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The Role of Ocular Perfusion Pressure in Glaucoma

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Content Source

This continuing medical education (CME) activity captures content from a roundtable discussion held on May 1, 2015, in Denver, Colorado

Activity Description

Evidence from epidemiologic studies and clinical trials alike suggests that ocular perfusion pressure (OPP) as well as other factors such as blood pressure, vasospasm, and ischemia may all contribute to glaucoma risk. The evidence and interest in the role of OPP is progressing and growing. A panel of glaucoma specialists with clinical and academic expertise in the vascular aspects of glaucoma herein present a conceptual framework for the role of OPP in glaucoma, review the evidence to support this association, and provide guidance for assessing and incorporating OPP into the evaluation and management of glaucoma patients in the office.

Target Audience

This activity intends to educate glaucoma specialists and general ophthalmologists.

Learning Objectives

Upon completion of this activity, participants will be better able to • Outline the role of ocular perfusion pressure as a

- risk factor for glaucoma
- Describe the assessment of ocular perfusion pressure in patients with glaucoma

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Introduction

Glaucoma is among the most common causes of irreversible vision loss worldwide. While its primary etiology remains incompletely understood, we have developed a robust understanding of the risk factors that contribute to the development and progression of the disease. Among these, intraocular pressure (IOP) remains the most important risk factor, both because of its strength of association with the disease and because it remains the only modifiable risk factor. In addition to IOP, vascular factors have long been suspected of playing a role in the glaucomatous process. Evidence from epidemiologic studies and clinical trials alike suggests that ocular perfusion pressure (OPP)—in simplest terms, the difference between IOP and systemic blood pressure (BP)—as well as other factors such as BP, vasospasm, and ischemia may all contribute to glaucoma risk. A panel of glaucoma specialists with clinical and academic expertise in the vascular aspects of glaucoma herein present a conceptual framework for the role of OPP in glaucoma, review the evidence to support this association, and provide guidance for assessing and incorporating OPP into the evaluation and management of glaucoma patients in the office.

Defining Ocular Perfusion Pressure

Dr Liebmann: Ocular perfusion pressure can be thought of as the pressure at which blood enters the eye. Mathematically, OPP is defined as the arterial BP minus IOP. Both of these determinants are dynamic biological parameters. Intraocular pressure varies throughout the day and from day to day. Blood pressure is even more variable, with significant changes throughout each cardiac cycle. During each heartbeat, systemic BP rises to a peak, the systolic BP, and then drops to a trough, the diastolic BP. Thus, OPP is also a dynamic parameter, varying as both BP and IOP vary.

> Ocular perfusion pressure can be thought of as the pressure at which blood enters the eye. —Jeffrey Liebmann, MD

Just as the complex variability of BP can be described using summary parameters—systolic, diastolic, and mean BP—the same summary parameters can be applied to OPP. Mean OPP (MPP) is the difference between mean arterial BP and IOP. Mean arterial BP is calculated using a formula (Table 1) that accounts for diastole taking up most of the cardiac cycle. Systolic OPP (SPP) and diastolic OPP (DPP) are calculated as systolic (or diastolic) BP minus IOP (Table 1).

Table 1. Definitions of Ocular Perfusion Pressure Parameters

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

BP=blood pressure; IOP=intraocular pressure; OPP=ocular perfusion pressure.

Clearly, OPP changes with changes in BP, IOP, or both. When BP is high and/or IOP is low, OPP is high; likewise, when BP is low and/or IOP is high, OPP is low. Because BP is significantly greater than IOP, OPP is more sensitive to changes in BP than to changes in IOP. Blood pressure in the normal range varies on the order of 40 to 60 mm Hg within each cardiac cycle, while typical circadian variations in IOP are generally on the order of 5 to 8 mm Hg. Therefore, patients with significantly elevated BP (systemic

Patients with significantly elevated BP (systemic hypertension) or those with significant dips in BP at night (nocturnal hypotension) may experience dramatic changes in OPP throughout the day. —Jeffrey Liebmann, MD

hypertension) or those with significant dips in BP at night (nocturnal hypotension) may experience dramatic changes in OPP throughout the day.

