Keeping an EYE on Pressure
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Purpose and Target Audience
The armamentarium of intracocular pressure (IOP)-lowering pharmacologic and surgical treatments for glaucoma continues to grow. Nonetheless, patients with glaucoma are still at risk for vision loss and blindness due to their disease. Unfortunately, treatments to protect retinal ganglion cells from degeneration — the ultimate cause of vision loss — are lacking. New drugs, new fixed combinations of existing drugs, and new procedures constantly challenge the traditional treatment paradigm and are showing promise in lowering IOP and slowing disease progression by multiple mechanisms of action. Ophthalmologists who treat glaucoma must stay abreast of new treatments and understand their role in the context of the pathophysiology and cell biology of glaucoma to optimize patient outcomes. The purpose of this activity is to review recent advances in the understanding of the pathophysiology and treatment of glaucoma that are challenging traditional treatment paradigms. This educational activity is intended for ophthalmologists.

Learning Objectives
Upon completing this educational activity, participants should be able to:
- Discuss the etiology of glaucoma
- Select and document IOP-lowering treatment plans for patients with glaucoma based on efficacy, safety, guidelines, and patient preferences
- Describe the potential role of emerging therapeutics in the management of glaucoma

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- 256 MBs or more of RAM
- Internet Explorer 6.0 or higher
- Windows Media Player 10.0 or higher
- Adobe Acrobat 7.0 or higher
- Course content compatible with Mac OS

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PATHOPHYSIOLOGY OF GLAUCOMA

Primary open-angle glaucoma (POAG) presents numerous challenges in terms of both diagnosis and management. In the absence of a definitive test for the disease, the diagnosis of glaucoma remains a clinical impression based on the synthesis of physical findings and both structural and functional testing. A fairly nebulous definition of POAG, the language of which underscores the imprecision of the diagnostic features of the disease, further complicates the process. According to the American Academy of Ophthalmology:

Primary open-angle glaucoma (POAG) is a chronic, progressive optic neuropathy in adults in which there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This condition is associated with an open anterior chamber angle by gonioscopy.

At the most basic level, POAG is an optic neuropathy; however, definitive causal factors have remained elusive. The role of elevated IOP in glaucoma, once thought to be the primary cause of POAG, has become more complex over time. Epidemiologic and longitudinal studies have demonstrated that elevated IOP is neither necessary nor sufficient to explain the development of POAG. Instead, IOP is considered a risk factor for both the development and progression of glaucoma. Interventional clinical trials support this relationship; the reduction of IOP reduces the risk of developing glaucoma and its progression across the full range of IOPs. In these studies and others, however, one consistent observation remains clear: some eyes with glaucoma continue to progress despite significant IOP reduction. One explanation may be that these eyes required even greater IOP reductions to achieve disease stability. Another explanation is that other factors beyond IOP also play a role in the pathophysiology of glaucoma.

Pathophysiologic Mechanisms

Many candidate contributors to glaucoma pathogenesis have been postulated (Figure 1). These all share 1 key feature; they have the potential to damage retinal ganglion cells (RGCs). The health of both the RGCs and the cells of the lateral geniculate nucleus depends on anterograde and retrograde axoplasmic flow to deliver crucial nutrients and prosurvival factors. Intraocular pressure is believed to lead to RGC loss by deforming the lamina cribrosa in the optic nerve head and blocking axoplasmic flow.

Figure 1. Key contributors to POAG pathophysiology

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The optic nerve head’s microcirculation may also be impaired in some eyes, leading to hypoxia and ischemia. Clinical evidence in support of this theory includes the frequent observation of disc hemorrhages in eyes with glaucoma as well as the common finding of migraine and vasospastic comorbidities, such as Raynaud phenomenon, in patients with glaucoma, which may be related to progression in these patients. Other putative factors include circulating autoantibodies to RGCs and proinflammatory cytokines that may also contribute to RGC death.
Established Risk Factors for Glaucoma

Clinically, many risk factors for the development of POAG have been identified in clinical trials. These include elevated IOP, increasing age, thin central corneas, as well as both optic nerve and visual field parameters. Other risk factors exist as well. Corneal hysteresis is a biomechanical property that reflects the viscoelastic nature of the cornea, that is, how easily it can be deformed and how easily it returns to its normal configuration after deformation. Like corneal thickness, corneal hysteresis may alter the accuracy of applanation tonometry. However, corneal hysteresis is a significant risk factor for glaucoma independent of corneal thickness, suggesting that it may provide additional information on glaucoma risk, such as a possible measure of the eye’s biomechanical susceptibility to glaucomatous optic nerve damage.

