

MAJOR REVIEW

24-hour Intraocular Pressure and Ocular Perfusion Pressure in Glaucoma

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Abstract. This review analyzes the currently available literature on circadian rhythms of intraocular pressure (IOP), blood pressure, and calculated ocular perfusion pressure (OPP) in patients with open-angle glaucoma. Although adequately powered, prospective trials are not available. The existing evidence suggests that high 24-hour IOP and OPP fluctuations can have detrimental effects in eyes with glaucoma. The currently emerging continuous IOP monitoring technologies may soon offer important contributions to the study of IOP rhythms. Once telemetric technologies become validated and widely available for clinical use, they may provide an important tool towards a better understanding of long- and short-term IOP fluctuations during a patient's daily routine. Important issues that need to be investigated further include the identification of appropriate surrogate measures of IOP and OPP fluctuation for patients unable to undergo 24-hour measurements, the determination of formulae that best describe the relationship between systemic blood pressure and IOP with OPP, and the exact clinical relevance of IOP and OPP fluctuation in individual patients. Despite the unanswered questions, a significant body of literature suggests that OPP assessment may be clinically relevant in a significant number of glaucoma patients. (*Surv Ophthalmol* 58:26–41, 2013. © 2013 Elsevier Inc. All rights reserved.)

Key words. glaucoma • circadian rhythm • intraocular pressure • blood pressure • ocular perfusion pressure

I. Physiological Considerations

The principal physiological entities that affect intraocular pressure (IOP) and its characteristics are the aqueous humor (AH) dynamics in healthy and glaucomatous eyes.

The production of AH involves two consecutive processes. First, a portion of the plasma that reaches the vascular plexus of the ciliary processes is filtered through the fenestrated capillaries into the interstitial space between the vessels and the ciliary epithelia. Next, a portion of the filtrate is actively

secreted by the ciliary epithelial cells into the posterior chamber.

In humans, these processes are affected by age, circadian rhythm, topical and systemic medications, and the presence of glaucoma.^{63,64,70,109,121} The rate of AH formation decreases with age: by 15–35% between age 20 and 80 years.^{15,30} The rate of AH production in humans is significantly lower at night,^{99,119} attributed to decreased endogenous circulating catecholamine levels, which may partly explain the decreased nocturnal efficacy of topical

beta blockers.^{5,65,68,80} Other medications affecting AH flow are α -agonists and carbonic anhydrase inhibitors. Although the efficacy of α -agonists to suppress AH production is limited at night, carbonic anhydrase inhibitors have similar efficacy throughout the 24-hour cycle.^{68,69,119} Larsson et al found that the diurnal rate of AH formation in untreated open-angle glaucoma (OAG) patients was similar to age-matched controls;⁵⁵ glaucoma patients, however, had a higher rate of AH formation at night.

A. THE CONVENTIONAL PATHWAY

The bulk of aqueous humor in human eyes drains through the conventional outflow pathway in a largely pressure-dependent fashion. This pathway comprises the inner uveal and the deeper corneoscleral parts of the trabecular meshwork, the juxtacanalicular connective tissue, the endothelial lining of Schlemm's canal, Schlemm's canal itself, the collecting tubules and aqueous veins, and the episcleral veins. The site of increased resistance in eyes with glaucoma is thought to be located at the juxtacanalicular connective tissue and the endothelial lining of Schlemm's canal as a result of composition changes in extracellular matrix components.^{14,26,32,33,42,72,74,114} Outflow facility in ocular hypertensive¹²⁰ and OAG patients is significantly lower than in age-matched controls.⁵⁵ Recent results indicate that outflow facility is decreased at night in older healthy individuals.⁶³ Additionally, studies in healthy and OAG patients have shown that outflow facility decreases with age,^{7,121} although this reduction in outflow is paralleled by an age-related reduction in aqueous formation.¹⁵

B. THE UVEOSCLERAL (UNCONVENTIONAL) PATHWAY

A significant proportion of aqueous in humans drains through the uveoscleral or unconventional pathway. This route is often referred to as pressure-independent because, at least within the normal IOP range, the uveoscleral flow does not depend on the level of IOP to the same extent as trabecular outflow.² Based on indirect measurements and estimations, this route constitutes 12–54% of total outflow in healthy human eyes.^{2,121} There is no conclusive evidence that flow through this pathway is reduced in human eyes with glaucoma. Uveoscleral outflow at night decreases as measured by tonographic outflow facility,⁶³ but these findings were not reproduced when fluorophotometric outflow facility was used for the calculations.⁶³ Uveoscleral flow decreases with age,¹²¹ which is attributed to the progressive increase of connective tissue in the aging ciliary muscle.¹¹⁵ Several medications exert

clinically relevant effects on this pathway. Prostaglandin derivatives induce an early, as well as a delayed, ocular hypotensive effect by increasing uveoscleral outflow. The former effect is thought to result from relaxation of the ciliary muscle, which augments the egress of aqueous through the ciliary body,¹⁵ whereas the later is attributed to interstitial tissue remodeling.^{73,124} Early reports¹¹ and animal experiments¹⁰ indicated that pilocarpine minimizes uveoscleral flow by increasing the ciliary muscle tone and thus obliterating intramuscular spaces; these observations, however, have not been confirmed in human studies. For example, Toris et al have shown that pilocarpine does not inhibit the increase of uveoscleral outflow induced by latanoprost.¹²² Although the interaction of pilocarpine and prostaglandin derivatives can be complex,⁴⁵ pilocarpine does not seem to adversely affect uveoscleral flow in humans and can be combined with prostaglandins.³⁸

A retrospective analysis of data from fluorophotometry studies³⁴ described new associations between parameters of aqueous dynamics in healthy eyes and those with ocular hypertension. In both groups, a significant positive correlation was found between aqueous inflow and trabecular meshwork facility, suggesting a possible autoregulatory mechanism. On the other hand, a positive correlation was found between aqueous inflow and uveoscleral outflow in controls, but not ocular hypertensives. Finally, in both groups, thicker corneas were associated with lower aqueous production and lower uveoscleral outflow. Neither the pathophysiologic basis nor the clinical significance of these findings is currently clear.

