Ocular perfusion pressure and glaucoma: a review

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Abstract

Glaucoma is one of the leading causes of blindness globally. Increasing evidence shows that the disease is secondary to optic nerve head hypoperfusion and autonomic dysfunction. Ocular perfusion pressure, representing ocular blood flow, is a key factor that should be evaluated in the management of glaucoma. Ocular perfusion pressure is subject to influence by a myriad of factors, and its calculation has been conventionally simplified as the difference between mean arterial blood pressure and intraocular pressure. Nonetheless, the direct effect of various factors on blood pressure and intraocular pressure should not be neglected. Bearing in mind the regional prevalence of normal-tension glaucoma, we review the literature and summarize the pathophysiology of glaucoma, definition of ocular perfusion pressure, relationship between ocular perfusion pressure and glaucoma development and progression, and key factors that influence ocular perfusion pressure. We also highlight the potentials of home monitoring of ocular perfusion pressure, and promote interdisciplinary management of glaucoma.

Key words: Blood pressure; Glaucoma, open-angle; Intraocular pressure; Perfusion

Introduction

Glaucoma is characterized by progressive loss of retinal ganglion cells and their axons, resulting in characteristic optic nerve head (ONH) cupping. It is increasingly important in a globally aging population, and the irreversible nature of visual impairment brought by glaucoma poses a considerable challenge to public health, especially since it is largely asymptomatic in the chronic form. In a recent meta-analysis, Tham et al found a 3.54% global prevalence of glaucoma for the population aged 40 to 80 years. While 64.3 million patients were estimated to be affected in 2013, an exponential increase is expected, and 76.0 million and 111.8 million patients are predicted worldwide in 2020 and 2040, respectively. Asians represent 47% of those with glaucoma, with recent studies showing an age-standardized glaucoma prevalence of 3.2% and 3.6% in Singapore and Northern China, respectively.

A multitude of recent literature suggest that, apart from mechanical effects of increased intraocular pressure (IOP), ONH vascular insufficiency plays an important role in the pathogenesis of glaucomatous optic neuropathy. The Baltimore Eye Survey revealed that around 50% of patients with primary open-angle glaucoma (POAG) had an initial IOP of < 21 mm Hg at the time of diagnosis, with around 20% having normal IOP for all first 3 visits. Asians show a particular tendency for this subtype. In Korean- and Japanese-based cross-sectional epidemiological studies, 94.4% and 92% had IOP of < 21 mm Hg, respectively.

Ocular blood flow is estimated by ocular perfusion pressure (OPP), conventionally defined as the difference between mean arterial blood pressure (MAP) and IOP. The impact of OPP and its fluctuations on the maintenance of adequate ONH perfusion has been reviewed. In view of the increasingly recognized role of vascular dysregulation in glaucoma pathogenesis, the link between OPP and the development and progression of glaucoma is essential, as are the myriad factors that influence OPP, IOP, and MAP.
This review aimed to summarize the relevant literature and data regarding the pathophysiology of glaucoma, definition of OPP, relationship between OPP and the development and progression of glaucoma, as well as key factors that influence OPP.

Methods and materials

A comprehensive literature search on PubMed was performed for studies published up to October 2015 with keywords ‘ocular perfusion pressure’, ‘glaucoma’, ‘autonomic dysregulation’, ‘intraocular pressure’, ‘risk’, ‘progression’, ‘severity’, ‘circadian rhythm’, ‘body posture’, ‘anti-hypertensive medications’, and ‘anti-glaucomatous medications’. Combinations of these terms were used as well. Selected papers were then reviewed thoroughly and evidence was summarized.

Pathophysiology of glaucoma

Glaucoma is a heterogeneous group of diseases, and its pathophysiology is believed to be multifactorial. The pathogenesis of glaucoma is poorly understood, and contributory factors have not been fully characterized.

