

THE ROLE OF PERFUSION PRESSURE

Risk factors other than IOP play a role in the pathogenesis of glaucoma.

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The pathogenesis of glaucoma remains an active area of ophthalmic research. Both mechanical and vascular factors may contribute to glaucomatous optic neuropathy. In this article, Dr. Weinreb and colleagues discuss the role of vascular dysregulation, specifically low ocular perfusion pressure, in both the development and progression of glaucoma. The authors review blood flow physiology, the definition of ocular perfusion pressure (OPP), and epidemiological studies that have shown an association between low perfusion pressure and an increased prevalence of glaucoma. A better understanding of hemodynamic risk factors in the pathogenesis of the disease might improve patients' outcomes by expanding both diagnostic and therapeutic options.

—Sarwat Salim, MD, section editor



Elevated IOP has long been considered the primary risk factor for open-angle glaucoma (OAG). Not all patients with this form of the disease have high IOP, however, and not all those with ocular hypertension develop glaucoma, suggesting that other risk factors play a role in the pathogenesis of glaucoma.

There has been increased recognition of the influence of vascular factors on glaucoma's onset and/or progression. Evidence from epidemiologic studies has pointed to a role for OPP, specifically reduced OPP, in the pathogenesis of the disease. This association may be more pronounced in glaucoma patients who have lower IOP. Adequate perfusion with sufficient blood flow is critical to maintaining the metabolic and nutritional needs of any tissue so that it can function normally. Although the relationship between reduced OPP and glaucoma is not clear, the premise is that reduced perfusion and/or vascular dysregulation and the subsequent ischemia of the optic nerve head contribute to glaucomatous damage. This article describes evidence linking OPP to glaucoma.

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CALCULATION OF OPP

OPP is the pressure at which blood enters the eye and is defined as the difference between arterial and venous pressures in the eye. Because venous pressure in the eye approximates the IOP, IOP can be used in place of venous

pressure when calculating OPP.

Specifically, mean OPP is calculated as two-thirds of the systemic mean arterial pressure (MAP) minus the IOP. Multiplying MAP by two-thirds here accounts for the characteristic pressure difference between the brachial and ophthalmic artery in the upright position. Thus,

$$\begin{aligned} \text{Mean OPP} &= 2/3 \text{ MAP} - \text{IOP} \\ \text{MAP} &= \text{DBP} + [1/3 \times (\text{SBP} - \text{DBP})] \end{aligned}$$

where DBP is diastolic blood pressure and SBP is systolic blood pressure.

Other methods for calculating mean OPP have been described.¹

Systolic OPP (SOPP) or diastolic OPP (DOPP), defined as the difference between systolic blood pressure (BP) and IOP and between diastolic BP and IOP, respectively, are also often calculated and assessed as risk factors in the scientific literature.

Regardless of the calculation method used to define OPP, it is clearly reduced in the presence of low BP, high IOP, or both. Because BP is much greater than IOP, however, changes in BP affect OPP to a greater extent than changes in IOP. Furthermore, BP and IOP both follow circadian rhythms—from day to day, within the day (daytime/night-time), and, for BP, within each cardiac cycle. OPP is therefore highly variable and prone to fluctuation.

TABLE. STUDIES DEMONSTRATING AN ASSOCIATION OF LOW PERFUSION PRESSURE WITH OAG

Survey/Study	Design	Finding
Baltimore Eye Survey (Tielsch et al 1995) ²	Population-based prevalence survey	DOPP < 30 mm Hg associated with a six-fold increase in OAG prevalence
Egna-Neumarkt study (Bonomi et al 2000) ³	Population-based prevalence survey	DOPP < 68 mm Hg associated with a threefold increase in OAG prevalence
Proyecto VER (Quigley et al 2001) ⁴	Population-based prevalence survey	DOPP < 50 mm Hg associated with a four-fold increase in OAG prevalence
The Los Angeles Latino Eye Study (LALES; Memarzadeh et al 2010) ⁵	Population-based prevalence survey	SOPP ≤ 80 mm Hg, DOPP ≤ 40 mm Hg, or mean OPP ≤ 50 mm Hg associated with a 2.5-, 1.9-, and 3.6-fold increase, respectively, in OAG prevalence
The Barbados Eye Study (Leske et al 2008) ⁷	Population-based longitudinal study	SOPP < 101 mm Hg, DOPP < 55 mm Hg, or mean OPP < 42 mm Hg associated with a 2.6-, 3.2-, and 3.1-fold increased risk, respectively, of developing glaucoma at 4 years

Abbreviations: OAG, open-angle glaucoma; DOPP, diastolic ocular perfusion pressure; SOPP, systolic ocular perfusion pressure; OPP, ocular perfusion pressure.

EVIDENCE THAT OPP CONTRIBUTES TO GLAUCOMA

Several large epidemiological studies provide solid support for the role of reduced OPP in glaucoma (Table). The Baltimore Eye Survey examined the prevalence of ocular disease among more than 5,000 African- and European-derived residents of the city.² A sixfold increase in the prevalence of primary OAG was found in patients with a DOPP of less than 30 mm Hg compared to those whose DOPP was higher than 50 mm Hg.

