The Clinical Meaning of Intraocular Pressure Fluctuation

Sanjay G. Asrani, MD

Intraocular pressure fluctuation—assessed by serial assessments at different times of day—may be an important ancillary metric of glaucoma risk, one that we should look for and treat.

It is generally agreed that elevated intraocular pressure (IOP) is a major risk factor for glaucoma development and/or progression and that lowering IOP can improve outcomes in glaucomatous eyes.1,2 But IOP is not static; we have known since the 1950s that any single IOP reading is simply the summation of multiple, changing time-dependent influences that vary throughout the day. Individually with and without glaucoma experience IOP fluctuation.

To what degree, then, can we trust a single IOP measurement taken during an office visit? Does that IOP value represent a peak, a trough, or something in-between? Would there be, perhaps, greater value in a series of IOP measurements? These questions, along with the observation that many patients with apparently good IOP reduction on antihypertensive medication continue to worsen, have spurred renewed interest in IOP fluctuation and its role in glaucoma progression.

DEFINING FLUCTUATION

It is useful to regard IOP fluctuation in three time frames. Fluctuations that occur over seconds to minutes are termed ultra-short-term fluctuations. Coughing, holding your breath, Valsalva-type straining, or rubbing the eye induce very short-lived IOP elevations that are not thought to heighten glaucoma risk. The term short-term fluctuations covers IOP changes that occur over hours to days. Diurnal IOP fluctuation, the rise and fall of IOP that occurs over 24-hour periods, is a form of short-term fluctuation. Long-term variations (variations is preferred to fluctuation) are those that occur over months to years.

Short-term fluctuations and long-term variations of 5 mmHg or greater are thought to influence glaucoma progression, even if the peak value is within normal limits.3,4 For example, a patient with an IOP of 12 mmHg at one visit and 18 mmHg a month later (a difference of 6 mmHg) should be considered to have significant IOP fluctuation. This is also the case if those values—12 and 18—are present at different times on the same day. In 2000, my group published a study that showed that short-term IOP fluctuations predicted worsening of glaucoma, independent of office-measured IOP, gender, age and baseline visual field deficit.5 Retrospective analyses of multiple glaucoma trials have shown that long-term IOP variations are associated with progressive disease.

Some studies, however, have demonstrated a lack of correlation between IOP variation and glaucoma progression. Such
studies include the Early Manifest Glaucoma Treatment Trial (EMGT) and the European Glaucoma Prevention Study (EGPS). These studies evaluated either ocular hypertensives or patients with very early glaucoma, and it is possible that it may take longer than the duration of such studies to demonstrate the effect of variation at early stages of glaucoma.

Some IOP variability is normal. IOP that varies by up to 3 or 4 mmHg (within the normal range of 10 to 21 mmHg) is not, by itself, concerning for glaucoma progression. For example, patients with IOP in the low teens who stay in the low teens at each visit, or those in the high teens who stay there, are demonstrating normal variations in IOP.

PATIENT TYPES

Significant IOP fluctuation is likely a sign of inconsistency in aqueous fluid outflow through the trabecular meshwork; and the resulting IOP elevations may be enough to damage the optic nerve. A genetic predisposition to trabecular meshwork dysfunction may play a role, as some forms of glaucoma associated with IOP fluctuation—including primary open angle glaucoma and juvenile open angle glaucoma—cluster in families and are likely at least partially genetically determined. Patients with trauma-associated, uveitis-associated, pseudoexfoliation, and pigmentary glaucoma, all of which may also be associated with trabecular meshwork dysfunction, are at increased risk for IOP fluctuation and its consequences.

Patients with normal tension glaucoma—that is, IOP within the normal range despite evidence of optic nerve damage—often have significant fluctuations in IOP. Since their IOP tends, by definition, to stay in normal range, this group of patients is easily (and often) missed on IOP screenings, particularly if the optic nerve is not well visualized or if fundus exam is skipped. Serial screenings revealing IOP fluctuation (within a single day or within a week or month) would prove extremely helpful in identifying at-risk normal tension patients.