Dr Weinreb: Mathematically, diastolic BP has a greater effect than systolic BP in calculating mean OPP.

Dr Greenfield: The formula for calculating mean OPP reveals that a 10-mm Hg change in systolic BP results in a 2.2-mm Hg change in mean OPP, while a similar 10-mm Hg change in diastolic BP produces a 4.4-mm Hg change in mean OPP.

Dr Weinreb: Likewise, the systolic and diastolic BPs have greater effect than the IOP in determining OPP. A 10-mm Hg change in either systolic or diastolic BP is likely a very common event in most people. A 10-mm Hg change in IOP, however, is likely a fairly uncommon event for most people with or without primary open-angle glaucoma (POAG). Reduced OPP is emerging as a significant risk factor for glaucoma. Dr Varma reviews the data supporting this association.

Ocular Perfusion Pressure and Glaucoma: The Evidence

Dr Varma: Five major epidemiologic studies have provided data on the relationship between BP, OPP, IOP, and glaucoma. Four of these studies (Baltimore Eye Survey, Egna-Neumarkt Study, Proyecto VER, Los Angeles Latino Eye Study) were crosssectional studies,¹⁻⁴ while the fifth (Barbados Eye Study) was a prospective, longitudinal study.⁵ Key design features and findings of these studies are summarized in **Table 2**.

The Baltimore Eye Survey was a cross-sectional study of persons of European and African ancestry in Baltimore, Maryland. The relevant finding from this study was that lower OPP was strongly associated with a higher prevalence of POAG. In fact, patients in the lowest category of DPP (<30 mm Hg) had a 6-fold higher risk for having glaucoma compared with those whose DPP was >50 mm Hg.¹

Table 2. Summary of Epidemiologic Studies Linking Diastolic Perfusion Pressure and Glaucoma¹⁻⁵

Study	Design	Participants	Glaucoma Risk From Low DPP vs Normal DP					
Baltimore Eye Survey	Cross-sectional	Non-Hispanic Whites and African Americans	6-fold					
Egna-Neumarkt Study	Cross-sectional	Non-Hispanic Whites	2.5-fold					
Proyecto VER	Cross-sectional	Hispanics	4-fold					
Los Angeles Latino Eye Study	Cross-sectional	Latinos/Hispanics	1.9-fold					
Barbados Eye Study	Longitudinal	Afro-Caribbeans	3.2-fold (4 years)					

The Egna-Neumarkt Study was a cross-sectional study of persons of European ancestry in northern Italy. Persons with low DPP were at higher risk for having glaucoma. In this case, those with DPP <60 mm Hg had a 2.5-fold higher risk for glaucoma compared with those with DPP >76 mm Hg.²

Proyecto VER was a cross-sectional study of Hispanics in Nogales and Tucson, Arizona. This study found that people with DPP <50 mm Hg had a 4-fold higher risk for having glaucoma than those with DPP >80 mm Hg.³

The Los Angeles Latino Eye Study was a cross-sectional study of Latinos/Hispanics residing in Los Angeles, California. Compared with people whose DPP was between 51 and 60 mm Hg, those whose DPP was below 40 mm Hg had a 1.9-fold higher risk for glaucoma.⁴ In fact, low DPP, SPP, and MPP were all highly associated with the risk for glaucoma in this study (Figure 1).





Republished with permission from *Investigative Ophthalmology & Visual Science*, from Los Angeles Latino Eye Study Group. Blood pressure, perfusion pressure, and open-angle glaucoma: the Los Angeles Latino Eye Study, Memarzadeh F et al, 51(6), 2010.

In contrast to these 4 studies, the Barbados Eye Study was a prospective, longitudinal study of predominantly Afro-Caribbeans on the island of Barbados in the eastern Caribbean Ocean. Participants were enrolled in a cross-sectional prevalence study similar to the ones described above, but were reexamined 4 and 9 years after enrollment. This study design provides insight into the risk for *developing* glaucoma, in contrast to cross-sectional studies that describe *preexisting* glaucoma. At 4 years, low MPP, SPP, and DPP were all associated with a higher risk (2.6- to 3.2-fold) for developing new glaucoma.⁵ At 9 years, all 3 perfusion pressures remained significantly associated with developing glaucoma.⁶ **Dr Ritch:** Blood pressure is highly variable. How was it characterized in the studies?

