Ocular Perfusion Pressure: An Important New Parameter?

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While vascular factors such as ocular perfusion pressure have been implicated in the development of glaucomatous damage, their role may be secondary. The orbital cerebrospinal fluid pressure likely contributes directly to the risk of glaucoma.

Glaucoma is a difficult, perplexing disease whose pathogenesis has remained largely elusive in spite of extensive research. A progressive optic neuropathy with visual field loss and structural damage such as excavation of the optic nerve head and thinning of the retinal nerve fiber layer, glaucoma is frequently associated with increased intraocular pressure (IOP). It is hypothesized that glaucomatous damage originates from mechanical injury produced by IOP deforming the optic nerve head and lamina cribrosa. But, to this day, the precise mechanism whereby elevated pressures contribute to the glaucomatous process is not established, and the nature of glaucomatous optic nerve damage is poorly understood.

In addition to IOP, vascular factors have long been suspected to have a pathogenic role in glaucoma. In particular, the presence of a vascular component is thought to provide a plausible explanation for normal tension glaucoma (NTG), a distinctive and common form of open-angle glaucoma where glaucomatous optic neuropathy develops in the absence of an elevated IOP. One vascular parameter that has recently attracted significant attention and become a focus of study is ocular perfusion pressure (OPP). Reduced OPP has come to be widely considered a causative risk factor for glaucoma, especially NTG.

DEFINING OPP

OPP is the pressure at which blood flow enters the eye. Conventionally, it is calculated as 2/3 of systemic mean arterial blood pressure minus IOP, 2/3 being the factor accounting for the pressure drop between the brachial and ophthalmic artery in the upright position. It is important to note that, in this formula, IOP serves as a substitute for the venous pressure in the eye. As with most tissues, OPP can be defined as the difference between the local—retinal in

FIGURE 1 Fundus images of typical glaucomatous optic neuropathy.

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Managing Ocular Hypertension: A Practical Approach
by Anthony Realini, MD, MPH
GLAUCOMA

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this case—arterial and venous blood pressure.9 Pressure in the intraocular veins has been equated with IOP based on earlier experimental data.4-6 Recent studies, though, suggest that the pressure in the central retinal vein is considerably higher than IOP, and that conventionally calculated values of OPP can be falsely high.7,8

A QUESTIONABLE ROLE

Although several large population-based studies have linked lower OPP to the risk for glaucoma,9-13 many questions remain unanswered. There is little direct evidence as yet that vascular risk factors are primarily involved in the pathogenesis of glaucomatous optic neuropathy. OPP depends on the systolic and diastolic blood pressure, and the vascular hypothesis is largely based on the observation that patients who have NTG also tend to have relatively low body mass index (BMI), low systemic blood pressure, and vasospastic symptoms such as cold hands and feet and migraine headache.14-16 Yet the epidemiologic evidence has not consistently shown an association between low blood pressure and the development of glaucomatous optic nerve damage.

Furthermore, the appearance of a glaucomatous optic nerve head markedly differs from that of optic neuropathies resulting from vascular and blood pressure abnormalities (eg, retinal artery occlusion and diabetic retinopathy) (Figures 1 and 2). While the optic nerve damage from open-angle glaucoma including NTG is characterized by loss of the neuroretinal rim, deepening of the optic cup (ie, optic disc cupping), and development and enlargement of parapapillary atrophy, no vascular disease associated with decreased ocular perfusion is known to cause such optic disc changes, with the exception of arteritic anterior ischaemic optic neuropathy, which can cause enlargement and deepening of the optic cup. This morphological discrepancy between vascular and glaucomatous optic neuropathy contradicts the notion that vascular factors play a primary role in the pathogenesis of glaucoma.

Instead of contributing to primary glaucomatous damage, reduced ocular perfusion pressure could be secondarily involved: structural changes in the lamina cribrosa during the glaucomatous process may increase the venous outflow assistance, leading to greater retinal vein blood pressure, lower ocular perfusion pressure, and thus an additional risk for optic nerve damage.

