

Should We Measure (and Treat) Ocular Perfusion Pressure in Glaucoma Patients?

Mounting evidence indicates that this parameter may affect an individual patient's risk of developing glaucoma and/or its progression, but there are currently multiple challenges to and limitations on incorporating this concept into everyday clinical practice.

BY JAMES C. TSAI, MD

The AAO's *Preferred Practice Patterns* define *open-angle glaucoma* (OAG) as a "multifactorial optic neuropathy in which there is a characteristic acquired loss of retinal ganglion cells (RGC) and atrophy of the optic nerve."¹ Elevated IOP is known to be a major risk factor for the disease, and at present, decreasing IOP is the only proven means of halting the development and/or progression of OAG.² Lowering pressure is therefore the main therapeutic effect of all current medications, laser procedures, and incisional surgeries. The paradox is that 90% of patients with elevated IOP never develop significant damage to the optic nerve head and at least 33% of patients with OAG never have documented elevations in IOP.²

There is increasing evidence that the cardiovascular system (eg, altered blood flow) may play a major role in the pathogenesis of OAG.^{3,4} The major cause of this reduction in ocular blood flow is thought to be secondary to vascular dysregulation in susceptible patients, resulting from abnormal/insufficient autoregulation rather than atherosclerosis.^{3,5} In an observational cohort study of patients with normal-tension glaucoma (NTG), retinal laser Doppler measurements of the inferotemporal retinal artery showed differing variation in ocular blood flow in response to postural changes when compared with control patients.⁶ The investigators concluded that there was a lack of retinal vascular autoregulation in a select group of patients with OAG.⁶

$$\text{MAP} = \text{DBP} + 1/3 \times (\text{SBP} - \text{DBP})$$

$$\text{MOPP} = 2/3 \times \text{MAP} - \text{IOP}$$

Figure 1. The calculation of ocular perfusion pressure. Note: in the eye, venous pressure should be marginally higher than the IOP to allow for adequate blood circulation. IOP can be substituted for venous pressure in the calculation of ocular perfusion pressure. Abbreviations: MAP, mean arterial pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; MOPP, mean ocular perfusion pressure.

The term *ocular perfusion pressure* refers to the net pressure gradient causing blood to flow to the eye. Thus, ocular perfusion pressure may be considered the difference in blood pressure between the arterial and venous parts of vascular beds throughout the eye, including at the optic nerve head. Ocular perfusion pressure must remain above a certain minimum level, since too little pressure could cause ocular tissues to become ischemic. Although the venous pressure should be marginally higher than the IOP to allow for the adequate circulation of blood, IOP can effectively be substituted for venous pressure in the calcu-

OCULAR PERFUSION PRESSURE IN THE DIAGNOSIS AND MANAGEMENT OF GLAUCOMA

PROS

- Vascular risk factors have been reported to influence the status of open-angle glaucoma (OAG)¹¹⁻¹³
- Basic scientific studies outline the importance of oxidative stress (ie, state of mitochondrial function) in the pathophysiology of OAG³⁻⁵
- In theory, enhanced ocular circulation (ie, tissue oxygenation) is beneficial in relieving oxidative stress in retinal tissues³⁻⁵
- Known abnormal autoregulatory responses to changes in ocular perfusion pressure have been observed in patients with OAG^{3,5,6}
- Population-based studies document the role of ocular perfusion pressure in the development and progression of OAG¹⁴⁻¹⁹

CONS

- Conflicting results of negative studies (eg, Beijing Eye Study²⁰)
- Brachial blood pressure unlikely to reflect true perfusion pressure at the optic nerve head
- How does one measure blood pressure? While the patient is sitting, standing, or supine (or more than one position needed)?
- Limitations of exact IOP measurements (eg, effect of central corneal thickness)
- Diurnal variation in the measurements of blood pressure and IOP
- Other variables influence perfusion pressure at the optic nerve head (eg, low intracranial pressure)²¹
- Significant diurnal-to-nocturnal decreases in blood flow in the optic nerve head and macula in older patients appear to be independent of ocular perfusion pressure²²
- Which therapeutic method would be most effective? Would it be aggressively lowering the IOP, increasing the blood pressure, or a combination of both? What would be the most effective therapeutic options in these cases?

lation of ocular perfusion pressure (Figure 1). The potential consequences of abnormally low levels of ocular perfusion pressure include optic nerve head and retinal ischemia as well as reperfusion injury. For example, the presence of migraine, thought to be associated with temporary alterations in blood flow and peripheral vasospasm, is a significant risk factor for visual field progression in NTG.⁷

Does the literature support the measurement of ocular perfusion pressure as part of the management of glaucoma?

VARIATIONS IN PRESSURE

Although clinicians have known for decades that the IOP varies throughout a 24-hour period, only recently have circadian patterns been detected for other factors that influence ocular health such as systemic blood pressure, ocular perfusion pressure, and ocular blood flow.⁴ For example, patients with NTG have a significantly greater variability of nighttime systolic, diastolic, and mean arterial blood pressure compared with control patients.⁸ Patients with primary open-angle glaucoma show a larger diurnal fluctuation of ocular blood flow.⁹ Circadian fluctuations in mean ocular perfusion pressure were also reported to be the most consistent clinical risk factor for glaucoma's severity in eyes with NTG.¹⁰ Thus, unstable ocular perfusion pressure—rather than a steady reduction in ocular blood flow—may contribute to the process of glaucomatous optic neuropathy.