II. Circadian Blood Pressure Variation

Blood pressure (BP) is one of the numerous metabolic systems in humans that exhibit a circadian rhythm (Fig. 1).^{82,104,113} For example, Millar-Craig et al⁸² have shown that BP is lowest at around 3 AM and increases gradually during the early morning hours before waking, reaching a peak at mid-morning. The BP rise that begins before waking was not associated with physical activity. These fluctuations have been attributed to the nocturnal decrease of sympathetic activity and circulating catecholamines. Importantly, cardiovascular events such as myocardial ischemia and infarction or stroke follow a circadian pattern that has been associated with cardiovascular parameter changes.⁸⁴

Based on the magnitude of the nocturnal BP reduction, patients are often categorized as non-dippers if the nocturnal decline is small or absent

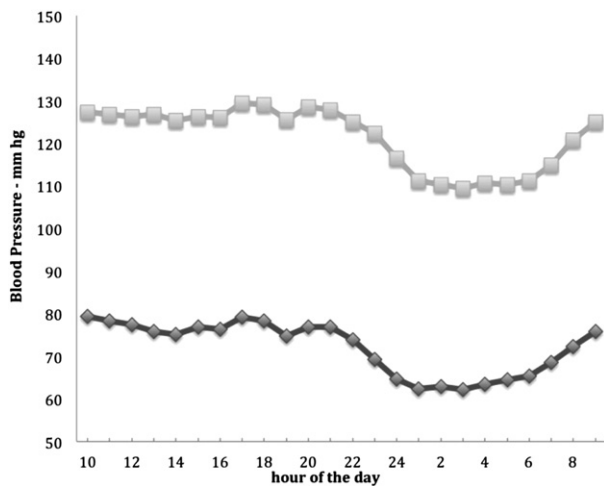


Fig. 1. Circadian mean pattern of systolic and diastolic blood pressure in 34 combined dipper and non-dipper patients. Modified from Staessen et al.¹⁰⁷

(<10%), dippers if their BP falls by 10–20%, and over-dippers if their pressure falls excessively (>20%). This classification was adopted following observations that hypertensive patients who did not exhibit a nocturnal BP drop (non-dippers) had a higher risk of vascular damage than the majority of patients with a dipping pattern.^{27,105,123} Compared with dippers, both non-dippers and over-dippers may have a suboptimal mechanism of circadian BP regulation, which is associated with a higher risk of vascular end-organ damage.^{27,28,123} Based on these findings, there is a potential relationship between glaucoma and nocturnal variations in BP.^{31,36,117} Tokanuga et al¹¹⁷ compared dippers with non-physiologic dippers (non-dippers and over-dippers) and found that non-physiologic dippers had a higher incidence of visual field progression over a 4-year period. Similarly, Graham and Drance³¹ showed that patients with greater nocturnal BP dips were more likely to have shown visual field progression despite seemingly adequate IOP control.

Studies on circadian BP curves are usually performed on inpatients. Twenty-four-hour BP measurements performed in a hospital setting may not accurately reflect a patient's usual circadian rhythm during routine daily life.⁹¹ Thus, findings from institution-based BP measurements may need to be interpreted with caution.

III. Circadian Intraocular Pressure Variation

Existing literature is divided on the importance of IOP variability as an independent factor of glaucoma development and progression. The term “fluctuation” loosely describes variation in IOP

during a given day, across days to months, or across years. We use the following terminology:

- Diurnal fluctuation: Daytime IOP variation measured during a particular day or 24-hour cycle.
- Nocturnal fluctuation: Night-time IOP variation measured during a particular 24-hour cycle.
- Circadian fluctuation: IOP variation measured during a particular 24-hour cycle.
- Short-term fluctuation: Inter-visit IOP variation measured across days to months.
- Long-term fluctuation: Inter-visit IOP variation measured across months to years.

Corneal biomechanical properties may influence circadian IOP measurements as evidence exists for their phasic alteration throughout the 24-hour cycle.⁴⁶ The observed circadian variations in parameters such as central corneal thickness or hysteresis, however, do not seem to account for the respective IOP rhythms.

An inherent problem with circadian IOP investigations is the assumption that awakening patients at night for IOP measurements does not significantly affect their endogenous IOP rhythm. To further compound the problem, patients are often asked to walk to a nearby slit-lamp and have their IOP measured in the sitting position. A newly developed 24-hour telemetric contact lens-embedded IOP sensor allows undisturbed tonometry of OAG patients at home⁷⁸ and corroborates some of the existing evidence regarding the circadian IOP pattern found in sleep laboratory studies.^{64,65,70}

A. EVIDENCE FOR THE ROLE OF SHORT-TERM IOP VARIATION IN GLAUCOMA

The rationale for IOP measurements throughout the 24-hour cycle is that IOP exhibits time-dependent variation that can reach up to 6 mm Hg over a 24-hour period in healthy eyes, even more in eyes with glaucoma.^{24,25,54,71} Therefore, a single office-hour IOP measurement offers little information regarding the IOP profile of a particular patient. This variation may be associated with optic nerve injury because, at least in principle, the continuous and excessive fluctuation of parameters in any biological system may overwhelm the homeostatic mechanisms responsible for buffering stresses and thus cause tissue damage.