REFERENCES


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This activity is supported by an unrestricted educational grant from Bausch + Lomb, Inc.
THE CEREBROSPINAL FLUID PRESSURE (CSFP)

One alternative theory of glaucoma pathogenesis that has largely been overlooked until lately is pressure dysregulation across the lamina cribrosa. Anatomically, the lamina cribrosa forms the barrier between the intraocular space and the retrobulbar compartment, with IOP slightly higher than retrobulbar or orbital CSFP. The difference between these two counter pressures across the lamina cribrosa helps maintain the optic nerve in its proper shape and position, and an abnormal pressure gradient will have direct influence on the physiology and pathophysiology of the optic nerve head.\(^{17,18}\) Specifically, a greater translamina pressure difference—from either elevated IOP and/or reduced CSFP—can lead to backbowing of the lamina cribrosa and neuroretinal rim loss, the kind of damage that is typically found in glaucomatous optic neuropathy.

![Fundus images of typical vascular optic neuropathy.](Image)

Based on these facts, researchers have hypothesized that orbital CSFP plays an important role in glaucoma pathogenesis. According to the theory, elevated IOP and low CSFP are likely two primary risk factors for glaucomatous optic neuropathy. Patients with NTG likely have an abnormally low orbital CSFP leading to an abnormally high translamina pressure difference, just as how elevated IOP in high tension glaucoma could lead to increased translamina pressure, with or without low CSFP. This could explain why the optic nerve head in NTG and angle-open glaucoma has a similar appearance.

THE EVIDENCE

Consistent with the hypothesis, studies have shown that patients with primary open-angle glaucoma (POAG) and NTG have significantly lower CSFP than normal individuals.\(^{19-21}\) Patients with ocular hypertension, in contrast, had significantly higher CSFP than controls.\(^{20}\) One prospective study found that the CSFP in NTG patients was significantly lower than POAG with elevated IOP; the amount of glaucomatous optic nerve damage as measured by neuroretinal rim area and visual field defect correlated with lower CSFP and with higher translaminar pressure difference.\(^{21}\) Most recently, population-based studies showed a better association of lower CSFP with presence of glaucoma and amount of glaucomatous optic neuropathy compared to IOP.\(^{22,23}\)

Additionally, clinical studies have suggested that low CSFP is associated with low blood pressure, low IOP, and a low BMI.\(^{21,24,25}\) Such associations imply that there may be underlying regulatory mechanisms between these variables, raising the possibility that low blood pressure and BMI may also contribute to glaucoma risk, albeit indirectly through CSFP. Japan, for example, is known to have an especially high prevalence of NTG in glaucoma patients.\(^{26,27}\) The predominance of NTG in Japanese patients may be associated with not just lower CSFP but also relatively low BMI.

THE IMPLICATIONS

Although the available evidence supports the importance of translamina pressure difference in relation to glaucoma, it is unclear yet what the implications will be. Provided that a high translamina pressure difference proves to be associated with glaucoma, it may be possible to develop CSFP-modifying therapeutic modalities for glaucoma treatment. When selecting an IOP-lowering therapy, taking into consideration orbital CSFP and its association with systemic blood pressure may be important. The prostaglandin analogs have no significant vascular effect, whereas the beta blockers can lower blood pressure when absorbed systemically such that CSFP may be lowered to further increase the patient’s risk for glaucomatous damage. For the beta blockers, therefore, it may be particularly important to teach patients to close their eyes shortly after administration of the eye drops to prevent the drug from reaching the nasopharyngeal region through the nasolacrimal tract and getting absorbed systemically from there. Similarly, systemically applied carbonic anhydrase inhibitors such as Diamox should be better avoided as treatment of chronic open-angle glaucoma since they lower the pressures (ie, IOP and CSFP) on both sides of the lamina cribrosa.

OPP and other vascular factors in glaucoma have been studied to a great extent. Up to now the results have not been conclusive; however, one new agent, latanoprostene bunod, which is not approved in the US but is in phase III clinical trials, combines the PGA latanoprost with a nitric oxide-donating moiety and may have a positive impact on OPP as well as on IOP.