Dr Varma: In most of these studies, BP was measured at least twice at baseline in a sitting position, so the analyses did not rely on a single snapshot value.

Dr Liebmann: The theme throughout is that low OPP is a significant risk factor for glaucoma. The absolute numbers were a bit different in these studies, but the message is the same: Low DPP is a risk factor for glaucoma. Do these studies reveal a risk associated with elevated OPP?

Low DPP is a risk factor for glaucoma. —Jeffrey Liebmann, MD

Dr Varma: The risk for glaucoma decreases as OPP increases, and it plateaus at the higher levels.

Dr Greenfield: Ocular perfusion pressure may be reduced in 2 clinical scenarios: when BP is low or when IOP is high. In these epidemiologic studies, do we know if OPP was reduced because of low BP or because of high IOP? This is an important point because if elevated IOP was the reason for the low OPP, then BP may be less relevant and the increased glaucoma risk could be attributable primarily to elevated IOP.

Dr Varma: In most of these studies, mean IOP was in the 'normal' range. Interestingly, in these studies and in other epidemiologic studies, half or more of the newly diagnosed open-angle glaucoma cases have IOP in the normal range. We often think of glaucoma as being a high-pressure disease. This is more myth than fact. The average untreated IOP of Hispanics newly diagnosed with glaucoma in the Los Angeles Latino Eye Study was 17 mm Hg, with only 18% of all eyes with glaucoma having an IOP greater than 21 mm Hg.⁷ The median IOP of all glaucomatous eyes in non-Hispanic Whites and African Americans in the Baltimore Eye Survey was 20 mm Hg, with 41% of all eyes having an IOP greater than 21 mm Hg.⁸ So we cannot entirely attribute IOPs greater than 21 mm Hg for this increased risk for glaucoma. The low BP is relevant.

We often think of glaucoma as being a high-pressure disease. This is more myth than fact. —Rohit Varma, MD, MPH

Dr Weinreb: I find it fascinating and important that in the Barbados study, OPP was a much more powerful risk factor for glaucoma than was IOP. I wish we had information about nocturnal IOP and BP from these epidemiologic studies. At night, IOP goes up and BP—particularly diastolic BP—goes down, so the DPP is dually affected. I wonder if nocturnal DPP is even more strongly associated with glaucoma risk than are daytime values.

I find it fascinating and important that in the Barbados study, OPP was a much more powerful risk factor for glaucoma than was IOP. —Robert N. Weinreb, MD

Dr Gupta: Our concept of glaucoma is shifting from a disease of a single pressure—IOP—to a disease of multiple pressures. Ocular perfusion pressure is clearly an important factor in glaucoma. Other research points to a potential role for intracranial pressure (ICP). Glaucoma is more than just IOP.

Dr Weinreb: Dr Gupta has spent many years investigating the role of the cerebrovascular system in glaucoma. She provides us with an overview of her work.

Our concept of glaucoma is shifting from a disease of a single pressure—IOP—to a disease of multiple pressures. —Neeru Gupta, MD, PhD, MBA

The Cerebrovascular System in Glaucoma

Dr Gupta: We tend to think of glaucoma as a primary eye disease. As such, ophthalmologists have sole responsibility for its management, and all treatment options are directed at the eye. A substantial body of research stretches this view, and considers glaucoma disease in the context of central nervous system degeneration. In fact, most of the neurovisual system resides within the white matter of the brain. Glaucoma is much more than a disease of the eye, with evidence that it is a neurodegenerative disorder of the central visual system. There is demonstrable atrophy of the lateral geniculate nucleus—the terminus for optic nerve axons—in glaucoma (**Figure 2**).^{9,10} This has been demonstrated in primates¹¹ as well as in humans,¹⁰ the latter both by magnetic resonance imaging (MRI) in vivo and in histological specimens taken postmortem.