An elevated IOP plays a major role in retinal ganglion cell apoptosis, and has been well demonstrated in multi-centered, randomized controlled trials.10,11 Elevated IOP often results from alterations in aqueous humor dynamics, and the balance between production of aqueous humor by the ciliary body and its drainage is determined by 2 major independent pathways. The majority of aqueous humor drains through the conventional trabecular meshwork outflow pathway in a largely pressure-dependent fashion. Increased resistance at the juxta-canicular connective tissue and endothelial lining of Schlemm’s canal causes ocular hypertension. A proportion of aqueous humor also drains through the uveoscleral or unconventional pressure-independent pathway. Such uveoscleral flow does not depend on the level of IOP to the same extent as trabecular outflow. In patients with open-angle glaucoma (OAG), there is increased resistance to aqueous outflow through the trabecular meshwork causing IOP-induced stress and strain. This results in compression, deformation, and remodeling of the lamina cribrosa with mechanical axonal damage.12

Among glaucoma patients, around one-third to half have elevated IOP at the initial stages.6,13,14 Vascular dysregulation has been hypothesized to be involved, and is believed to be more pronounced in normal-tension glaucoma (NTG).15,16 Ocular blood flow is highly regulated to maintain temperature and nutrient homeostasis according to metabolic needs. Nonetheless, it is postulated that in a proportion of pathological eyes, dysregulation causes fluctuations in vascular supply.17 This dysregulation may occur because of an individual’s innate deficiency, inborn tendency to respond differently to environmental stimuli, or secondary to vasospastic diseases.18 Consistently unstable perfusion with wide fluctuations and repeated ischemic stress then lead to ONH injury.9,15 Consequently, OAG has been included as part of vascular dysregulation syndromes, and is associated with migraine, Raynaud’s phenomenon, obstructive sleep apnea, and autoimmune diseases.19-21 Clinicians must be particularly alert to the possibility of NTG, because IOP rise, a surrogate marker for some glaucomas, is less pronounced.

Ocular perfusion pressure

Normal functioning of tissues depends on an adequate perfusion pressure to meet metabolic needs, and is generated by the difference between MAP and venous pressure. In the eye, OPP reflects ocular blood flow, with IOP used as a substitute for venous pressure.22 Mean OPP (MOPP) is expressed as two-thirds of the difference between MAP and IOP, with the formula as: MOPP = 2/3 x [MAP - IOP]. OPP is less pronounced.23 whereas DBP stands for diastolic blood pressure and SBP for systolic blood pressure. Systolic OPP (SOPP) and diastolic OPP (DOPP) are defined as the difference between systemic systolic or diastolic blood pressure (BP) and IOP, respectively.

This may nevertheless serve as an oversimplified surrogate formula for OPP. Brachial artery pressure is used as a substitute for systemic BP in calculating ophthalmic arterial pressure, but the hydrostatic water column effect creates discrepancy in BP at ophthalmic compared with brachial arteries.24 Since the head is at a higher position, IOP should be reduced in the upright position (Figure).24 Bill and Nilsson25 have offered adjusted formulas to better correct for seated and supine positions, yet their adoption has been limited, both clinically and in research.

Similar controversy occurs for venous pressure measurement. Animal studies have demonstrated near equivalence of IOP and retinal venous pressure,27,28 but stark differences in anatomical structure limit direct application in humans. In fact, in human eyes, absence of spontaneous central retinal vein pulsations has been recorded in > 50% of glaucomatous eyes, compared with only 23.7% to 28% of healthy eyes.27,28 This suggests a venous pressure that is lower than IOP in most pathological eyes.

To overcome the shortcomings of surrogate parameters, direct measurement of OPP has been attempted via ophthalmodinamometry.29,30 It is a method of measuring BP in the ophthalmic artery accomplished by iatrogenic elevation of IOP through application of a specific amount of force on the eyeball while simultaneously observing pulsation of vessels surrounding the optic disc. The level of the artificially elevated IOP was correlated with the applied force, and conversion tables were established, and finally converted to IOP. Nonetheless, as this measurement technique was difficult, and the use of correlation tables was cumbersome and introduced potential sources of error, most ophthalmodinamometers have been abandoned in clinical practice.