Additionally, family history remains a relevant risk factor for glaucoma. First-degree relatives of patients with glaucoma have higher than expected rates of glaucoma, although identification of genes that explain more than a tiny proportion of glaucoma cases remains elusive. It is likely that the genetics of glaucoma is a highly complex relationship involving epigenetic mechanisms, such as gene-gene or gene-environment interactions, among others. 11

Emerging Risk Factors

Cerebrospinal fluid pressure. The optic nerve head is the site of injury in glaucoma, and within the optic nerve head, the lamina cribrosa, in particular, is relevant. The lamina cribrosa provides structural support for the nerve head, and the axons of the RGCs pass through the lamina en route to their synaptic junction in the lateral geniculate nucleus. The lamina cribrosa separates the spaces under the influence of IOP anteriorly and intracranial pressure posteriorly. Any force that alters the anatomy or configuration of the lamina can threaten the health of RGC axons. On the anterior side of the lamina cribrosa is IOP, which, when elevated, can cause backbowing of the lamina cribrosa. This deformation of the lamina may create shearing forces that can impinge on the axons and interrupt axoplasmic flow, to the detriment of RGC health.

On the posterior side of the lamina cribrosa is intracranial pressure. The space within the optic nerve that lies between the nerve tissue and the dura mater is filled with CSF and is contiguous with the intracranial space. Like aqueous humor, CSF is not stagnant but is continually produced by the choroid plexus of the lateral ventricles; bathes the brain, spinal cord, and cranial nerves (including the optic nerve); and is absorbed by the cranial and spinal arachnoid villi. Also, like aqueous humor, the CSF is under constant positive pressure, CSF pressure, which is determined by the balance between CSF production and resorption.

Because both aqueous humor and CSF generate positive pressures, under homeostasis, a laminar configuration that reflects the balance between these 2 opposing forces exists. But because the relative magnitudes of IOP and CSF pressure vary, laminar deformation can occur. The role of CSF pressure in the pathophysiology of glaucoma has received significant attention. In 2008, a retrospective study from the Mayo Clinic was the first to demonstrate a statistically significant difference in mean CSF pressure among subjects with and without primary POAG. In this study, the medical records of patients referred to the Mayo Clinic for lumbar puncture for a variety of indications were reviewed. The CSF opening pressure of 28 patients with POAG and 49 nonglaucomatous control subjects was recorded. The mean opening pressure of the POAG group was significantly lower than that of the control group (9.2 ± 2.9 mm Hg vs 13.0 ± 4.2 mm Hg; P < .00005). Subsequently, a prospective study conducted in China confirmed this finding, in which the mean CSF opening pressure of subjects with normal-tension glaucoma, those with high-tension POAG, and healthy subjects was 9.5 ± 2.2 mm Hg, 11.7 ± 2.7 mm Hg, and 12.9 ± 1.9 mm Hg, respectively. The CSF pressure of the normal-tension group was significantly lower than that of the other 2 groups (P < .001).

The relationship of CSF pressure measured by lumbar puncture in these studies with intracranial pressure is unclear. The observation that CSF pressure is low in eyes with glaucoma might help explain some paradoxes surrounding the relationship between glaucoma and IOP. For instance, why do some eyes with high IOP never develop glaucoma, whereas many eyes with normal IOP develop glaucoma? These studies demonstrate that CSF pressure is lower in eyes with normal-tension glaucoma, suggesting that even low IOP is adequate to deform the lamina in the presence of low CSF pressure on the posterior side of the lamina. Further evidence for this hypothesis comes from a recent case report, in which a patient with normal-tension glaucoma demonstrated sudden progression upon undergoing ventriculoperitoneal shunting to lower CSF pressure in the setting of normal-pressure hydrocephalus.