Figure 2. Atrophy of the lateral geniculate nucleus associated with glaucoma (left image) compared with normal controls (right images).^{9,10} Adapted from Gupta N et al. *Br J Ophthalmol.* 2006;90(6):674-678 and Gupta N et al. *Br J Ophthalmol.* 2009;93(1):56-60.

Glaucoma is much more than a disease of the eye, with evidence that it is a neurodegenerative disorder of the central visual system.

-Neeru Gupta, MD, PhD, MBA

Further, blood vessels of the lateral geniculate nucleus demonstrate oxidative damage when stained appropriately.¹² More posteriorly, the visual cortex also manifests damage in glaucoma compared with controls in both primate¹³ and human studies.⁹ Functional deficits can be demonstrated in humans with glaucoma by functional MRI, which reveals reduced levels of blood oxygen in areas of the visual cortex that correspond to known visual field defects.¹⁴

According to what we know about the vascular contributions to the central visual system, much of it lies in a watershed zone of the brain. Watershed zones are more vulnerable to hypoperfusion and ischemia. It is possible that under conditions of unstable perfusion, such as low BP, the visual system becomes even more susceptible to neural degeneration.



Figure 3. Vascular circulations of the brain, with the visual pathway falling within a watershed zone (outlined in red) between the anterior and posterior circulatory systems.

Image Courtesy of Yeni Yücel, MD, PhD

When the vascular supply to the brain is considered (Figure 3), the role of cerebrovascular factors in glaucoma are better appreciated. The branches of the carotid artery—anterior, middle, and posterior cerebral arteries—supply most of the front aspect of the brain and, via the ophthalmic artery, the eyes. The vertebrobasilar system supplies the rear aspect of the brain. These 2 circulations are connected through the circle of Willis. Between these 2 circulations is a segment of brain that is supplied by minor branches of these major vessels—and within this so-called watershed zone lie the optic tracts, the lateral geniculate nuclei, the optic radiations, and the visual cortex.

An anatomic configuration of the vascular circulations of the brain provides insight into the importance of OPP. When BP is low, these watershed zones are quite vulnerable to hypoperfusion and ischemia. It is possible that under conditions

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-Neeru Gupta, MD, PhD, MBA

of unstable perfusion, ischemic insults to these tissues could contribute to the neurodegenerative changes seen throughout the visual system in glaucoma.¹⁵

Dr Ritch: This watershed zone could be endangered by impairment of either the cerebral or the vertebrobasilar system. Is there a known role for vertebrobasilar insufficiency in glaucoma?

Dr Gupta: To my knowledge, this has not been reported. However, anything that compromises the BP within the cerebrovascular arterial system would affect both cerebral and ocular perfusion pressure. Visual structures in the watershed areas of the brain would be particularly more susceptible to global hypoperfusion.

Dr Weinreb: Hypoperfusion of the optic nerve may play a role in the development of glaucoma; it also is thought to be the basis of acute anterior ischemic optic neuropathy (AION). Could these 2 entities differ in terms of the vascular beds affected? For example, could AION be related to ischemia within the anterior circulation of the optic nerve and glaucoma to the more posterior vascular beds?

Dr Greenfield: I find it intriguing that while there are many well-established systemic disorders of chronic ischemia—such as congestive heart failure, ischemic heart disease, chronic ischemic dementia, and chronic ischemic renal disease—we have not characterized a chronic ischemic optic neuropathy. Perhaps that condition is glaucoma.

Dr Varma: Tools under development—such as optical coherence tomographic (OCT) angiography—may be able to provide insight into these issues. This technology has the potential to noninvasively image at the level of the capillaries and may provide functional data on blood flow. With that information, perhaps we will then better understand the relative contributions of IOP and blood flow to glaucomatous optic nerve damage.

Dr Liebmann: As we have said, there are many vascular risk factors associated with glaucoma, among them, potentially, cerebral hypoperfusion. This raises an interesting question: If glaucoma can be a manifestation of cerebral hypoperfusion, should we be alerting glaucoma patients and their internists to be alert for signs of cerebral hypoperfusion? Is there a cerebrovascular workup that should be undertaken for glaucoma patients?