Modern technologies for ocular blood flow evaluation...
Figure. Hydrostatic column effect of postural position on blood pressure and ocular perfusion pressure in (a) a normal subject in erect position with brachial blood pressure of 140/85 mm Hg, and (b) a patient with normal-tension glaucoma in supine position with brachial blood pressure of 90/45 mm Hg. In Fig b, the effect of low blood pressure on ocular perfusion pressure is illustrated.
have also been utilized in clinical ophthalmology. Since the ophthalmic artery is the main blood supply to the optic nerve, abnormalities of its blood flow may cause ischemia. Colour Doppler imaging is a technology of choice because of its low invasiveness and reliability. Deduction of arterial resistive indices are also postulated to be useful in identifying eyes that are more likely to suffer further visual field deterioration, aiding in prognostic stratification. Other methods of detection of flow and velocity in the optic nerve include laser Doppler velocimetry, scanning laser ophthalmoscopy, scanning laser Doppler flowmetry, indocyanine green angiography, and transcranial Doppler ultrasound.

**Ocular perfusion pressure and glaucoma development**

Low DOPP has been strongly associated with increased prevalence of glaucoma. In the Barbados Eye Study, low DOPP (< 55 mm Hg) was a risk factor for development of glaucoma, with a relative risk of 3.2. After 9 years of further follow-up, it was shown that individuals with the lowest 20% of DOPP were 2.2 times more likely to develop glaucoma, although baseline BP did not predict OAG risk.

In another Caucasian-based study, the Baltimore Eye Survey found a 6-fold increased OAG prevalence in subjects with low diastolic perfusion pressure (< 30 mm Hg). Similarly, the Egna-Neumarkt Study reported a 4.5% increase in glaucoma prevalence in patients with DOPP of < 50 mm Hg compared with those with DOPP of ≥ 66 mm Hg. In Proyecto VER, Quigley et al also confirmed a 4-fold increase in OAG prevalence at DOPP of < 50 mm Hg.

Thus, a low DOPP has been strongly associated with OAG prevalence in multiple population-based epidemiological studies.

On the contrary, the relationship between SOPP and prevalence of OAG is less consistent. After adjusting for OAG risk factors, the Blue Mountains Eye Study found an increased prevalence of 10% with each 10 mm Hg increase in SOPP. Yet, in the Barbados Eye Study, patients with lower SOPP (< 101.3 mm Hg) had 2.6 times increased relative risk of developing OAG. The controversial evidence associating SOPP with glaucoma prevalence leads to the postulation that low DOPP may be more important in the development of glaucoma, and is in accordance with the concept that most tissue perfusion occurs during diastole. Further data are needed to evaluate whether the atherosclerotic risk in high SBP truly contributes to vascular insufficiency of the ONH.

**Ocular perfusion pressure and glaucoma progression**

Age is a key factor in glaucoma progression. As reported in the Early Manifest Glaucoma Trial, after population-based follow-up for 8 years, older patients had an increased and faster progression than younger patients. In the Collaborative Initial Glaucoma Treatment Study, the relative risk increased by 35% for every decade, while in the Advanced Glaucoma Intervention Study, the odds of progression increased by 30% with every 5-year increase in age. It is postulated that with aging, vessels undergo atherosclerosis, resulting in increased shear stress, and compromise of capillary flow and nutrient exchange.

Since OPP is derived from IOP and BP, their respective relationship with glaucoma progression is crucial. Regarding OPP, associations between higher IOP with glaucoma progression have been consistently shown in major clinical trials in the past decades. Patients with higher mean IOP during follow-up were more likely to progress, while IOP reduction was significantly effective in delaying glaucoma progression. The Canadian Glaucoma Study found up to a 19% increase in progression per mm Hg increase in IOP, while the Advanced Glaucoma Intervention Study found a lower baseline IOP (< 18 mm Hg) to be associated with decreased visual field progression. The Early Manifest Glaucoma Trial demonstrated a 12% to 13% increased risk per mm Hg increase in IOP, and proved the significance of an initial reduction in IOP for prediction in glaucoma progression, where each mm Hg decrease in IOP from baseline was associated with an 8% decrease in hazards ratio.