Conversely, perhaps some individuals with elevated IOP also have elevated CSF pressure, which might neutralize the pressure gradient across the lamina cribrosa and prevent deformation of axons. A third study, in which 17 patients with ocular hypertension and 71 nonglaucomatous control subjects underwent lumbar puncture, with measurement of CSF opening pressure, supports this hypothesis. The mean opening pressure in the ocular hypertensive group was significantly higher than that of the control group (16.0 ± 2.5 mm Hg vs 12.9 ± 1.9 mm Hg; P < .001).

These studies and observations suggest that the relative magnitudes of IOP and CSF pressure, also called the translaminar pressure difference, may be important when considering the relationship between IOP and glaucoma. Additional research is necessary to add strength to this intriguing hypothesis. Further elucidation of the role of CSF pressure in IOP and glaucoma could lead to a novel therapeutic strategy for glaucoma, given that CSF pressure is modifiable. However, the invasive nature of current methods for CSF pressure assessment and modification might limit such a strategy.

Ocular perfusion pressure. In simplest terms, OPP can be thought of as the arithmetic difference between blood pressure and IOP. In more specific terms, OPP represents the relative intraluminal blood pressure within the ocular circulation. Table 1 gives the formulas for calculating mean, systolic, and diastolic OPP. 16

| Mean OPP | 2/3 [diastolic BP + 1/3 (systolic BP – diastolic BP)] – IOP |
| Systolic OPP | Systolic BP – IOP |
| Diastolic OPP | Diastolic BP – IOP |

When OPP is high, ocular tissues are well perfused, and when OPP is low, ocular tissues are less well perfused. Just as the interplay between CSF pressure and glaucoma may represent a physiologic theoretical basis for mechanical glaucomatous optic nerve damage, variations in OPP may provide a basis for the ischemic theory of glaucoma damage.

Numerous epidemiologic studies have demonstrated that low OPP and, more specifically, low diastolic OPP, increases the risk for developing glaucoma 2- to 6-fold (Table 2). 17-22

Like CSF pressure, OPP is modifiable, and OPP assessment is less invasive. Spot estimates of OPP can be easily obtained in the
Global Risk Assessment in Glaucoma

When facing the decision to treat or not to treat a glaucoma suspect, or to treat more aggressively in established glaucoma, a global risk assessment can inform decision making. A global risk assessment is a synthesis of all known and suspected risk factors for the development and/or progression of glaucoma. Validated calculators exist to aid in the synthesis of data and provide quantitative estimates of the risk of developing glaucoma or its progression. These instruments are limited by our lack of knowledge of risk factors, which are gleaned primarily from relatively small studies compared with those of other disease states. Also, they do not incorporate all known risk factors, each of which must be considered separately and in addition to the calculator’s estimates of risk. Importantly, risk profiles change over time, so risk assessment should be considered an ongoing process rather than a one-time event. Risk calculators for the development of POAG in eyes with ocular hypertension have been developed.29,30 One of these, developed from data collected in both the Ocular Hypertension Treatment Study and the European Glaucoma Prevention Study,29 can be accessed, at no cost, at http://ohst.wustl.edu/risk/calculator.html. After entering a small amount of patient-specific data, the calculator determines the patient’s 5-year risk of developing POAG. This risk estimate can be useful in determining the value of prophylactic therapy.

THERAPEUTIC OPTIONS FOR IOP REDUCTION: TODAY AND TOMORROW

—Robert M. Feldman, MD

Glaucoma therapy has 3 major goals. First, we must apply adequate therapy to achieve our target IOP. Second, we should prevent, or at least slow, the progression of glaucoma to prevent blindness. Third, and often overlooked, we should strive to optimize the quality of life for our patients with glaucoma with every clinical decision, considering the effect of both the disease and our treatment choices on quality of life.

Selecting Initial Therapy

The selection of initial therapy should be tailored to the needs of individual patients. Considerations should include the magnitude of IOP reduction needed, comorbidities that might make some therapies contraindications, lifestyle issues that might make some therapies undesirable, and any physical or cognitive impairment that might affect the ability to reliably self-dose. For most patients, prostaglandin analogues are the optimal first-line therapy. These drugs are highly effective, exceedingly safe, well tolerated, conveniently dosed once daily, and, with the availability of generic latanoprost, also affordable. Several recent studies suggest that selective laser trabeculectomy is a reasonable alternative to medications for first-line therapy.31,32 Primary surgical intervention is typically reserved for patients with extremely high IOP, those with end-stage disease, monocular patients at high risk for blindness, and those with difficult-to-manage secondary glaucoma.