Different levels of evidence regarding the role of IOP characteristics in glaucoma can be found in several reports.^{8,9,23,35,85,88,98} Large, well-designed, prospective studies on the importance of circadian IOP fluctuation are currently lacking, and the

existing literature has not produced consistent results. For example, Asrani et al³ found a strong association between diurnal fluctuations of IOP and progression in 105 eyes of 64 treated OAG patients using self-tonometry. Both the diurnal IOP and the short-term fluctuation over multiple days were significant predictors of progression. The mean office IOP had no predictive value, and the mean home IOP showed a weak association with progression. Others, however, have failed to find similar associations.⁴³ Consequently, the importance of 24-hour IOP parameters in glaucoma remains an area of controversy even among glaucoma experts.⁵⁷

B. CIRCADIAN IOP VARIATIONS IN UNTREATED HEALTHY OR GLAUCOMATOUS EYES

The traditional view is that IOP is generally higher in the morning, but recent research in both healthy and glaucomatous eyes has questioned this. Liu et al⁶⁴ performed 24-hour IOP measurements with a pneumotonometer every 2 hours in two groups of young healthy volunteers in a sleep laboratory. In the first group of 12 participants, IOP was measured in the seated position during the day and the supine position at night, whereas in the second group of 21 volunteers, IOP was determined in the supine position only. For the first group, IOP measured in the supine position at night was significantly higher than in the seated position. This could be explained, at least in part, by the posture-related increase of IOP usually attributed to the increase of episcleral venous pressure.¹¹⁰ There was, however, also a significant nocturnal IOP elevation in the group measured only in the supine position (20.0 ± 0.4 vs 21.3 ± 0.7 mm Hg, respectively; $p < 0.05$). This may indicate that a true circadian IOP rhythm, aside from posture-related changes, is responsible for the nocturnal IOP increase in these healthy adults. The same investigators also examined the IOP profile of 16 healthy volunteers who had pneumotonometer measurements performed every 2 hours for 24 hours in both the sitting and supine positions.⁶⁵ The mean IOP was significantly higher during the night both for the sitting and the supine positions. Considering the fact that aqueous production is decreased at night⁶⁵ and that changes in episcleral venous pressure cannot account for the differences in sitting 24-hour IOP values, Liu et al suggest that increased outflow resistance at night, an as yet undescribed phenomenon, may be responsible for the increase of nocturnal IOP. Furthermore, both the sitting and the supine 24-hour IOP curves were synchronous, with no difference in the magnitude of variation. Complementing previous

findings,⁶⁷ these results indicate that the nocturnal IOP elevation can also be detected in the sitting position in healthy adults. In both reports, the IOP troughs appeared at 9:30 PM, and the peaks at 5:30 AM.

These results on healthy volunteers are in contrast with data from a number of institution-based studies on untreated glaucoma patients. Konstas et al found that although peak IOP in up to 45% of untreated exfoliation glaucoma and 22.5% of untreated primary open-angle glaucoma (POAG) patients are outside office hours,⁵² the mean peak IOP in 24-hour curves is generally between 6 AM and 10 AM.^{48,49,51} Quaranta et al found similar IOP profiles.⁹²⁻⁹⁴ These discrepancies in the observed circadian IOP patterns may be explained by differences in equipment (pneumotonometer vs Perkins or Goldmann tonometers) or study samples. Age differences in particular need to be taken into account when comparing IOP curves derived from different studies. Mansouri et al⁷⁹ found that older healthy individuals in a sleep laboratory, irrespective of body posture, had a mean cosine-fitted peak IOP at around 10:20 AM, whereas the respective peak for younger healthy individuals was earlier, between 5:30 AM and 6:30 AM depending on body posture. Additionally, sleep lab conditions may create an environment that affects biological rhythms. On the other hand, contrary to hospital-based investigations, sleep laboratory studies may allow for some adjustment to the patient's usual routine of food intake or activities in the sitting or recumbent positions better simulating normal life.

For the majority of patients, 24-hour IOP phasing is impossible. Therefore, the identification of surrogate measures that may reflect nocturnal IOP profiles is desirable. Mosaed et al, in a retrospective chart review in a sleep laboratory, investigated the relationship between nocturnal and office-hours IOP.⁸³ They analyzed 24-hour IOP data obtained with pneumotonometer from 33 young healthy participants, 35 older healthy participants, and 35 untreated, older glaucoma patients. Measurements were taken every 2 hours in the sitting and supine positions during the diurnal/wake period (7 AM to 11 PM) and in the supine position during the nocturnal/sleep period. The mean supine office-hours (9:30 AM to 3:30 PM) IOP had a strong correlation with peak nocturnal IOP in older glaucoma patients ($r = 0.713$, $p < 0.001$). The correlation was weaker in older healthy participants and absent in younger healthy participants. Similarly for the sitting position, the mean office-hours IOP had a strong correlation with peak nocturnal IOP in older glaucoma patients, but the correlation was weaker in older healthy participants and absent in

younger healthy participants. Using linear regression, the authors developed two formulae:

$$\text{Peak nocturnal IOP} = 12.04 + 0.616 \\ \times \text{average office-hour sitting IOP} \quad (r^2 = 0.361)$$

$$\text{Peak nocturnal IOP} = 5.98 + 0.771 \\ \times \text{average office-hour supine IOP} \quad (r^2 = 0.508)$$

The investigators suggested that these formulae may assist clinicians predict peak nocturnal IOP values, based on office-hour supine or sitting measurements in a significant proportion of older glaucoma patients.

A recent prospective, multicenter study⁹³ also addressed the relationship between daytime sitting IOP as a surrogate to nocturnal supine IOP in untreated POAG patients (Fig. 2). The investigators used Goldmann tonometry around the 24-hour cycle and Perkins tonometry for nocturnal supine measurements. The mean diurnal sitting readings (23.3 ± 3.4 mm Hg) were higher than the mean nocturnal sitting readings (21.5 ± 4.0 mm Hg, $p < 0.001$), but similar to nocturnal supine readings (22.8 ± 4.4 mm Hg, $p = 0.07$). The peak daytime Goldmann readings, however, could not consistently predict the peak nighttime sitting or supine IOP, as only 70% of the participants were within 1.0 mm Hg of the highest daytime reading for all nighttime supine and sitting values.