Currently available evidence sug-
gests that the orbital CSFP is an important parameter in understanding the pathogenesis of glaucoma, though its role is yet to be better defined. From the anatomic point of view, orbital CSFP is the true counter pressure against the IOP at the lamina cribrosa, but how they interact in glaucoma needs to be further explored. What must also be addressed are the dynamic aspects of CSFP and its relationship to IOP, not only the influence of body posture but also time-associated changes in all relevant pressure parameters (ie, IOP, CSFP, blood pressure, and retinal arterial and venous pressure). Perhaps most important of all, we need a simple and reliable method to measure orbital CSFP noninvasively. Lumbar CSFP has been used in studies for estimation, but we cannot perform a lumbar puncture in all patients, and whether lumbar CSFP is directly related to the orbital CSFP is still in question.

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REFERENCES
Managing Ocular Hypertension: A Practical Approach

**Anthony Realini, MD, MPH**

Ocular hypertension can be managed to prevent or delay the development of glaucomatous optic nerve damage. The challenge is determining which patients to treat.

In ocular hypertension, patients have intraocular pressures (IOPs) above the accepted threshold value of 21 mm Hg, yet they show no indication of optic nerve damage. These patients lack detectable optic disc and/or visual field changes characteristic of primary open-angle glaucoma (POAG); and no other ocular or systemic conditions—eg, steroid use, narrow anterior chamber angles, pigment dispersion syndrome, pseudoxfoliation, or trauma—are present to explain the pressure elevation. In the US, it is estimated that ocular hypertension occurs in 4% to 7% of the population over 40.1,2 For this group of seemingly healthy individuals, whose only indicator of potential disease is elevated IOP, the central clinical question is: what should physicians do for them?

**BENEFIT OF TREATMENT**

Although ocular hypertension patients manifest no matching abnormalities, they are at risk of progression to POAG. Elevated IOP is the most recognized and the only modifiable risk factor for the development of glaucoma. It makes little clinical sense to lower pressure for the sake of lowering the pressure, but for patients with ocular hypertension, reducing the IOP has a greater benefit: delaying or preventing progression to glaucoma.

Two large, randomized, controlled clinical studies have evaluated the benefit of pressure-lowering on the prevention of glaucoma development. In the European Glaucoma Prevention Study (EGPS)3,4 patients were randomized to receive either dorzolamide or the dorzolamide vehicle as a placebo. The goal was to determine whether IOP reduction would reduce glaucoma risk after several years. However, the study failed to demonstrate any significant difference in pressure reduction between the dorzolamide and placebo groups, and a comparison of pressure reduction’s benefit between the two groups was therefore not feasible.

The other clinical trial, the Ocular Hypertension Treatment Study (OHTS), was more successful and informative. The OHTS randomized 1636 patients with IOP between 24 and 32 mm Hg to either observation or treatment with commercially available topical ocular hypotensive medication.5-7 Unlike the EGPS, the treated and untreated groups in the OHTS demonstrated a meaningful pressure difference (23% vs 4%), allowing analysis of the effect of pressure reduction on the development of glaucoma. Over the 5-year period (OHTS phase 1), 9.5% of untreated vs 4.4% of treated subjects developed glaucoma—about a 55% reduction in relative risk of progression.

**WHO TO TREAT**

While topical ocular hypotensive treatment proved effective in reducing the incidence of glaucoma in hypertensive patients, the actual number of individuals who convert from ocular hypertension to glaucoma is negligible. Indeed, those who did not develop glaucoma constituted the major fraction of both patient groups in OHTS: 95% for the treated and 90% for the untreated group.5 Since the conversion rate is so low to begin with, the 55% relative reduction in the overall risk of conversion is far less significant than it appears. Imagine what happens when discussing the matter with patients. Probably anyone would choose to undergo treatment given a 95% chance of being glaucoma-free in 5 years—until being told that there is still a 90% chance of remaining glaucoma-free in 5 years without any treatment.

Since the majority of ocular hypertension patients are unlikely to benefit from prophylactic therapy, it makes sense to treat only those at higher risk of developing glaucoma. The question is, can we identify the higher-risk patients?

**RISK ASSESSMENT**

Determining an individual’s risk...
of progression is among the most important issues in the clinical approach to ocular hypertension. The OHTS and EGPS identified a number of risk factors for progression from ocular hypertension to POAG. These include older age, higher baseline pressure, thinner cornea, larger vertical cup/disc ratio, and higher pattern standard deviation on visual field. Central corneal thickness appears to be a particularly strong predictor of progression, with a 3-fold greater risk of developing POAG in subjects with a corneal thickness < 555 microns compared with those who had a >588 microns corneal thickness. Diabetes was identified as a protective factor in the initial analysis of OHTS, but the finding is contradictory to many other studies and could not be confirmed by detailed reanalysis of the data.