Dr Ritch: This may be a reasonable approach. But in our health care system, it is impractical to expect all glaucoma patients to undergo imaging with MRI or even magnetic resonance angiography. Many internists with whom I work remain unconvinced that BP is relevant in glaucoma—thus, it would be difficult to convince them to conduct a more extensive workup. On the other hand, can we formulate an equation for intracranial perfusion pressure similar to that for OPP? If we consider that the driving force of blood pressure to the eye and brain are similar, would it be a legitimate analogy to substitute ICP for IOP in the equation used for deriving mean OPP and thus have an estimate for mean intracranial perfusion pressure? We still have no simple and reliable means of noninvasive measurement of ICP, but several groups are working on developing one.

Dr Liebmann: Consider starting on a smaller scale. At a bare minimum, let us ask patients if they know their BP. Currently,

when taking a medical history, we ask about hypertension and medications. Should we also ask about *hypo*tension? Or we could go a step further. Perhaps all our glaucoma patients should undergo BP measurement in our offices. Knowing their BP allows us to calculate their OPP, which then aids us in risk assessment. If we detect low BP, it might be prudent to notify the patient's internist and let him or her decide what, if any, workup might be warranted. Likewise, perhaps the internist should consider referring patients with low BP for glaucoma screening.

Dr Weinreb: At this point, it seems appropriate to move on to consideration of the clinical applications of OPP. Dr Greenfield presents a framework for this discussion.

Ocular Perfusion Pressure in Current Clinical Practice

Dr Greenfield: We have reviewed the definition of OPP, the evidence linking it to the development of glaucoma as a risk factor, and have learned of some interesting research findings that may reveal a potential mechanism within the central nervous system by which low BP might be causally related to the development of glaucoma.

Several key questions remain. Is the value of OPP firmly enough established that we should be routinely assessing OPP in our glaucoma patients? Or, if not in all our patients, are there subsets of our patients in whom knowledge of OPP might be clinically relevant? If so, how should we best characterize OPP?

Dr Weinreb: Let us address these questions individually. Firstly, should we routinely measure OPP in all our glaucoma patients?

Dr Greenfield: In an ideal world, yes, we would, because OPP measurement is noninvasive, inexpensive, and easy to obtain, and provides clinicians with data to more fully assess not only patients' glaucoma risk, but also their overall systemic health. In a busy clinical practice, however, in which a clinician sees 40 to 50 patients per day, the added time necessary to obtain BP readings and to calculate and record OPP will cost money and reduce clinical efficiency, and will likely not be effective for treatment planning in most patients.

OPP measurement is noninvasive, inexpensive, and easy to obtain, and provides clinicians with data to more fully assess not only patients' glaucoma risk, but also their overall systemic health.

-David S. Greenfield, MD

Dr Ritch: I agree. For instance, if I discovered a low OPP in a patient whose glaucoma has remained stable for many years, I might notify the internist of this finding, but I would be unlikely to change the patient's glaucoma management to try to further lower IOP by 1 or 3 mm Hg; but if the glaucoma was not stable, I would obtain 24-hour blood pressure measurements, which we do routinely, and consider salt loading if nocturnal OPP was reduced. There are many risk factors which make me consider glaucoma occurring at normal IOP to be a nocturnal disease.

Dr Weinreb: But, secondly, is it correct to assume that there are subsets of patients in whom knowledge of OPP might be beneficial?

There are many risk factors which make me consider glaucoma occurring at normal IOP to be a nocturnal disease. —Robert Ritch, MD

Dr Greenfield: You are correct in your assumption. Measurement of OPP would be beneficial **(Table 3)** in POAG patients with IOP in the normal range. We can agree or disagree as to whether normal-tension glaucoma is a separate clinical entity or is merely POAG occurring within the normal range of IOP. But in 2 major clinical trials of patients with glaucoma and IOP in the normal range, vascular risk factors were found to be the strongest predictors of progression. The Collaborative Normal-Tension Glaucoma Study identified optic disc hemorrhage and migraine as predictive factors for progression, ¹⁶ and the Low-Pressure Glaucoma Treatment Study (LoGTS) identified reduced mean OPP and the use of systemic antihypertensive medication as risk factors for visual field progression.¹⁷