C. CIRCADIAN IOP VARIATIONS IN TREATED EYES

Jonas et al⁴³ performed a retrospective chart review of 855 eyes from 458 treated patients with normal tension glaucoma (NTG), POAG, or ocular hypertension. They investigated the potential association of 24-hour IOP parameters with disease

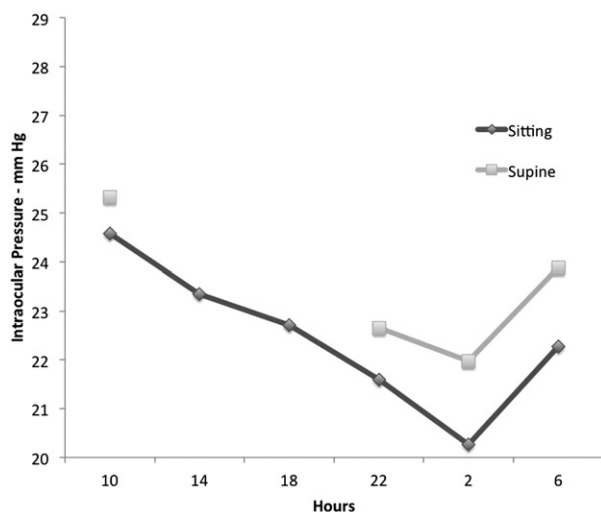


Fig. 2. 24-hour IOP results for sitting and supine position. Adapted from Quaranta et al.⁹³

progression after a mean follow-up of almost 56 months. In a multiple Cox proportional hazards analysis, for the whole study population progression was associated with age and neuroretinal rim area. For the POAG group specifically, only age ($p < 0.001$) was a significant prognostic factor, whereas in the NTG group, higher mean IOP ($p = 0.036$) and lower fluctuation ($p = 0.045$) were identified as predictors of disease progression. Participants were receiving topical medication that is known to reduce IOP levels and its fluctuation, and the effect of 24-hour IOP variation may have been blunted.

In a retrospective chart review of 29 treated POAG and NTG patients, Hughes et al³⁹ found that although the mean office IOP determined in previous visits was similar to the mean 24-hour values, the peak IOP during 24-hour monitoring was almost 5 mm Hg higher than the peak office IOP. The mean circadian IOP variation amplitude was 9.4 mm Hg. More than half of the patients had peak IOP values outside office hours, and in 14% of them the peak circadian IOP was at least 12 mm Hg higher than the office-hour peak. Importantly, circadian IOP measurements led to clinical management modifications in almost 80% of patients, with 45% of them being offered trabeculectomy. The high proportion of patients whose management was modified may reflect the fact that these patients were offered a 24-hour monitoring because they were deemed to be progressing despite apparently adequate IOP control. The authors also compared IOP values determined in an outpatient setting using Goldmann tonometry versus values measured during 24-hour phasing using Tono-pen, but argue that the use of Tono-pen in circadian measurements may in fact have underestimated IOP peaks and fluctuation, because data suggest that the Tono-pen may produce lower values than Goldmann at the higher part of the IOP spectrum.⁴

In a similar study, Barkana et al⁶ reviewed the records of 32 OAG patients who underwent Goldmann tonometry in the sitting position every two hours from 7 AM until midnight and Perkins tonometry in the supine position at 6 AM. They compared office-hours and outside office-hours values recorded on the same 24-hour IOP curve for each patient, as well as IOP values determined in up to five previous outpatient visits. All eyes were treated or had undergone laser trabeculoplasty and/or trabeculectomy. Although the authors report that the mean 24-hour IOP was 13.0 mm Hg, they do not report the mean office-hour (outpatient or inpatient) IOP. The mean peak 24-hour IOP was higher than the peak office IOP (16.8 ± 3.2 vs 14.7 ± 3.2 mm Hg, $p < 0.001$) and the mean 24-hour fluctuation was higher than the office-hours

fluctuation (6.9 ± 2.9 vs 3.8 ± 2.3 mm Hg, $p < 0.001$). The peak IOP in at least one eye was outside of office hours in almost 70% of the patients. These findings led them to immediate treatment modification in 19 of 32 patients (59%), including laser and incisional surgery. Similar to the study by Hughes et al,³⁹ these patients underwent 24-hour phasing because of progression despite apparently good office-hour IOP control. Therefore, the study identified a higher-than-expected proportion of eyes that needed treatment modification.

Nakakura et al⁸⁷ also investigated the relation between office and 24-hour IOP characteristics in 71 treated eyes of 42 POAG patients. Office IOP was derived from three outpatient measurements (9 AM to 6 PM) during a six-month period with the same treatment. Circadian measurements were obtained with a Goldmann tonometer in the sitting position at 3-hour intervals. They found no significant difference between mean office and mean 24-hour IOP (16.2 ± 4.6 vs 16.3 ± 4.9 mm Hg, respectively), but peak 24-hour IOP was recorded during office hours in only one-third of eyes. Circadian IOP fluctuation (peak minus trough 24-hour IOP) was significantly greater than office-time fluctuation (6.7 ± 2.3 vs 2.7 ± 1.7 mm Hg, respectively, $p < 0.001$), but there was no correlation between them. In these treated patients, only 6 of 71 eyes (8.5%) had a circadian curve with fluctuation less than 3 mm Hg, whereas 10 eyes (14.1%) had circadian fluctuation greater than 10 mm Hg.