Several risk calculators have been developed for estimating the 5-year probability of glaucoma onset in hypertensive individuals, the original one being the OHTS-EGPS calculator derived from the pooled data from the OHTS and EGPS trials. The OHTS-EGPS calculator is available online, at the OHTS web site (http://ohts.wustl.edu/risk/calculator.html). It is free to use, and requires only a few baseline factors gathered from each patient.

Long-term follow-up of the OHTS patient cohort has found that the risk of progression in ocular hypertensive patients can be stratified into three levels: low risk, which corresponds to a less than 6% chance of developing glaucoma over the next 5 years; medium risk, which corresponds to a chance of conversion between 6 and 13%; and high risk, which corresponds to a 13% or greater chance of conversion to glaucoma in five years.

WHEN TO TREAT

One of the great contributions of the second phase of OHTS is that it quantified the benefit of treatment in patients at different levels of risk. Unsurprisingly, there was no evident benefit in treating patients who had a low risk of progression at baseline. In fact, as many as 98 low-risk patients must be treated in order to prevent one case of glaucoma during 13 years. For the medium risk group, the benefit of treatment was modest—16 patients have to be treated to prevent one from developing glaucoma. In the high risk group, however, the number of patients needed to treat is just seven. This confirms that the benefit of treatment is the greatest for high-risk patients, and that physicians should routinely assess risk of progression on an individual basis.

In OHTS phase 2, the original observation group was put on treatment after an average of 7.5 years without medical treatment while the original treatment group continued their medication. This allowed the researchers to compare the cumulative 13-year incidence of POAG between one early treatment (treated for an average of 13 years) and one late treatment (treated for an average of 5.5 years) cohort. Delaying treatment for 7.5 years had little effect on the overall incidence of POAG in low-risk patients but a much larger effect in the high-risk group, corroborating that high-risk patients may benefit from early treatment.

MANAGING OCULAR HYPERTENSION

My approach to managing untreated patients involves following up every six months and evaluating the optic nerve (imaging using spectral domain optical coherence tomography) and visual field testing at least once a year. As reported in the OHTS, ocular hypertensive patients who progress to glaucoma may demonstrate either optic nerve or visual field changes as the initial sign of conversion to open-angle glaucoma. To detect these early cases of glaucoma, it is important to watch for both structural and functional progression.

For patients deemed higher risk, early prophylactic treatment is clearly beneficial. Based on the OHTS study, the target pressure should be at least 20% lower than baseline. When selecting an initial therapy, IOP-lowering efficacy is not the only consideration. One thing to keep in mind when treating ocular hypertension is that these individuals do not have a disease. Most patients with established glaucoma are willing to accept some side effects and risks with therapy only because they are faced with a real possibility of going blind. When there is no disease, no evidence of damage, the tolerance for side effects would be much lower for a purely prophylactic medication.

The ideal therapy, therefore, should not be just effective in reducing the pressure but also highly tolerable and minimally impactful on quality of life. Cost is also a factor to consider. This explains why prostaglandin therapy has been the first-line treatment for ocular hypertension. The prostaglandins produce 25% to 30% IOP reductions, with few side effects; they have a convenient once-daily dosing schedule, and are available in inexpensive generic form. It would be difficult for any new class of medication to supplant them.

One potential alternative to topical medical therapy is selective laser trabeculoplasty (SLT), which frequently produces a 20% to 25% IOP reduction when used as monotherapy. The laser procedure is simple, safe, and can be cost-effective over time, as it eliminates the need for daily eye drops. An intriguing retrospective analysis presented at the 2014 ARVO meeting also suggests that annual low-power SLT may be a highly effective primary treatment for patients with ocular hypertension. Given SLT’s established efficacy and safety in providing IOP reduction, coupled with a desire to avoid the obligation of daily medication adherence, I would personally opt for primary SLT, if I had high-risk ocular hypertension.