Table 3. Patient Subgroups In Which to Consider the Value of Assessing Ocular Perfusion Pressure

- Normal-tension glaucoma
- Eyes with optic disc hemorrhage
- Patients with progression at low IOP
- History of low BP, multiple systemic antihypertensives, symptoms of orthostasis
- Patients with nocturnal hypotension

Patients with optic disc hemorrhage might benefit from OPP assessment. Disc hemorrhages can occur in both normal-tension and high-tension glaucoma and the exact mechanism by which they appear remains elusive. In LoGTS, low mean OPP as well as low mean systolic BP, migraine headache, and use of systemic beta-blockers were all associated with the development of optic disc hemorrhage.¹⁸

Patients whose glaucoma is progressing at what appears to be an adequately low IOP level also may benefit from OPP assessment. Charlson and colleagues conducted a study in which a reduction in mean arterial pressure from daytime to nighttime was found to be a significant predictor of visual field progression in such patients.¹⁹

Finally, patients who report a history of low BP, who are using multiple systemic antihypertensive medications, or who have symptoms of orthostatic hypotension, may benefit from OPP assessment.

Dr Weinreb: The third key question is, How should we best characterize OPP? Which of the many ways to measure OPP should we use? Mean? Systolic? Diastolic? And is a single random measurement adequate? Or should we assess OPP at multiple time points, such as a diurnal curve? Or should we obtain 24-hour IOP and BP monitoring to ensure adequate characterization of the important nocturnal period?

Dr Greenfield: All valid options. A single BP and IOP measurement allows a quick snapshot, but because both BP and IOP vary widely, it will not be a complete characterization. This is the same challenge we face with IOP. If there is particular

concern that low OPP may be contributing to glaucoma progression, a single-day diurnal assessment might be worthwhile, or a modified diurnal assessment can be constructed by seeing the patient at different times of the day on different visits. Certainly 24-hour ambulatory BP monitoring is the most robust approach and will reveal "nocturnal dippers" whose BP bottoms out at night, but such monitoring is both cumbersome and expensive, and we do not yet have satisfactory 24-hour IOP monitoring tools with which to characterize 24-hour OPP.

Dr Weinreb: The fundamental questions are the following: Do we have adequate evidence to justify the clinical use of OPP in glaucoma management? Do we know enough about OPP to know what to do with the information we obtain? Is the strength of evidence strong enough to recommend that OPP be made a routine part of glaucoma management?

Dr Varma: I believe that with the evidence we have to date, it is reasonable to obtain an assessment of BP in our patients with glaucoma. And, based on the strength of evidence from the studies to date, I would pay more attention to DPP.

Dr Weinreb: And what would we do with this information? Are there interventions to improve OPP? And is there any evidence that improving OPP has any beneficial effect on glaucoma?

I believe that with the evidence we have to date, it is reasonable to obtain an assessment of BP in our patients with glaucoma. —Rohit Varma, MD, MPH

Dr Greenfield: In my opinion, identifying a low OPP in a patient progressing at low IOP represents a potentially actionable scenario. The data reported by Charlson and colleagues¹⁹ indirectly suggests that patients with glaucoma progression using systemic antihypertensive agents may benefit from adjusting the dose or time of antihypertensive administration to avoid low mean arterial pressure, particularly during the nocturnal period.

My colleagues and I recently published a paper showing that the visual field can improve in the short term following surgical IOP reduction, and that the magnitude of the visual field improvement is significantly associated with the mean OPP.²⁰ We prospectively compared a group of 30 eyes that had surgical IOP lowering via trabeculectomy or glaucoma drainage device implantation with a group of 41 control eyes that had stable IOP during the same time period. Following IOP reduction on average from 18 to 10 mm Hg, a significantly greater number of visual field points improved in the surgical group than in the control group. This improvement was not correlated with the change in IOP, but was significantly related to improvement in postoperative mean OPP. Our study is consistent with other reports of visual field improvement after IOP reduction^{21,22} and provides indirect support that OPP may be related to both visual field progression and visual field improvement.