Controlling IOP fluctuation may be of benefit in patients with normal tension glaucoma and can serve as a measurable objective in an otherwise hard-to-track condition. A recent Japanese study showed that visual field deficit progression significantly correlated with greater standard deviations in IOP values among patients with primary open angle and normal tension glaucoma.

DETECTING IOP FLUCTUATION

Clinicians looking for IOP fluctuation will typically conduct serial in-office measurements at various intervals over the course of a single day. This is not ideal, since the circumstances surround-
ing a patient sitting in an office for 6 to 8 hours are relatively static, and the IOP variability experienced by a patient living his life in the real world may not manifest in the office. In my experience, serial IOP measurements spread out across different times on different days are more reliable for capturing variability. For instance, I’ll check pressures at 7:00, 8:00, and 9:00 AM on one day and 4:00, 5:00, and 6:00 PM on a different day.

Multiple measurements are superior to, and supply more data than, a single measurement; however, fluctuations between the readings can still be missed. A method of continuous monitoring would bridge the gaps that remain in a multiple measurement approach. A contact lens-based sensing device to approximate IOP over a 24-hour period is currently far along in development.12 The sensing technology detects changes in corneal shape and then, via an algorithm, attempts to correlate corneal surface change with IOP. Patients would wear the contact lens device for up to 24 hours at a time while going about their usual daily activities, making it similar to the use of a Holter monitor for cardiac monitoring. If contact lens IOP sensing devices prove accurate, which remains to be seen, using it on multiple, nonsequential days (rather than a single 24 hour period) would provide a meaningful assessment of IOP dynamics.

Intraocular IOP monitoring via an implantable device is currently being evaluated and may also become a viable option in the future.13 Intraocular monitoring would share some of the advantages of contact lens monitoring, including ambulatory convenience and the ability to capture IOP data in patients’ normal settings, but with two key advantages: more direct and thus more reliable measurements due to the location of the sensor and the ability to monitor IOP continuously rather than in isolated 24 hour increments.

MEDICATION COMPLIANCE

To this point we have been considering only naturally occurring IOP fluctuations. However, another important source of IOP fluctuation that must be considered is nonadherence to IOP lowering treatment. A patient, for example, who takes her medication for 4 days then fails to do so for the next 3 days will likely have an IOP rise on the nonadherent days. This short-term fluctuation could significantly reduce the overall efficacy of her treatment.

Medication adherence can be a real challenge for patients, caretakers, and the clinical team. Embarrassment over missing doses, a desire to appear to be a good patient, or other factors may color patients’ reporting of their compliance; nonetheless, patient reporting is all the information we have with respect to medication use. For patients who report very good compliance, a rise in IOP or IOP fluctuation must be attributed to the disease. For patients who admit to being noncompliant or partially compliant with medication, IOP increases may reflect noncompliance alone or a combination of the disease and inadequate treatment.

In my experience, patients are generally highly compliant with their eye drops in the days leading up to their eye appointment, assuming they have not exhausted their supply of medication. Thus, I tend to regard statements like “I usually take my drops but I haven’t lately” with some suspicion; such a patient may be even less complaint than they are letting on.

IMPROVING ADHERENCE

Better medication compliance is an important aim. In my practice, I suggest to patients that they should not miss more than 3 days each month of their medications. Sometimes I will ask, “How many days do you miss per month—3 days, 5 days, or 7 days?” Then I typically assume they are missing a few more than they state. Regardless of their IOP at the visit, I take the opportunity to reiterate the importance of missing no more than 3 days per month.

Another strategy for reducing IOP fluctuation among patients who are struggling with compliance is to, whenever possible, prescribe long acting medications, such as once daily prostaglandin analogs or beta-blockers. Medications with longer half-lives can be expected to regulate IOP more steadily—allowing fewer peaks and troughs—and reduce sharp IOP spikes associated with missed doses of shorter-acting medications.