Emerging Glaucoma Therapeutics

In large part, the unparalleled efficacy and safety of prostaglandins have set the bar high for future drug development. A novel glaucoma drug has not been introduced to the marketplace since the launch of latanoprost in the 1990s. This may soon change. Several new molecules are in late-stage clinical development and may reach the US marketplace in the near future.
**Latanoprostene bunod.** This modification of the latanoprost molecule adds a nitric oxide (NO)-donating moiety to the compound. The result is a dual-action therapeutic, in which the latanoprost component increases aqueous outflow through the uveoscleral pathway and the NO component activates the cyclic guanosine monophosphate pathway, leading to trabecular relaxation and increased conventional outflow. In a phase 2 study, latanoprostene bunod provided an approximately 1 to 1.5 mm Hg greater IOP reduction than did latanoprost (P ≤ .009). A phase 3 evaluation revealed that, compared with timolol, 0.5%, dosed twice daily, once-daily dosing of latanoprostene bunod, 0.024%, produced a lower mean IOP at each of the 9 time points: 8 AM, 12 PM, and 4 PM at weeks 2, 6, and 12. Further, more patients treated with latanoprostene bunod than with timolol achieved IOP ≤ 18 mm Hg and IOP reduction ≥ 25%, with comparable adverse events between the 2 groups.

**Rho kinase inhibitors.** Like latanoprostene bunod, the Rho kinase inhibitor netarsudil mesylate (AR-13324) has multiple mechanisms of action. The molecule inhibits the enzyme Rho kinase and also inhibits the norepinephrine transporter, which increases adrenergic activity. The net effect is a reduction of IOP via increased trabecular outflow and reduced episcleral venous pressure, which are both mediated by Rho kinase inhibition, and reduced aqueous production mediated by norepinephrine transporter inhibition. Two phase 3 trials have been completed but not yet published. Future development for this drug includes a fixed combination with latanoprost.

**Advances in drug delivery.** One important limitation shared by all topical glaucoma medications is the need for daily administration by the patient. Adherence with glaucoma medications has been shown in numerous studies to be consistently poor. Several products under development seek to reduce the frequency of dosing by using sustained-release technology. Among these is a sustained-release formulation of bimatoprost, which is packaged in a biodegradable implant injected into the anterior chamber in the clinic setting and expected to provide IOP reduction for 4 to 6 months. A phase 3 trial vs timolol is under way. Both a punctal plug delivery system and an intraocular implant for travoprost are also in development. Other novel delivery systems, including the use of nanoparticles, are also being developed.

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**CASE STUDY**

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**Neeru Gupta, MD, PhD, MBA**

This patient was a 48-year-old woman with a complex medical history that included fibromyalgia, depression, headache, and sleep disorder. Her medications included fluoxetine and amitriptyline. She had a sulfonamide allergy. Her father had glaucoma. On examination, her visual acuity was 20/30 in the right eye and 20/25 in the left eye. Anterior segments and angles were unremarkable. Her IOP was 14 mm Hg in both eyes, with a corneal thickness of 545 μm in both eyes. Figure 2 shows her optic nerves, and Figure 3 shows her visual fields.

Her target IOP was set at 10 mm Hg, and she was started on a prostaglandin analogue, but did not tolerate it.

**Dr Weinreb:** Dr Feldman, is there any other history or evaluation that might be relevant?

**Dr Feldman:** Given the advanced stage of disease with such a low untreated IOP, a diurnal IOP curve might be useful.

**Dr Gupta:** We considered that as well. Her diurnal IOP range was 8 to 14 mm Hg on no treatment.

**Dr Feldman:** In that pressure range, I start thinking beyond IOP. Does she have any vascular risk factors? What is her blood pressure?

**Dr Fujishima:** We considered that as well. Her diurnal IOP range was 8 to 14 mm Hg on no treatment.

**Dr Weinreb:** Dr Varma, you have studied the relationship between OPP and glaucoma in the Los Angeles Latino Eye Study. What is the significance of this low blood pressure reading in this patient?