Dr Weinreb: On the basis of the foregoing discussion and in light of the data presented, is it reasonable to propose that OPP is potentially a new modifiable risk factor for glaucoma care?

Dr Greenfield: In cross-sectional and longitudinal studies, we have seen that OPP is an important risk factor for glaucoma

We should consider measuring OPP in selected patients, particularly those in whom glaucoma progression is occurring at low levels of IOP, and/or patients who develop optic disc hemorrhage. —David S. Greenfield, MD

onset and glaucoma progression. Therefore, OPP might be a potentially modifiable risk factor. We know that at present IOP is the only modifiable risk factor. Intraocular pressure and diastolic BP contribute more from a mathematical calculation to OPP than does systolic BP, and clinicians need to pay attention to the various factors that influence OPP. We should consider measuring OPP in selected patients, particularly those in whom glaucoma progression is occurring at low levels of IOP, and/or patients who develop optic disc hemorrhage.

Dr Weinreb: If OPP is a modifiable risk factor, how might we modify it?

Dr Ritch: The first step is to review a patient's medical and medication history. Patients with systemic hypertension may be overmedicated, with their diastolic BP dropping lower than necessary. Most important, in my view, is the nocturnal diastolic pressure, which is lowered by the patient's taking of BP medications at bedtime. Just as IOP has a 24-hour fluctuation, so does BP, which may be high during the day but normal nocturnally, and taking BP medication in the evening can produce a significant drop in nocturnal mean arterial pressure. Being mindful of the nocturnal dip in diastolic BP, I would communicate with the internist or cardiologist and ask if treatment can be shifted from the evening to the morning to best protect against nocturnal dips. Topical beta-blockers may also lower BP at night in some patients²³ and measuring 24-hour BP with and without topical beta-blockers may provide useful information. If the patient is dependent on beta-blockers for IOP control, this must be taken into account.

Patients with systemic hypertension may be overmedicated, with their diastolic BP dropping lower than necessary....Being mindful of the nocturnal dip in diastolic BP, I would communicate with the internist or cardiologist and ask if treatment can be shifted from the evening to the morning to best protect against nocturnal dips. —Robert Ritch, MD

Dr Varma: Consider a patient who is not being overmedicated, or in whom the current antihypertensive regimen cannot be reduced. Is there any value to salt addition as a means of preventing diastolic BP from bottoming out during the night?

Dr Ritch: Although the evidence is limited, we have recommended salt loading to some patients in order to increase OPP. We initially start with salty snacks, such as pretzels and potato chips, then move to V8 juice, which has a high sodium content, or salt tablets. We have had patients whose nocturnal dipping did improve significantly. Granted, these examples are from individual case reports. There are no data from epidemiologic studies or trials to support salt loading in this setting.

Dr Gupta: I agree with you. We all have patients who are progressing at low IOP and who are nocturnal dippers. Twenty-four-hour BP monitoring may help to identify these patients. Salty snacks or beverages at night may help, although the evidence is anecdotal.

Case From the Files of Robert Ritch, MD

Salt loading may or may not be successful at elevating nocturnal BP. A case in point is a patient who was extremely difficult to control. This was a 50-year-old white woman with -7.00 diopters of myopia and recurrent disc hemorrhages with progression of her glaucoma with IOPs in the low to mid teens. She had lamina cribrosa defects on enhanced depth imaging-OCT, and polysomnography was negative for obstructive sleep apnea. Twenty-four-hour BP measurement showed extensive nocturnal dipping. A repeat measurement showed improvement, but recurrent disc hemorrhages prompted a third measurement, which showed regression and an apparent loss of continued effect of salt loading (Figures 4A, 4B, 4C). She eventually underwent trabeculectomy OU.



Figure 4. Patient 1 BP monitoring. A) August 2012—12-hour BP monitoring: No salt loading; B) May 2013—12-hour BP monitoring: Salt loading; C) November 2014—24-hour BP monitoring: Diurnal curve. *Images Courtesy of Robert Ritch, MD*

This is in contrast to another patient who had significant improvement after salt loading with cessation of progression to date, although repeat testing has not since been performed (Figures 5A, 5B).