IMPLICATIONS FOR MANAGEMENT

When following glaucoma suspects, a finding of IOP fluctuation (of at least 5 mmHg) is an indication that they may in fact be developing glaucoma. I make sure to follow such patients very closely. I also look for fluctuation in patients with normal tension glaucoma, particularly if they are clinically progressing, as they may have been misdiagnosed based on IOP readings taken at the nadir of wide swings.

In my view, controlling both peak IOP and IOP fluctuation provides the greatest hope for holding back glaucoma progression and is an appropriate goal in most patients. Fortunately, currently available medications reduce overall IOP and simultaneously reduce fluctuation.14 Among patients who have achieved their target IOP range, fluctuation should be ruled out and treated if found, particularly in patients with advanced or progressing disease. Strategies for augmenting treatment might include changing to a longer acting agent, add-
CONCLUSION

Until we have the technology for continuous or 24-hour IOP monitoring, we are left with the somewhat inconvenient but undervalued practice of serial measurements for detecting IOP fluctuation and variation. Diligent efforts to uncover and address IOP fluctuation can mean improved IOP control and better outcomes for patients.

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REFERENCES


Lifestyle and Other Non-pharmaceutical Approaches to Managing Glaucoma

Robert Ritch, MD

The climate around lifestyle-mediated and non-pharmaceutical approaches to care has changed dramatically in recent years. A number of ideas from outside mainstream medicine can, perhaps, be fruitfully employed to treat glaucoma.

For more than 100 years, the trabecular meshwork has borne the brunt of the blame for the morbidity associated with glaucoma. Glaucoma researchers have characterized a range of diseases that increase IOP by affecting the trabecular meshwork, and we know that lowering intraocular pressure (IOP)—the main goal of glaucoma management today—works in glaucoma patients with both high and normal IOP, a fact that reinforces the IOP-centric paradigm of disease.

Right now, lowering IOP remains the only treatment modality proven effective in preventing the progression of glaucoma. However, medical treatment may not succeed at this, and laser and surgical treatment may be required. Despite this, patients often continue to blindness. If we hope to offer patients better treatment, we need to understand the nuances of glaucoma pathophysiology, particularly those events that initiate or occur early in the disease process. We must identify molecular, cellular, and genetic abnormalities so we know what to target as
new technologies, such as genetic editing, become available.

However, even the best glaucoma treatment is meaningless to people with glaucoma but no knowledge of their condition. In the US and other developed countries it is generally accepted that half of all glaucoma is undiagnosed, with higher rates of undiagnosed glaucoma in places with limited access to eye doctors. Some hold that low rates of diagnosis are the result of failure of surveillance or referral. Alternatively, a number of studies suggest that ophthalmologists underdiagnose glaucoma, often due to misinterpretation of evidence, for example by making errors in determining cup-to-disc ratio. In the Glaucoma Optic Neuropathy Evaluation Project, underestimating the vertical cup-disc ratio and cup shape and missing retinal nerve fiber layer defects and disc hemorrhage were common errors that led to underdiagnosis. I suspect that both failure to screen and failure to correctly interpret data from screenings contribute to the high prevalence of undiagnosed glaucoma.

BEYOND IOP

And we must look beyond IOP. IOP is a risk factor and a treatment target, but it is not the disease itself. Research on glaucoma prevention and determinants of optic nerve health is sorely needed.

In addition, lifestyle medicine—which goes by a variety of other names—concerns itself with disease prevention and early intervention. Lifestyle practitioners conceive of the body as a whole system and are drawn to non-pharmacologic remedies that work at the origins or early stages of a disease and encourage patients to participate in their own care. In this review, we will discuss several lifestyle interventions, as well as some specific bionutrient supplements, as they pertain to glaucoma.

ISCHEMIA

In the 1990s, it became evident that ocular ischemia played an etiologic or exacerbating role in glaucomatous injury. A wide range of primary processes can contribute to ocular ischemia, including: obstructive sleep apnea syndrome (OSAS); Raynaud’s phenomenon, migraine and other vasospastic disorders; atrial fibrillation; changes related to nighttime posture including nocturnal hypotension and lateral decubitus position; globe pressure during sleep; high myopia; and low intracranial pressure.