The effect of topical glaucoma medication on IOP profile has been the subject of intense investigation and debate. Prostaglandins administered either in the morning or the evening have been shown to have a similar IOP lowering efficacy throughout the 24-hour cycle.^{108,109} Similarly, topical carbonic anhydrase inhibitors seem to have comparable day- and night-time efficacy.^{92,109} Most reports indicate that β -blockers have a significant, albeit reduced, night-time efficacy^{58,92,109} that may be explained by the decreased nocturnal aqueous formation.^{99,119} These findings were not confirmed in the sleep laboratory studies by Liu et al, in which topical β -blockers had a virtually non-existent nocturnal IOP-lowering effect.^{67,68} Finally, brimonidine has been found by most investigators to have a reduced nocturnal efficacy.^{69,92,109}

There is limited research on the effects of laser treatment and filtration surgery on circadian IOP rhythm.^{1,106} In a study by Lee et al,⁵⁶ there was no significant reduction in mean, peak, or range of office hour IOP or diurnal IOP after laser trabeculoplasty on 28 treated eyes of 18 glaucoma patients; significant nocturnal IOP reduction was observed, however. Kothy et al⁵³ performed selective laser

trabeculoplasty in 26 eyes of 13 patients after appropriate washout and reported that no eyes showed mean circadian IOP reduction of 20% or more. Nonetheless, the treatment resulted in a significant decrease in the amplitude of circadian IOP fluctuation.

Filtration surgery may provide greater 24-hour IOP control and smaller IOP fluctuation compared to medical therapy. Medeiros et al⁸¹ studied 60 POAG patients considered to be well-controlled who had either undergone one or more trabeculectomies and were untreated ($n = 30$) or had never had filtering surgery and were receiving a variety of topical medications ($n = 30$). They evaluated diurnal IOP curves and the response to the water drinking provocation test (WDT) for each group. The WDT was used in the 1950s and 1960s as a diagnostic aid in OAG and was later advocated as a tool to predict IOP peaks during diurnal phasing, as well as to assess the patency of filtering surgery.^{17,126} The authors found that the diurnal IOP peak was higher and the IOP fluctuation was greater in the medically treated group. The same pattern in IOP peak and fluctuation was seen after the WDT.

In a prospective observational study, Mansouri et al⁷⁷ examined the diurnal IOP curves of 20 POAG patients considered well controlled (IOP < 18 mm Hg) with latanoprost monotherapy, 20 patients after successful trabeculectomy with mitomycin C (untreated IOP < 18 mm Hg), and 20 patients after successful deep sclerectomy with collagen implant (untreated IOP < 18 mm Hg). The mean diurnal IOP of the trabeculectomy-treated patients (10.1 mm Hg), was significantly lower than the mean diurnal IOP of the other two groups (13.7 mm Hg and 15.7 mm Hg for the deep sclerectomy and the latanoprost-treated groups, respectively; $p = 0.1$ for the latanoprost vs deep sclerectomy groups). The diurnal IOP fluctuation was comparable in the three groups. They also examined the patients' IOP changes following the WDT. After the provocation, the latanoprost-treated group had significantly greater IOP elevation compared with the trabeculectomy-treated patients ($p = 0.0002$) and marginally greater elevation compared to the deep sclerectomy group ($p = 0.052$).

In another prospective observational study, Konstas et al⁵⁰ compared 30 advanced OAG patients successfully treated with trabeculectomy and 30 patients on maximal medical therapy considered to be adequately treated. They found that the patients with a successful trabeculectomy had lower mean IOP, as well as lower peak and range of IOP over 24 hours, compared with patients on maximal medical therapy. The 24-hour range of IOP was 2.3 ± 0.8 mm Hg for the surgical group and 4.8 ± 2.3

mm Hg for the medical group ($p < 0.0001$). Most IOP peaks occurred outside of usual office hours.

Despite early recommendations about the clinical usefulness of the WDT, this technique is not performed in most centers because of a number of concerns. First, its sensitivity and specificity may be low when used as a diagnostic tool.^{97,101} Secondly, the test was never standardized, so that the amount and duration of fluid intake or the IOP measurement time points vary widely. Other issues that have not been addressed in relation to the WDT is the possible need for adjustment factors depending on the patient's body weight or prior hydration status. Finally, results of the WDT in medically treated patients may be influenced by when the provocation is performed in relation to the time-dependent hypotensive effects (peak and trough efficacy) of glaucoma medications.

IV. Circadian Ocular Perfusion Pressure Variation

Lowering of the IOP is the only evidence-based treatment strategy that reduces the risk of development and progression of OAG, but the disease may progress despite adequately controlled IOP, indicating that other factors are often implicated. In particular, the role of vascular dysregulation and the interplay of ocular perfusion pressure (OPP) and blood flow may be important factors in glaucoma.^{29,37,102}

Blood flow in any organ is ensured by perfusion pressure, that is, the difference between arterial BP and venous BP (Fig. 3). Mean arterial blood pressure (MAP) can be calculated as follows:

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

where DBP and SBP are the diastolic and systolic blood pressures, respectively.

In the case of the eye, as IOP can be considered equal to venous pressure, mean ocular perfusion pressure (MOPP) is the difference between ocular MAP and IOP.³⁷ As the true MAP at the level of a patient's eye cannot be measured, MAP at the approximate level of the heart from routine brachial artery BP measurement has been used to calculate ocular MAP. Non-human primate experiments have shown that MAP at the level of the eye is approximately two-thirds of the MAP determined at the level of the brachial artery in the upright position.^{12,75} Hence, the following equation is commonly used for the calculation of MOPP from brachial artery MAP values:¹²

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

On the other hand, systolic (SOPP) and diastolic (DOPP) ocular perfusion pressures are sometimes calculated without taking into consideration the difference of MAP at the level of the eye and the level of the brachial artery:¹³

$$\text{SOPP} = \text{SBP} - \text{IOP}$$

$$\text{DOPP} = \text{DBP} - \text{IOP}$$

Some investigators have suggested MOPP be calculated according to the patient's position (sitting or supine), using the following equations:^{12,67,100}

$$\text{MOPP (sitting)} = (95/140 \times \text{MAP}) - \text{IOP}$$

$$\text{MOPP (supine)} = (115/130 \times \text{MAP}) - \text{IOP}$$

Regardless of the equations used in these calculations, the resultant values are only a surrogate for the true OPP. Furthermore, there are inevitable measurement inaccuracies during BP and IOP assessment and the scales differ (IOP values are typically in the 10–30 mm Hg range, but BP values approximate 100 mm Hg). Despite these limitations, several large studies have shown that calculated OPP is a highly relevant parameter in glaucoma.