Regarding BP, its circadian rhythm has to be taken into account. Due to decreased circulating catecholamines and cortisol during sleep, BP is characterized by a nocturnal ‘dip’. Approximately two-thirds of the general population exhibit this physiological phenomenon. ‘Non-dippers’ refer to patients with absent or reduced nocturnal decline, while ‘extreme / big / over-dippers’ are patients with a greater nocturnal fall than usual. Different definitions exist regarding the cut-offs for physiological nocturnal dips, varying between 5% and 10% or between 10% and 20%. The concept remains, though, that extremes of BP fluctuation are correlated with glaucoma progression. Studies that monitored ambulatory BP and visual field changes have demonstrated more marked deviation in non-physiological dippers than physiological ones. It is consistent with the association of non-physiological dippers with more cardiovascular, cerebrovascular, and systemic diseases, suggesting its role in vascular dysregulation. Recently, Lee et al also showed that NTG eyes, in particular, had significantly larger daytime and nighttime MAP and OPP variabilities in over-dippers than non-dippers.

While these studies demonstrated the roles of BP variability and IOP control in glaucoma progression, it should be noted that neither low BP nor high IOP alone can be regarded as the cause of low perfusion. NTG patients who sustain ONH damage, despite IOP being within the recognized ‘normal range’, is an archetypal illustration. Differences in individuals’ autonomic regulatory capacity may potentially explain why not all patients with reduced OPP develop glaucomatous optic neuropathy. Further analysis and association studies are needed.

**Factors that influence ocular perfusion pressure**

As mentioned, OPP is a complex variable that may be
affected by multiple factors, and neither BP nor IOP can account entirely for its regulation. A number of factors that influence BP and IOP, and thus OPP, have been studied.

**Postural changes**
Numerous studies have investigated the influence of body and head position on IOP fluctuation, and noted these to be important factors for IOP elevation at night. In general, IOP is elevated by 3 to 4 mm Hg in the supine position, and varies according to the angle of tilt and duration of exposure.\(^6^7,^6^8\) Mechanisms underlying this postural change have been hypothesized, including choroidal vascular engorgement and increase in episcleral venous pressure secondary to body fluid redistribution.\(^6^9,^7^0\) Patients with shorter axial lengths have also been noted to have a larger increase in IOP with a supine position, explained by the greater vessel engorgement expected in smaller hyperopic eyes compared with larger myopic eyes.\(^7^1,^7^2\) Of note, the magnitude of IOP elevation following postural changes is regulated by autonomic and mechanical means, and is independent of iatrogenic interventions that aim to lower IOP.\(^7^3\) This holds significance particularly for NTG patients, since IOP could rise to glaucomatous levels only when adopting a supine position during sleep, and remain within normal range during seated ophthalmology consultations.

**Diurnal rhythm**
Like BP, IOP is a parameter that demonstrates dynamic fluctuations. While studies have recorded a range of daily cycles, IOP classically peaks in the morning upon awakening, with a daily variation of 3 to 6 mm Hg.\(^7^4\) Hormonal, autonomic, and mechanical factors have all been implicated to modulate this diurnal pattern. Boyd et al\(^7^5\) observed synchronized fluctuations in the variation of plasma corticoid levels and IOP in glaucomatous and normal eyes. As mentioned previously, IOP is a function of aqueous humor drainage from the eye, and aqueous flow, too, has a distinctive reduction in flow at night compared with daytime.\(^7^6,^7^7\) Lastly, mechanical factors such as intraocular muscle tension levels, contraction of ciliary muscles, and alterations in blink pattern have also been implicated.\(^7^4\)