Patients with OSAS have been shown to have significantly higher rates of glaucoma than the general population. Reciprocally, high rates of sleep-disordered breathing have been identified in patients with primary open-angle glaucoma. In OSAS, a disturbance of the normal autoregulatory mechanisms that occur during sleep leads to hypoxia and sympathetic activation, which may lead to hypoxia-induced blood vessel damage and altered blood flow to the optic nerve head. Eventually, this cascade, alone or in combination with other predisposing factors, can reduce ocular perfusion pressure and either directly damage the optic nerve or increase its susceptibility to injury from other insults.

Fortunately, OSAS is treatable with nasal or oral CPAP; but it remains markedly underdiagnosed. Suspect OSAS in patients with obesity, increased neck girth, upper airway abnormalities, snoring, daytime sleepiness, or insomnia, although it may also be present without these findings and has been reported to actually have a higher incidence in patients with normal-tension glaucoma and in Japan, where normal-tension glaucoma accounts for the preponderance of POAG.

FLAMMER SYNDROME

Flammer syndrome is a cluster of findings in otherwise healthy individuals that is associated with vascular dysregulation including an increased incidence of normal-tension glaucoma. Patients are generally thin, myopic females with cold hands (Raynaud’s phenomenon) and low blood pressure. Flammer syndrome should be on the radar of eye care providers who treat normal-tension glaucoma. Proposed vascular stabilizing treatments include magnesium supplementation, Gingko biloba, and very low dose calcium channel blockers (Dr. Flammer feels that 3 mg nifedipine dissolved in a liter of water and sipped throughout the day improves ocular blood flow without lowering blood pressure). Other measures include: lifestyle practices such as yoga (but not with inverted posture positions), stress avoidance (which needs to be proven in controlled studies), supplemental omega-3 fatty acids (the triglyceride form, as the acid and alcohol forms are largely ineffective), and sufficient caloric intake to maintain adequate weight, as the development of glaucoma has been suggested to correlate inversely with body mass index (BMI).

Twenty-four hour blood pressure monitoring reveals that most healthy people experience a minor dip in blood pressure (about 10% below mean arterial pressure) at night. Those who do not dip are prone to developing strokes. However, overdipping (eg, a 20% to 30% reduction) is a risk factor for progression of glaucoma, particularly normal-tension glaucoma, and this can lead to...
decreased ocular perfusion pressure, which can contribute to ocular ischemia. A recent major study showed that the magnitude and depth of nocturnal blood pressure dip predicted progression of glaucoma.6

While we are currently uncertain about how to treat this phenomenon, we should take steps to minimize iatrogenic insult. Ophthalmologists treating glaucoma patients with comorbid systemic hypertension and taking antihypertensive medication at bedtime should discuss alternative dosing regimens with the patients’ cardiologist or internist. Patients whose IOP is apparently well controlled but who continue to lose visual field should have 24-hour blood pressure monitoring and if they are overdipping, should have their blood pressure medications moved to the early part of the day.

CSF PRESSURE

Low cerebrospinal fluid (CSF) pressure may also contribute to glaucoma by reducing the translaminar gradient, the gradient between the eye and the CSF pressure at the optic nerve. Like ocular perfusion pressure, the ratio of IOP to CSF pressure correlates with glaucoma risk and damage. For example, high IOP with normal or low CSF pressure, and normal IOP with low CSF pressure, can all increase risk for glaucoma. Since CSF pressure is only detectable by spinal tap, the practical applications of this association are not clear.

In examining the compartmental physics of ischemia-related causes of glaucoma, one starts to see why lowering IOP may at least partially succeed in treating patients with normal-tension glaucoma since it effectively reduces the resistance to blood flow. But one can also see that lowering IOP in such cases is not the ultimate solution—it might make more sense to target ischemia when ischemia is the underlying cause, assuming that were possible.

