optimizing selection
of a treatment that ensures the highest chance of long-term suc-
cess in lowering IOP.

Aqueous Angiography

Toward this end, our research group developed a new
technique to image AHO known as aqueous angiography.15
We modified the procedure of injecting indocyanine green and
fluorescein into the veins to examine retinal blood flow with
angiography, to better view the anterior chamber and the AHO
system. Our goal was to have a real-time approach, suitable for
humans, to gauge physiologic pressure and provide a compre-

We started with an experimental model by performing aque-
ous angiography on enucleated pig and cow eyes before mov-
ing to enucleated human eyes.15

As an example, in a human model, we performed aqueous
angiography on the enucleated eyes of two women (ages 79
and 83) who both died of cardiac issues. Interestingly, we deter-
mined that flow patterns were distinct between the two different
sets of eyes and even within an individual pair of eyes.

In another eye, from a male who died from leukemia, aque-
ous angiography revealed that a signal at twelve o’clock moved
in the following directions: superior nasal, inferior nasal, nasal,
and inferior temporal. However, there was very little angio-

Our research group performed aqueous angiography on the enu-
clated eyes (top) of a 79-year-old female who died from a myocardial
infarction and on those (bottom) of an 83-year-old female who died
from cardiac arrest.15 We determined that the segmental flow pat-
tterns were often different between the two sets of eyes (vertical)
and within an individual set of eyes (horizontal). This image was
adapted from the published paper findings.
In addition to looking at the function of flow, we also looked at the structure of flow through the use of OCT.14 We employed overlapping volume scans 360 degrees around the right eye of a living person, and enabled automated detection of the outflow pathways through a series of image processing techniques. With two-dimensional images, we created three-dimensional casts of Schlemm’s canal and collector channels branching off from behind. From various views, we observed a difference in the size and presence of Schlemm’s canal and collector channels.

As our research and knowledge of aqueous angiography advances, we will increasingly develop a more comprehensive understanding of the function and structure of the anterior segment of the eye. We hope that this information and the eventual widespread use of aqueous angiography will enable clinicians to treat glaucoma, not as a uniform disease, but as a unique disease condition in each eye, paving the way for customized and targeted treatment plans, particularly when it comes to MIGS.

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Clinical Applications

Encouraged by these results, we took a step back to consider how we could use this information clinically. For example, would an area of good flow be an appropriate target for trabecular therapy? Or would it be better to aim for a region of poor flow where there is room for improvement?

The answers continue to evolve, but we published a paper concluding that sequential aqueous angiography in an enucleated human eye model system suggests that regions without angiographic flow or signal could be recruited for AHO improvement using a trabecular bypass stent.15

In April 2016, our research group became part of a large, international collaboration to test this real-time imaging method in living primates. In China, with Dr. Ningli Wang, professor of ophthalmology and president of Tongren Eye Hospital, we collaboratively performed aqueous angiography on primate eyes.

Similar to our earlier findings, we observed that angiographic flow was segmental. And for the first time, real-time images revealed zones without much flow that could dynamically change patterns and develop outflow as surgeons were watching; inversely, they showed angiographic signaling that could quickly shut down as well.
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