**Dr Varma:** In our study and others, as you pointed out earlier, low diastolic perfusion pressure is a strong risk factor for developing glaucoma. It is also a strong predictor of glaucoma progression. In patients with hypertension, we have the opportunity to reduce systemic antihypertensive therapy or shift dosing from nighttime to morning to prevent nocturnal dips in blood pressure. But in this patient, the hypotension is intrinsic and not iatrogenic. That is more difficult to address.

**Dr Gupta:** This patient was sent for 24-hour blood pressure monitoring and found to have nocturnal hypotension. In an effort to address low diastolic perfusion pressure at night, salty bedtime snacks, such as pretzels, olives, tomato juice, or nuts, were suggested. She does this each night before bed, and, fortunately, she has remained stable, with no further progression.

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**SUMMARY**

Glaucoma is a complex and incompletely understood multifactorial disease, with many known and likely many unknown risk factors. New risk factors are emerging and may shed light on the pathogenesis of glaucoma. Reduction of IOP remains the only established treatment, but novel therapeutic targets may be on the horizon. A wider selection of available and emerging therapies may give clinicians more options to individualize glaucoma therapy on the basis of each patient’s unique needs and desires. Sustained-release drug delivery options may improve the patient experience by reducing the need for daily dosing. The role of sustained-release formulations of products available as topical medications in routine clinical practice remains to be clarified, and insurance coverage issues will also likely play a role in the clinical utility of these products.


35. Weinreb RN, Scassellati Sforzolini B, Vittitow J, Liebmann J, Marmor S. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO Study. Ophthalmology [published online ahead of print February 11, 2016]. doi:10.1016/j.ophtha.2016.01.019.


1. Which of the following is not a component of the definition of POAG?
   a. Optic nerve degeneration
   b. Elevated IOP
   c. Loss of RGCs
   d. Open anterior chamber angle

2. All potential contributors to the pathophysiology of POAG share which of the following mechanisms?
   a. Raised IOP
   b. Damage to the visual cortex
   c. Damage to the trabecular meshwork
   d. Damage to RGCs

3. Evidence in support of impaired microcirculation of the optic nerve head as part of the pathophysiology of glaucoma includes:
   a. Optic nerve cupping
   b. Optic atrophy
   c. Disc hemorrhages
   d. Elevated OPP

4. Established risk factors for POAG include:
   a. Elevated IOP and thick central corneas
   b. Increasing age and thick central corneas
   c. Positive family history of glaucoma and elevated IOP
   d. Young age and thin central corneas

5. Which of the following best describes the relationship between OPP and the risk of developing POAG?
   a. Elevated systolic OPP decreases the risk of POAG
   b. Low diastolic OPP increases the risk of POAG
   c. Low mean OPP decreases the risk of POAG
   d. Low systolic OPP decreases the risk of POAG

6. What is the preferred method for determining target IOP for glaucoma therapy?
   a. Use a validated formula based on risk factor analysis
   b. An educated estimate based on the risk profile of the individual patient
   c. Seek to lower IOP by 15% from untreated baseline for most patients
   d. Start a medication and see how effective it is

7. For a patient with early POAG who also has benign essential tremor and lives alone with no caregiver, which of the following is a reasonable first-line therapy for IOP reduction?
   a. Prostaglandin analogue
   b. Beta-blocker
   c. Laser trabeculoplasty
   d. Trabeculectomy

8. For a patient with newly diagnosed end-stage POAG who has IOP in the range of 35 mm Hg and has already lost central visual acuity in 1 eye because of the disease, which of the following is the best intervention for preventing blindness in the remaining eye?
   a. Prostaglandin analogue
   b. Beta-blocker
   c. Laser trabeculoplasty
   d. Trabeculectomy

9. In clinical trials, latanoprostene bunod is thought to reduce IOP by:
   a. Decreasing aqueous humor production and increasing trabecular (conventional) outflow
   b. Increasing both uveoscleral and trabecular outflow
   c. Decreasing aqueous humor production and increasing uveoscleral outflow
   d. Increasing aqueous humor production and decreasing uveoscleral outflow

10. A significant advantage of sustained-delivery devices for glaucoma medication is:
    a. Cheaper cost
    b. Less invasive than drops
    c. Better adherence
    d. Neuroprotection