POSTURAL CONSIDERATIONS

We spend up to a third of our lives asleep; and supine IOP increases may play a role in progression of glaucoma.9 In healthy subjects, sleeping in the lateral decubitus position (side-sleeping) or prone (face-down) with head turned has been shown to increase IOP in the lower eye.10 Usually this is a small number, such as 1 to 2 mmHg, but some patients may have rises as high as 10 mmHg. Patients with vascular dysregulation or elevated IOP may experience even sharper IOP increases in prone and lateral decubitus postures. One study showed that a significant majority of patients with bilateral normal-tension or high-tension glaucoma and asymmetric visual field loss reported sleeping on the more affected side.11 Ocular compression from side-sleeping with the lower eye pressed against a pillow or one’s hand can increase IOP markedly.

Sleeping on a sloping 20° wedge pillow has been shown to reduce IOP while not affecting perfusion pressure.9 Glaucoma patients should be encouraged to sleep on their back (presuming they do not have sleep apnea) or the side of the less affected eye. Specially designed belts that discourage rolling or eye shields that protect against physical pressure on the eye during sleep may be advised.

Standing on one’s head, not surprisingly, transiently at least doubles IOP in healthy patients and those with glaucoma.12 I once encountered a yoga practitioner who was nearly blind from glaucoma, diagnosed as normal-tension glaucoma, with IOPs of 15 mmHg, who stood on her head for 20 minutes a day for 20 years. When we tested her in this position, her IOP rose to 60 mmHg. At present, however, there is no evidence that brief inversions of a minute or two increase risk for glaucoma progression.

GINGKO BILOBA

In 1996, I came across an article on Ginkgo biloba extract (GBE) in the Journal of Ethnopharmacology.13 The article enumerated the plant’s myriad effects on living tissue, including inhibition of lipid peroxidation of membranes, inhibition of calcium and glutamate toxicity, and inhibition of cell death and apoptosis. In addition, GBE helped stabilize mitochondria, prevent mitochondrial aging, and stabilized ATP production. Further, according to the article, GBE had been shown to improve blood flow to the eye (Figure 1).

I immersed myself in the literature and came away impressed with the neuroprotectant properties attributed to GBE. We went on to show that GBE improved ophthalmic artery blood flow by 24%.14 Other studies, but not all, have shown similar improvements in ocular blood flow.14-16

An argument against the use of GBE in glaucoma management is that it lacks validation in large randomized, masked, placebo-controlled trials. True enough, but I’m not sure that means we should count it out. Those studies may never occur, as there is no incentive for industry to conduct expensive clinical trials on whole foods (like GBE) that cannot be given patent protection.

There is tissue and animal model evidence for antioxidant effects and platelet activating factor inhibition; in vitro and in vivo evidence of anti-ischemic and neuroprotective effects; as well as other reasons, including common sense and an awareness of the limits of research, for considering GBE.17 I take
GBE as a component of my own wellness routine, and I recommend it to patients with normal-tension glaucoma whom I think will benefit.

OTHER SUPPLEMENTS AND DIET
Derived from turmeric, curcumin is a potent anti-inflammatory, antiangiogenic, and antioxidant molecule. Curcumin is being investigated for the potential treatment of diverse disorders, most of which have an inflammatory component, from cancer to atherosclerosis to arthritis and Parkinsonism. Curcumin has been shown to reduce neuritic plaque formation in Alzheimer's disease in animals and to improve cognition and quality of life in Alzheimer's patients.

Curcumin inhibits a wide array of cytokines, growth factors, and transcription factors (eg, TGF-1, TGF-beta-1, TGF-beta-2, TNF-alpha) that have been implicated in glaucoma-related damage. Beneficial effects have been reported in uveitis, diabetic retinopathy, experimental cataract, ocular surface disease, and allergic conjunctivitis. Products are typically formulated with adjuncts, to aid in curcumin absorption since bioavailability is otherwise low.