Similarly, the Egna-Neumarkt study, which evaluated more than 4,000 subjects in northern Italy, found a progressive increase in the prevalence of OAG with reduced DOPP.³ In this study, individuals with a DOPP lower than 68 mm Hg had a threefold increased prevalence of OAG compared with those who had a DOPP higher than 76 mm Hg.

Proyecto VER (*ver* is Spanish for to see) was another survey of ocular disease prevalence, in this case specific to nearly 5,000 Latino individuals in Arizona.⁴ This study found a fourfold increase in OAG among subjects with a DOPP lower than 50 mm Hg compared to those with a DOPP above 80 mm Hg. Another study of Latinos, the Los Angeles Latino Eye Study (LALES), which evaluated ocular disease among more than 6,000 residents of California, reported that low SOPP, low DOPP, and low mean OPP were all associated with an increased prevalence of OAG, although very high perfusion pressures also appeared to be associated.⁵ Specifically, individuals with an SOPP of 80 mm Hg or less, a

DOPP of 40 mm Hg or lower, or a mean OPP of 50 mm Hg or less were 2.5-, 1.9- and 3.6-fold more likely, respectively, to have OAG than those considered to have normal perfusion pressures.

The Barbados Eye study was a population-based longitudinal study involving more than 3,000 Afro-Caribbean subjects.⁶ Individuals with a low baseline perfusion pressure—whether SOPP, DOPP, or mean OPP—had an increased risk of developing OAG. Specifically, those with an SOPP lower than 101 mm Hg, a DOPP below 55 mm Hg, or a mean OPP under 42 mm Hg at baseline had a 2.6-, 3.2-, and 3.1-fold increased risk, respectively, of developing glaucoma at 4 years. Furthermore, subjects with an SOPP of 98 mm Hg or less, a DOPP of 53 mm Hg or less, and a mean OPP of 40 mm Hg or less at baseline had a 2.0-, 2.1-, and 2.6-fold increased risk, respectively, of developing glaucoma at 9 years.⁷

Notably, in most studies, OPP was a better predictor of glaucoma than was IOP.

In addition to daytime variability, BP is typically lower during sleep. Some individuals experience significant dips in nocturnal MAP, and it has been hypothesized that excessive nocturnal hypotension and its secondary effect on OPP might have a disease-modifying role in many patients, particularly those whose IOP does not appear to be significantly elevated. A recent study by Charlson et al demonstrated that more pronounced nocturnal hypotension was associated with faster glaucomatous visual field progression.⁸



AT A GLANCE

- That not all patients with open-angle glaucoma have high IOP and that not all patients with ocular hypertension develop the disease suggest that other risk factors play a role in the pathogenesis of glaucoma.
- Evidence from epidemiologic studies has pointed to a role for OPP, specifically reduced OPP, in the pathogenesis of glaucoma. Although the relationship is not clear, the premise is that reduced perfusion and/or vascular dysregulation and the subsequent ischemia of the optic nerve head contribute to glaucomatous damage.

CONTROVERSIES SURROUNDING OPP AND OAG

The Rotterdam Study found no relation between OPP and incident OAG after adjustment for baseline IOP.⁹ Furthermore, investigators from Great Britain have pointed out that the concept of OPP is a problematic surrogate for true perfusion of the optic nerve, because adjustment for either IOP or for BP simply isolates the effect of the IOP or BP term.¹⁰ Subtracting IOP from BP may be an overly simplistic way of representing true ocular perfusion. The best approach to understanding how OPP relates to OAG might be to use instrumentation that would allow the dynamic visualization of blood coursing through vessels that feed the optic nerve head.

CONCLUSION

Controversies aside, current data indicate that glaucoma is more than just a disease of a single type of pressure (IOP) and that some assessment of OPP also needs to be considered when determining an individual's risk of developing glaucoma or experiencing disease progression.

Many key research questions remain. For instance, do 24-hour variations in IOP and BP—and therefore OPP—influence the onset and/or progression of glaucoma? This is a particularly interesting idea when one considers that, at night, IOP increases while the body is recumbent in more than two-thirds of individuals, whereas BP, particularly diastolic BP, typically decreases. Could nighttime perfusion pressure be a predictor of glaucoma risk? Might systemic antihypertensive treatment affect the risk of developing the disease and/or its progression? If so, could the dosing of these medications be adjusted to reduce the risk of progression? Of course, also meriting consideration are intracranial

pressure and its influence on the translaminar pressure difference.

Finally, the implications of OPP as a risk factor for glaucoma may be relevant to clinical practice. Should physicians routinely assess OPP? If OPP can be increased, will that reduce the chance of developing glaucoma in patients at risk or of glaucomatous progression in those with existing disease?

These questions should not seem abstract. A recent meta-analysis of the medical literature suggested that sufficient evidence exists to warrant a randomized clinical trial to answer them.¹¹ A new focus on addressing these potentially modifiable systemic risk factors would allow better care of glaucoma patients by increasing the options for treatment. ■

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