Figure 5. Patient 2 BP monitoring. A) 24-hour BP: No salt; B) 24-hour BP: Salt loading.

Images Courtesy of Robert Ritch, MD

Summary and Conclusions

The concept of OPP as the balance of 2 opposing forces—BP and IOP—has been offered. The evidence linking OPP to glaucoma has been reviewed. A biologically plausible mechanism by which central nervous system hypoperfusion may predispose to glaucoma has been presented. Further, we have described the notion of OPP as a modifiable risk factor for glaucoma progression independent of IOP reduction. In summary, the panel has drawn up a series of points to consider regarding the role of OPP in glaucoma.

Key Learning Points

- Many vascular risk factors have been associated with glaucoma
 - Low diastolic BP
 - Reduced nocturnal BP
 - Decreased OPP
- Several other vascular factors should be considered in select glaucoma patients
 - Migraine
 - Raynaud phenomenon
 - Hypertension (particularly when treated)
- OPP is an established risk factor for glaucoma onset and progression
- OPP may be a modifiable risk factor and treatment target in glaucoma
- IOP and diastolic BP contribute more to OPP than does systolic BP
- Many factors influence OPP
- Measurement of OPP in select patients (those with low IOP, especially those who are progressing, and those with disc hemorrhages) should be considered
- 24-hour IOP and BP measurements will provide more robust assessments than single daytime measurements

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- 1. Ocular perfusion pressure _
 - a. Is the pressure at which blood leaves the eye
 - b. Is constant throughout the day
 - c. Is more dependent on diastolic than systolic BP
 - d. Is potentially contributory to glaucoma damage when it is above 75 mm Hg
- 2. The evidence linking OPP to glaucoma has been observed in
 - a. Whites
 - b. African Americans
 - c. Hispanics
 - d. All the above
- 3. Which measure of OPP has been most strongly linked to glaucoma risk?
 - a. Mean OPP
 - b. Systolic OPP
 - c. Diastolic OPP
 - d. Mean arterial pressure
- 4. Compared with DPP in the normal range, the lowest levels of DPP are generally associated with a
 - _____ risk for glaucoma.
 - a. 1- to 2-fold
 - b. 2- to 6-fold
 - c. 8- to 10-fold
 - d. 15- to 20-fold
- 5. Within the central nervous system, the _____ has not been shown to be damaged in glaucoma.
 - a. Lateral geniculate nucleus
 - b. Blood vessels within the lateral geniculate nucleus
 - c. Visual cortex
 - d. Cerebellum

- 6. Why might the central visual pathways be susceptible to damage in the setting of hypoperfusion?
 - a. There is not enough cerebrospinal fluid to nourish the brain tissue
 - b. Most of the visual pathway lies within a vascular watershed area in the brain, which is particularly vulnerable to ischemic damage in the setting of hypoperfusion
 - c. The visual pathway is made up of gray matter that is hypersensitive to hypoperfusion
 - d. The axons of the optic nerve do not extend past the lateral geniculate nucleus
- 7. Nocturnal OPP is often low both because the BP is low and because _____.
 - a. The patient is asleep
 - b. Perfusion is reduced in the dark
 - c. IOP is highest at night
 - d. The heart rate is low at night
- 8. Which of the following patients would least likely benefit from OPP assessment?
 - a. A patient with progressive POAG
 - b. A glaucoma patient with a disc hemorrhage
 - c. A patient on 3 antihypertensive medications
 - d. A patient with low IOP and stable visual fields
- 9. The strength of evidence for modifying OPP in glaucoma patients is at the level of _____.
 - a. Meta-analysis
 - b. Randomized clinical trials
 - c. Epidemiologic studies
 - d. Case reports
- 10. In which of the following patient scenarios would measuring OPP be of greatest clinical value?
 - a. A well-controlled and stable patient
 - b. A patient with elevated IOP who is progressing
 - c. A patient with low IOP who is progressing
 - d. A patient with low IOP who is stable

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