INFORMED DECISION-MAKING

Patients who have a better understanding of their condition usually have better compliance. In the case of ocular hypertension, patients should be made aware of the following: first of all, most of them will never develop glaucoma; second, if they do develop glaucoma, most likely they will not notice the problem until the disease reaches moderate to advanced stages of severity; and third, to allow detection of the earliest signs of progression, they must keep their follow-up appointments so the doctor can perform diagnostic tests.

Depending on risk of glaucoma, I
take different approaches to helping patients make more informed decisions about treating their condition. For medium risk patients, I believe it is best to let them decide without me telling them whether they should or should not be treated. For patients that fall in the high or low risk category, however, I may be less ambivalent about what I think. The reality is that patients will never understand the issue the same way physicians do. My concept of informed consent is to care for patients the same way I myself would want to be treated. So when making decisions together with the patients, I will tell them what I would do for myself or my family and explain the risks and benefits of every choice.

CONCLUSIONS

Ocular hypertension is clinically important because it has the potential to progress to glaucoma. Preventing this conversion is the main goal of management. Current clinical approach to ocular hypertension is largely rooted in the findings of the OHTS, a landmark clinical trial that has provided valuable insight and tools to help us better manage hypertensive patients. Evidence available to date does not support treatment of all ocular hypertensive patients. Rather, assessing individual risk of progression and treating high-risk patients is an efficient and effective approach to preventing the development of glaucoma and subsequent visual morbidity.

Anthony Realini, MD, MPH, is an associate professor of ophthalmology at West Virginia University in Morgantown, WV. Dr. Realini has received grant/research support from Optovue, Topcon Corporation, and National Institutes of Health. He has also served as a consultant for Bausch + Lomb, Alcon, Reichert Technologies, and Alimera Sciences, and has served on the speakers’ bureau for Lumenis. Medical writer Ying Guo, MBBS, assisted in the preparation of this manuscript.

REFERENCES

1. Which of the following glaucoma therapies may have the potential to lower both IOP and CSFP?  
A. Beta blockers  
B. Prostaglandins  
C. Oral carbonic anhydrase inhibitors  
D. Both A and C

2. Translamina pressure difference is the difference between:  
A. IOP and orbital CSFP  
B. Retinal arterial and venous blood pressure  
C. The arterial blood pressure and IOP  
D. Retinal arterial blood pressure and orbital CSFP

3. According to OHTS phase 2, what are the chances high-risk hypertensive patients may develop glaucoma?  
A. 6% or higher  
B. 13% or higher  
C. 55% or higher  
D. None of the above

4. Which of the following symptoms is frequently found in patients with NTG?  
A. Anxiety  
B. Cold hands and feet  
C. Migraine  
D. Both B and C

5. According to Dr. Realini, what steps should physicians take when an ocular hypertensive patient is determined to have low risk of glaucoma?  
A. Follow up every six months  
B. Initiate treatment within 5 years  
C. Initiate treatment at the earliest signs of progression  
D. Both A and C

6. Clinical studies have found a higher than control CSFP in which of the following patients?  
A. Patients with NTG  
B. Patients with high tension POAG  
C. Patients with ocular hypertension  
D. Patients with angle-closure glaucoma

7. Based on the OHTS, which of the following is an appropriate target for IOP lowering in treating ocular hypertension?  
A. A 5% minimum reduction  
B. A 10% minimum reduction  
C. A 20% minimum reduction  
D. A 30% minimum reduction

8. Which of the following factors has NOT been associated with a low CSFP?  
A. Low blood pressure  
B. Low ocular perfusion pressure  
C. Low BMI  
D. Low IOP

9. Which of the following factors is NOT associated with a higher risk of glaucoma onset in patients with ocular hypertension?  
A. Older age  
B. Higher baseline IOP  
C. Thicker cornea  
D. Larger vertical cup/disc ratio

10. Which of the following statements is true about the prophylactic treatment of ocular hypertension?  
A. The treatment may reduce the relative risk of glaucoma by about 50%  
B. There is no obvious penalty for delaying the treatment in low-risk patients  
C. The prophylactic treatment may not be beneficial for all patients  
D. All of the above

**EVALUATION:**

11. Extent to which the activity met the identified objectives:  
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