I also typically recommend omega-3-fatty acids to my glaucoma patients. Abundant in fish oil, these fats have been associated with cardiovascular, neurologic, and retinal protection in animal studies. Improving omega-3-fatty acid intake (and reducing omega-6-fatty acids) has been associated with reduced risk for age-related macular degeneration. Further research is needed on the effects of omega-3-fatty acid supplementation in glaucoma and other ocular disorders; in the meantime, I believe its benefits exceed its risks.

Myriad other bionutrients warrant serious scrutiny for the management of glaucoma, including resveratrol, alpha-lipoic acid, coenzyme Q, Sarcia miltiorrhiza, green tea catechins, methylvcobalamin, N-acetyl-L-cysteine, wolfberry, red sage, and even bear bile. Supplementation should be used as an adjunct to a diet already rich in fruits and vegetables, particularly collard greens, kale, carrots, and peaches, which have been shown to lower risk for glaucoma development among women.

CONCLUSION
It is time to expand our thinking beyond IOP. Patients willing to participate in lifestyle-based practices—including exercise, stress reduction, dietary and sleep/postural modification—and supplement with antioxidant compounds might find greater control over their disease.

Robert Ritch, MD, holds the Shelley and Steven Einhorn distinguished chair in ophthalmology and is surgeon director emeritus and chief of glaucoma services at the New York Eye and Ear Infirmary, New York City. He states that in the past 12 months, he has not had a financial relationship with any commercial organization that produces, markets, resells, or distributes healthcare goods or services consumed by or used on patients. Medical writer, Noelle Lake, MD, assisted in the preparation of this article.

REFERENCES

To obtain CME credit for this activity, go to http://cme.ufl.edu/ed/self-study/tig/
1. Which of the following represents normal IOP fluctuation?
   A. 3-mmHg variation in the course of a day
   B. 7-mmHg variation between January and May measurements
   C. 6-mmHg decrease between Monday and Thursday at 8:00 AM and Friday 4:00 PM
   D. All of the above are within normal limits

2. Which of the following is unlikely to contribute to ocular ischemia?
   A. Nocturnal systemic hypotension
   B. Atrial fibrillation
   C. Exercise
   D. Raynauds phenomenon

3. Diurnal IOP fluctuation is an example of:
   A. Ultra-short term fluctuation
   B. Short term IOP fluctuation
   C. Long term IOP variation
   D. None of the above

4. Which of the following is NOT a source of IOP fluctuation?
   A. Eye rubbing
   B. Failure to adhere to an antihypertensive medication regimen
   C. Chronic use of low-dose aspirin
   D. Normal physiologic IOP fluctuation

5. Which of the following is an obstacle to large-scale clinical trials of Gingko biloba?
   A. Cost of Gingko biloba
   B. Lack of financial incentive
   C. Scarcity of Gingko biloba
   D. The toxic side effects of Gingko biloba

6. Which of the following is LEAST likely to help a patient reduce IOP fluctuation?
   A. A diet rich in omega 3 free fatty acids
   B. Adding IOP-lowering medication
   C. Laser trabeculoplasty
   D. All may be beneficial in reducing IOP fluctuation

7. Properties that have been associated with Gingko biloba extract include all of the following EXCEPT:
   A. Inhibition of lipid peroxidation of membranes
   B. Decreased calcium-related toxicity
   C. Anti-apoptosis
   D. Marked drop in ATP production

8. Appropriate goals for IOP-lowering therapy include:
   A. Reducing peak IOP
   B. Converting trough IOP into peak IOP
   C. Reducing IOP Fluctuation
   D. Both A and C are correct

9. Patients with unilateral visual field loss related to glaucoma should be advised to sleep:
   A. With the affected side lower than the unaffected side
   B. In prone, head turned position
   C. In a supine, slightly elevated position
   D. During the day

10. Flammer syndrome is characterized by which of the following?
    A. Thin build, female sex, cold hands
    B. Obesity, male sex, sleep apnea
    C. Hypertension, insomnia, heightened pain sensitivity
    D. None of the above

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