A. THE IMPORTANCE OF OPP IN OPEN-ANGLE GLAUCOMA PREVALENCE, INCIDENCE, AND PROGRESSION: EVIDENCE FROM LARGE TRIALS

The Baltimore Eye Survey included an equal proportion of white and black participants and indicated that individuals with DOPP lower than 30 mm Hg had a race- and age-adjusted risk of POAG six times higher than individuals with DOPP higher than 50 mm Hg.¹¹⁶ In participants of African-descent studied in the Barbados Eye Study, lower DOPP was associated with higher prevalence of OAG. Persons with DOPP values below the 20th percentile were 3.3 times more likely to develop glaucoma.⁶⁰ A subsequent analysis indicated that the 9-year relative risk of incident OAG with low DOPP, low SOPP, and low MOPP was 2.1, 2.0, and 2.6, respectively.⁶² Similarly, the Egna-Neumarkt study found a close relationship between OPP and OAG in white participants: disease prevalence increased at DOPP values less than 70 mm Hg, although no relationship was detected with either SOPP or MOPP.¹³ In the Proyecto VER study, the prevalence of OAG in a Hispanic population was found to increase four-fold with lower DOPP,⁹⁶

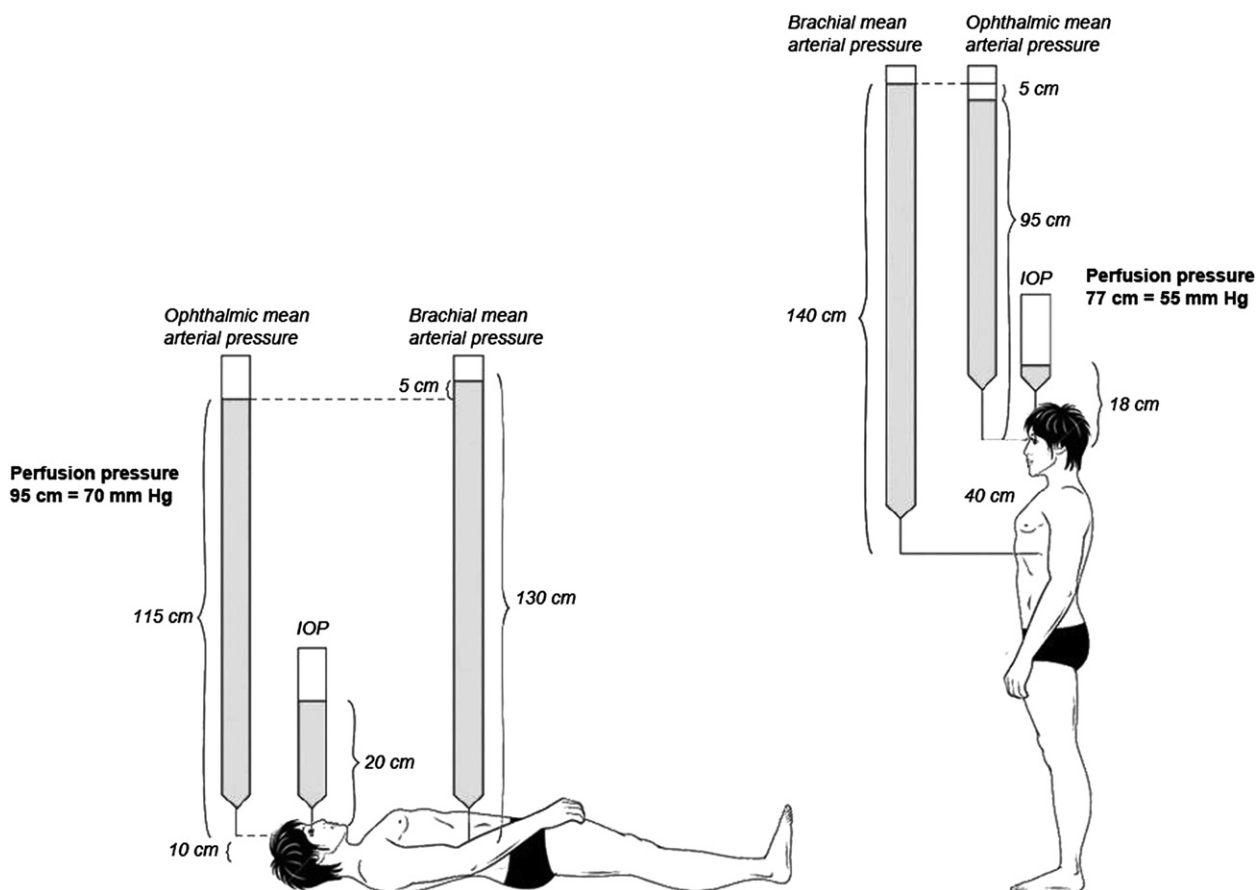


Fig. 3. Hydrostatic column effect of postural position on blood pressure and ocular perfusion pressure. Adapted from Caprioli and Coleman.¹⁶

whereas in the Rotterdam Study, low DOPP was associated with OAG in white patients with IOP > 21 mm Hg who were treated for systemic hypertension.⁴⁰ Data from the Singapore Malay Eye Study showed that OAG risk is significantly higher in ethnic Malay participants with DBP, MOPP, or DOPP in the lowest quartile than in participants in the highest quartile.¹²⁷ Interestingly, the Beijing Eye Study did not identify OPP as a risk factor for either high- or low-pressure OAG.¹²⁵ Possible reasons for such a discrepancy may result from differences in glaucoma definition, the fact that many patients were untreated, the relatively large proportion of patients with low IOP, and ethnic differences. The Early Manifest Glaucoma Trial (EMGT), a prospective randomized study that evaluated risk factors for progression in 255 white patients with OAG, indicated that low SOPP was a predictor of progression.⁶¹