VASCULAR RISK FACTORS IN GLAUCOMA

The relationship between vascular dysregulation and systemic vascular abnormalities has been explored. Selective dysfunction of the systemic vascular endothelium is known to occur in patients with NTG, with associated defects in the release of certain endothelium-derived vasodilators (eg, 5-hydroxytryptamine and endothelin-1) thought to contribute to abnormal vasospasm in these patients.¹¹ A high percentage of NTG patients (45%) have documented episodic myocardial ischemia on 24-hour electrocardiographic monitoring.¹² There is also a significant correlation between slower cerebrovascular blood flow and decreased central visual function indices (eg, visual field mean defect value, logMAR visual acuity) in patients with OAG.¹³

Previous population-based studies have documented the positive relationship between low diastolic perfusion pressure and an increased risk of

OAG. In the Baltimore Eye Survey, a diastolic perfusion pressure of less than 30 mm Hg carried a sixfold higher risk,¹⁴ and a diastolic perfusion pressure lower than 53 mm Hg conferred a 2.2 times greater risk in the Barbados Eye Studies.¹⁵ The Eigna-Neumarkt Study found an increased risk of OAG in patients with a diastolic perfusion pressure below 50 mm Hg,¹⁶ and the Proyecto VER Study documented a threefold higher risk among subjects with a diastolic perfusion pressure of less than 45 mm Hg.¹⁷

“In patients with pathologically low ocular perfusion pressure, which therapeutic method would be most effective—aggressively lowering IOP, increasing blood pressure, or a combination of both?”

Recent epidemiologic studies have also suggested that vascular risk factors may play a role in the different presentations of OAG. In the Rotterdam Study, patients with high-tension glaucoma had higher perfusion pressures.¹⁸ Among individuals treated for systemic hypertension, a lower diastolic perfusion pressure (< 50 mm Hg) was inversely associated with NTG (odds ratio = 0.25) and positively associated with high-tension glaucoma (odds ratio = 4.68).¹⁸ In addition, the lowest tertile of carotid distensibility compared with the highest third had a 2.84-times greater risk of having high-tension glaucoma.¹⁸

In the Barbados Eye Studies, traditional risk factors for the long-term development of OAG were age (relative risk = 1.04), family history (relative risk = 2.4), higher IOP (relative risk = 1.12), and thinner central corneal thickness (relative risk = 1.41 per 40 μ m lower).¹⁵ Additional risk factors included lower systolic blood pressure (relative risk = 0.91 per 10 mm Hg), systolic ocular perfusion pressure, diastolic ocular perfusion pressure, and mean ocular perfusion pressure. In patients with a low mean perfusion pressure (< 40 mm Hg), the relative risk for developing OAG was 2.6.¹⁵

The Early Manifest Glaucoma Trial showed cardiovascular risk factors to have marked effects on long-term disease progression.¹⁹ Baseline predictive factors were lower ocular systolic perfusion pressure ($\leq$ 160 mm Hg) in all patients, a history of cardiovascular disease in patients with a higher baseline IOP, and lower systolic blood pressure ($\leq$ 125 mm Hg) in patients with a lower baseline IOP.¹⁹ Optic disc hemorrhage was also a predictive factor for progression.¹⁹

In the Beijing Eye Study, the diagnosis of glaucoma was made by a glaucomatous appearance to the optic disc

alone.²⁰ Univariate or multivariate analysis did not demonstrate an association of OAG with systolic blood pressure, diastolic blood pressure, mean blood pressure, and ocular perfusion pressure. Of note, most subjects were untreated, and 80% of patients had an IOP below 22 mm Hg (ie, NTG).²⁰ Thus, there may be differences in definition and demographics in this population-based study compared with earlier ones.

CHALLENGES

The measurement and treatment of ocular perfusion pressure pose many challenges (see *Ocular Perfusion Pressure in the Diagnosis and Management of Glaucoma*). It is unlikely that measurements of brachial blood pressure reflect the true perfusion pressure at tissues in the optic nerve head. In addition, how does the clinician measure the approximate blood pressure? Should the measurements of blood pressure occur when the patient is standing, sitting, supine, or a combination of two or three of these positions? Certain limitations also exist in obtaining exact IOP measurements (eg, the effect of central corneal thickness measurements) to calculate the ocular perfusion pressure. In addition, how does one incorporate the diurnal variations that occur in the measurements of both blood pressure and IOP?

Other variables also influence ocular perfusion pressure at the optic nerve head. One potential factor is intracranial pressure, which has been shown to be lower in cases of primary open-angle glaucoma and NTG and elevated in eyes with ocular hypertension.²¹ Significant diurnal-to-nocturnal decreases in ocular blood flow in the optic nerve head and macula among older patients also appear to be independent of ocular perfusion pressure.²² Finally, in patients with pathologically low ocular perfusion pressure, which therapeutic method would be most effective—aggressively lowering IOP, increasing blood pressure, or a combination of both? What would be the most effective therapeutic options (eg, medical vs surgical intervention) in these cases?

CONCLUSION

Recent population-based studies have described the potential effects of low ocular perfusion pressure in the development and progression of OAG. Despite conflicting reports (eg, Beijing Eye Study) and the definite limitations on reliably measuring ocular perfusion pressure in patients with glaucoma, continued interest in the measurement of this parameter and potential therapeutic intervention in patients with documented low ocular perfusion pressure and continued disease progression may be warranted. Randomized clinical trials are therefore needed to identify

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the type(s) of patients who would most benefit from and/or the therapeutic modalities most effective for this specific approach to management. □

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