Owing to the complexity and multiple confounding factors in its calculation, direct investigation of diurnal patterns of OPP has been attempted. In newly diagnosed, untreated POAG patients, Quaranta et al\(^7^8,^7^9\) found early evening peaking of DOPP and an early morning DOPP trough. Costa et al\(^8^0\) noted nighttime DOPP drop in untreated POAG eyes. Sehi et al\(^8^1\) also found overall wider MOPP fluctuations in glaucomatous eyes when compared with controls, supported by Choi et al’s finding of a positive association between larger circadian MOPP fluctuations and more significant visual field defects.\(^8^2\) These findings suggest that MOPP fluctuations may be a risk factor for NTG, as reductions in OPP may lead to ocular tissue ischemia and consequent retinal ganglion cell loss.\(^8^3\)

**Oral antihypertensive medications**
From the physicians’ point of view, hypertension must be adequately controlled because it is one of the most important risk factors for cardiovascular morbidity and mortality, and the current paradigm is the tighter BP control the better. According to the 2014 American Academy of Family Physicians’ guideline, initial treatment for Asians should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker.\(^8^4\)

In glaucoma, hypertension may initially theoretically increase blood flow to the anterior optic nerve, but after a sustained duration, microvascular damage, impeded blood flow, and ischemia, will result.\(^8^5\) The Thessaloniki Eye Study,\(^8^6,^8^7\) a cross-sectional population-based study, concluded an association between aggressive antihypertensive treatment with larger cup area and higher cup-disc ratio. Individuals who reached recommended goals of DBP of < 90 mm Hg or SBP of < 140 mm Hg had a higher incidence and progression of glaucoma, while higher SBP of > 160 mm Hg was protective against progression.\(^8^6-^8^8\)

Odds ratios are significantly raised in users of systemic ACEI and CCB, with or without concurrent diuretics.\(^8^9\) This could be due to development of nocturnal hypotension as a combined effect of the antihypertensives and natural diurnal rhythm.\(^9^0,^9^2\) Lowered MAP accompanied by unaltered IOP results in reduced OPP. In addition, since arterioles and capillaries retain increased resistance, treated hypertension results in greater levels of tissue hypoxia.\(^9^3\) Cautious use of antihypertensives in patients with progressive visual field deterioration despite low IOP is advised, and should be avoided at bedtime.\(^9^2\) Systemic beta-blockers, though not recommended as first-line antihypertensive treatment, have been observed to be protective for glaucoma progression, and lower IOP significantly.\(^9^0,^9^4\)

**Topical antiglaucomatous medications**
In the management of glaucoma, even a small mean IOP reduction decreases the risk of disease progression, forming the basis for ocular hypotensive medications. IOP-lowering mechanisms vary in different classes, and efficacies also vary during the nocturnal and daytime period.\(^9^5-^9^7\)

Beta-adrenergic antagonists, such as timolol, lower diurnal IOP by reducing aqueous humor flow, but this effect on flow reduction decreases at night.\(^9^8\) Alpha-2 adrenergic agonists, such as brimonidine, have been shown to actively reduce aqueous humor production and increase uveoscleral outflow, but have a statistically significant different diurnal and nocturnal effect, possibly due to their short-acting effects and relatively weak IOP-lowering effects at trough and nighttime.\(^9^9,^1^0^0\) While these 2 medications have been reported to achieve a similar IOP reduction, a randomized multi-center clinical trial, which compared the efficacy of monotherapy with brimonidine and timolol eye drops, revealed that patients treated with brimonidine were less likely to have visual field progression.\(^1^0^1-^1^0^3\) This difference could be due to non–IOP-related effects of brimonidine, or
as a result of timolol producing greater systemic hypotension and bradycardia. Brimonidine usage, however, is limited by a relatively high rate of allergic conjunctivitis. Nevertheless, while one assumes that IOP reduction translates directly into improvement in OPP, in a small randomized controlled trial, mean 24-hour DOPP was higher than that at baseline after timolol administration, though not to statistically significant levels, while brimonidine induced a paradoxical significant decrease in mean 24-hour DOPP. Despite their favorable action in reducing IOP, the absence of a significant increase in DOPP suggests the need for more data from long-term studies before the importance of these drug-induced changes to DOPP is validated.