Thus, population-based studies and the EMGT show that low perfusion pressure is a risk factor for glaucoma. Nonetheless, these data should be interpreted with caution, because, with the exception of the EMGT,⁶¹ the Singapore Malay Eye

Study,¹²⁷ and the incidence report of the Barbados Eye Study,⁶² the other results were not adjusted for glaucoma medication or systemic antihypertensive treatment. Furthermore, the significance of low perfusion pressure may be different in persons treated for systemic hypertension. For example, in the Rotterdam Study low DOPP was associated with increased prevalence of glaucoma only in participants treated for hypertension.⁴⁰ Additionally, in the Thessaloniki Eye Study low MOPP was associated with increased cupping and decreased rim area in non-glaucoma patients with decreased diastolic pressure if antihypertensive treatment were used.¹¹⁸ Finally, different equations have been used for the calculation of ocular perfusion pressure. The investigators who wrote the incidence report of the Barbados Eye Study⁶² and the Thessaloniki Eye Study¹¹⁸ calculated MOPP as $(2/3 \text{ MAP} - \text{IOP})$. On the contrary, the authors of the EMGT⁶¹ and the Beijing eye study¹²⁵ calculated MOPP as $(\text{MAP} - \text{IOP})$.

Because both parameters used in the calculation of OPP (i.e., BP and IOP) exhibit a circadian rhythm, OPP is bound to be affected around the

24-hour cycle. Recent investigations have examined the characteristics of 24-hour OPP in healthy volunteers and glaucoma patients, and the potential role of such variation in OAG.

B. CIRCADIAN OPP RHYTHM IN HEALTHY EYES

Liu et al examined diurnal and nocturnal levels of posture-adjusted MOPP in 16 younger and 16 older healthy adults who were not using any systemic anti-hypertensive medication.⁶⁶ In habitual body positions (i.e., sitting at day and supine at night) they found that OPP peaked at night for both younger and older volunteers. Both OPP and the diurnal-to-nocturnal increase of OPP was larger in the older group throughout the 24 hours. Kida et al measured 24-hour OPP and blood flow of the optic disc and macula in 15 younger and 15 older healthy volunteers.⁴⁷ None of the younger participants were using systemic medication, but 12 of the older volunteers were routinely using at least one systemic medication and four of them were on anti-hypertensive drugs. The authors used a scanning laser Doppler flowmeter to record blood volume, flow, and velocity in the sitting position. Older participants had significant decreases in ocular blood flow parameters at night, despite the MOPP (calculated as $95/140 \times \text{MAP} - \text{IOP}$) remaining constant throughout the 24-hour cycle. In younger volunteers, there was no change in ocular blood flow parameters despite the finding that MOPP decreased significantly at night. They concluded that aging may compromise the autoregulatory capacity normally present in healthy younger individuals that ensures adequate ocular blood flow in the face of perfusion pressure reductions. Because all measurements in this study were made in the sitting position, the effects of habitual postural changes were not taken into account.

C. CIRCADIAN OPP RHYTHM IN EYES WITH GLAUCOMA

1. Circadian OPP and Diagnosis or Severity of Glaucoma

Two studies by Quaranta et al have investigated 24-hour DOPP in newly diagnosed, untreated POAG patients who were not receiving any systemic medication.^{92,94} In both reports, the calculated DOPP peaked in the evening (either 6 PM or 10 PM), and the DOPP trough was observed at approximately 4 AM. In general, the DOPP curves correlated with the systemic BP curves.

More recently, Costa et al²⁰ examined the circadian IOP, BP, SOPP, and DOPP profiles of 24 healthy adults and 29 washed-out POAG

patients with Goldmann tonometry during wake hours (8 AM–10 PM) and Perkins tonometry during sleep hours (12 AM–6 AM). None of the participants were receiving any systemic vasoactive medication. The authors found that both groups tended to have higher IOP values at night. In POAG patients, however, the nighttime IOP increase was accompanied by a simultaneous decrease in DBP, resulting in the reduction of DOPP. Interestingly, glaucoma patients had higher SBP readings than controls at most time-points. As a result, POAG patients had higher (8 AM and 10 AM) or similar SOPP values (12 PM–6 AM) compared with controls.

Sehi et al investigated diurnal OPP profiles of 14 untreated glaucoma patients and 14 age-matched healthy volunteers¹⁰³ who were not receiving any systemic vasoactive medication. They did not specifically indicate if the same applied to the glaucoma patients. Compared to the control group, the glaucoma patients had higher IOP, lower MOPP (calculated as $2/3\text{MAP} - \text{IOP}$), and wider MOPP fluctuations. The minimum MOPP in the glaucoma group was recorded at 7 AM, at the time when IOP was at peak and BP at trough. This may suggest that inadequate autoregulatory mechanisms in glaucoma patients could prevent maintenance of adequate blood flow in the face of nighttime changes in IOP and BP.

In a study of 12 NTG patients and 12 controls not using any systemic antihypertensive medication, Okuno et al did not detect significant differences in OPP when measurements were performed at 9 AM, 3 PM, and 9 PM.⁹⁰ As nocturnal OPP was assessed relatively early at 9 PM, nighttime changes in BP and IOP may not have brought about changes in OPP.