When compared with timolol, both prostaglandin analogs and carbonic anhydrase inhibitors increase 24-hour DOPP. Prostaglandin analogs lower IOP through the uveoscleral outflow pathway, and has been shown to have a sustained effect in lowering IOP during diurnal and nocturnal periods. Dorzolamide, a carbonic anhydrase inhibitor, maintains its efficacy during the night, but is less effective than latanoprost and timolol during the day.

As a note of caution, since topical beta-blockers can lead to reduced BP if absorbed systemically, BP and pulse rate monitoring should be advocated when these drugs are prescribed. Nasolacrimal duct occlusion and eyelid closure to enhance intraocular absorption and discourage systemic absorption can be advised. As increase in OPP is a consistent finding in prostaglandin analogs, together with its dosing convenience, tolerability, and efficacy, prostaglandin analog monotherapy may be considered as first-line therapy in OAG.

Topical CCB have also been tried in NTG management because of their vasodilatory effects. There are 2 schools of thought concerning their mechanism in glaucoma treatment are postulated: increased ONH perfusion following vasodilatation, and increased aqueous humor outflow after relaxation of trabecular meshwork cells. Nonetheless, while their effects have been confirmed in animal studies and cadaveric eyes, routine clinical application is yet to be explored.

Home monitoring of ocular perfusion pressure
Anatomical and functional deterioration can occur despite significant IOP reduction with antiglaucomatous medications, thus factors other than IOP are involved in glaucoma progression. For these reasons, OPP monitoring may be equally, if not more, important than IOP alone in determining ONH damage. Such monitoring can be performed by patients, since both parameters in the OPP calculation formula are accessible to measurement at home; home BP monitoring is easily carried out with widely available electronic manometers, while IOP can be recorded by patients using ICare (Tiolat Oy, Helsinki, Finland), a handheld tonometer that is gaining popularity due to its ease of use, and its independence from local anesthesia and slit lamp. It is based on the impact-induction principle known as rebound tonometry, and has consistently shown good correlation with Goldmann applanation tonometry. Good repeatability between practitioners has been reported, although measurement in a supine position shows slightly lower consistency.

If patients master home monitoring of BP and IOP, daily OPP can be theoretically monitored. Since ophthalmologists and physicians face a myriad of choices for ocular and systemic hypotensive therapy, home OPP monitoring will then provide clinicians with crucial data that reflect individualized treatment response and efficacy. In addition, for hypertensive patients with continual glaucoma progression despite good IOP control, 24-hour ambulatory BP monitoring may be considered as a means to identify excessive nocturnal dip that would then warrant close liaison with physicians to fine-tune BP control to avoid nocturnal optic nerve ischemia. Overall, OPP and IOP monitoring could assist in monitoring pressure fluctuations in OAG patients, and tailor the choices of local hypotensive treatment with better chronotherapeutic profile.

Conclusion
OPP has been identified as an important factor in the development and progression of glaucoma. This is particularly true in NTG, where autoregulatory dysfunctions have been implicated. Although the relationship between OPP and glaucoma has not been well documented in Asians, it is meaningful to evaluate vascular effects on the ONH considering NTG’s regional prevalence.

We evaluated proposed methods of calculation and measurement of OPP. While the accuracy of deriving OPP from the difference between MAP and IOP is inconclusive, until more advanced or convenient methods of direct measurement of OPP become available, it remains the general method. The formula offers a simple way to enhance the partnership of clinicians and patients to perform ambulatory OPP monitoring, and may assist in the evaluation of treatment efficacy and assess individual diurnal fluctuation.

Interdisciplinary treatment of hypertension and glaucoma should be emphasized. Both BP and IOP are subject to influence by multiple factors such as posture, timing, and the choice of medications. Monitoring of BP and OPP in OAG patients prescribed antihypertensives such as CCB and ACEI, and antiglaucomatous medications such as topical beta-blockers and alpha-adrenergic agonists, should be considered. Close liaison between physicians and ophthalmologists in glaucoma care should be further promoted.
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