In a retrospective analysis that included patients on systemic antihypertensive medication, Choi et al examined sitting IOP and BP over 24 hours in 132 untreated patients with NTG.¹⁸ Patients were classified into three groups based on the nocturnal MAP reduction from their daytime levels: non-dippers (<5% reduction), dippers (reduction $\geq 5\%$ but <10%), and over-dippers ($\geq 10\%$ reduction). A significant proportion of patients (41.7%) were classified as over-dippers. There were no differences among the groups in mean office IOP, IOP fluctuation, mean 24-hour MOPP (calculated as $2/3\text{MAP} - \text{IOP}$), and glaucoma severity at diagnosis, but over-dippers had significantly larger MOPP fluctuations than the other groups. In a subsequent report on 113 retrospectively reviewed NTG patients that did not exclude participants on systemic anti-hypertensive medication, Choi et al found that, in a multivariate regression model, larger circadian MOPP fluctuations were significantly associated with

decreased Humphrey Visual Field Analyzer mean deviation, increased pattern standard deviation, and increased Advanced Glaucoma Intervention Study scores.¹⁹ Besides the association with functional outcome variables, the model identified MOPP fluctuation as an important predictor of structural damage, such as a thinner retinal nerve fiber layer. They suggested that MOPP fluctuations may be a risk factor for NTG, as reductions of OPP may lead to short-term ocular tissue ischemia, followed by reperfusion injury and consequent loss of retinal ganglion cells.

2. Circadian OPP and Progression of Glaucoma

A number of investigations have found an association between increased circadian MOPP fluctuation and glaucoma progression. Sung et al published a retrospective chart review of 101 NTG patients with at least 4 years of follow-up and 24-hour sitting IOP and MOPP tracings.¹¹¹ Multivariate regression analysis identified baseline pattern standard deviation and 24-hour MOPP fluctuations as significant predictors of visual field progression. According to the model, each mm Hg increase in MOPP fluctuation was associated with approximately 27% greater hazard ratio of glaucoma progression during follow-up. The same authors subsequently published another report identifying high diurnal MOPP fluctuation as the most consistent predictive factor for central visual field progression in treated NTG patients.¹¹² In their retrospective chart review of 101 eyes, patients with high and low MOPP fluctuation had the same risk of progression in the 10–24 degrees of the visual field. The cumulative probability of visual field progression within the central 10 degrees was significantly higher for patients with higher MOPP fluctuation, however. Multivariate regression analysis found only 24-hour MOPP fluctuation to be a predictor of central visual field progression. In explaining their findings, the authors suggest that the similarity of functional defects often observed in NTG and non-arteritic ischemic optic neuropathy, and the fact that these conditions have been associated with BP decreases,³⁶ both point towards disturbances of retrobulbar hemodynamics as important contributing factors.

In a prospective study, Renard et al¹⁰⁰ used a nonlinear least-squares dual-harmonic regression analysis to examine 24-hour IOP, BP, and MOPP curves in a group of 27 NTG patients that had been appropriately washed-out of topical medications. They used two different equations for the calculation of MOPP at the sitting and the supine positions:

$$\text{MOPP}_{(\text{sitting})} = (95/140 \times \text{MAP}) - \text{IOP}$$

$$\text{MOPP}_{(\text{supine})} = (115/130 \times \text{MAP}) - \text{IOP}$$

They found a diurnal IOP peak in 54% of patients and a nocturnal peak in 36%, and no particular rhythm in 9%. Similarly, 24-hour MOPP was classified as either diurnal (58% of cases) or nocturnal (42% of cases) according to the time of the peak. The MOPP rhythm was closely related to the 24-hour BP curve, rather than the IOP curve. This implies that IOP changes hardly affect OPP changes. As the authors point out, this can be predicted by considering the relative weight of BP compared to IOP in the OPP equation. Moreover, the amplitude of MOPP was not significantly associated with glaucoma severity at inclusion.

D. THE EFFECT OF TOPICAL MEDICATIONS ON OPP RHYTHM

By influencing IOP and possibly BP profiles, medications used in the management of glaucoma are likely to affect OPP profiles. Ideally, pharmacological agents should lower IOP without adversely affecting OPP. Quaranta et al evaluated the effects of most common anti-glaucoma drugs on 24-hour DOPP⁹² in 27 newly diagnosed, untreated POAG patients given timolol 0.5% twice daily, brimonidine 0.2% twice daily, dorzolamide 2% three times daily, or latanoprost 0.005% in the evening. Diurnal sitting IOP was measured with a Goldmann tonometer and nocturnal supine IOP with a Tono-pen. Compared with baseline, all medications decreased the IOP significantly at all time points. Details of the 24-hour IOP results of this study were discussed in a previous paragraph. Timolol and brimonidine significantly lowered 24-hour mean BP; timolol caused a fairly uniform, significant decrease in both SBP and DBP at all time points, and brimonidine lowered them mainly during night hours. Compared with baseline, both dorzolamide and latanoprost significantly increased DOPP at all time points. The increase in mean circadian calculated DOPP with timolol was not statistically significant; brimonidine, however, significantly decreased mean 24-hour DOPP. In general, both latanoprost and dorzolamide had a statistically similar effect on mean 24-hour DOPP in these naive POAG patients.

In another cross-over study, Quaranta et al⁹⁴ investigated the effect of latanoprost and timolol-dorzolamide fixed combination (TDFC) on 24-hour IOP and DOPP in a group of 27 previously untreated, newly diagnosed POAG patients. Both TDFC and latanoprost significantly reduced mean 24-hour IOP, as well as IOP at individual time-points,

but TDFC had a better treatment effect over the 24-hour cycle (1.3 mm Hg, $p < 0.001$). Although TDFC lowered both systolic and diastolic 24-hour BP in a statistically significant way, DOPP was significantly increased compared with baseline because of the proportionally greater IOP reduction. Latanoprost did not induce a BP reduction but its IOP-lowering effect resulted in DOPP being increased. The observed elevation of DOPP from baseline was not significantly different for the two medications neither for the 24-hour curve (5.9 mm Hg with TDFC and 6.5 mm Hg with latanoprost, $p = 0.09$) nor for the night (5.7 mm Hg with either drug, $p = 0.970$). The increase from baseline during the day was marginally greater with latanoprost (6.8 mm Hg vs 6.0 mm Hg, $p = 0.049$).

In an open-label study, Ishibashi et al⁴¹ investigated the effect of latanoprost 0.005% on circadian sitting IOP and MOPP (calculated as $2/3\text{MAP} - \text{IOP}$) in 22 NTG patients. Latanoprost significantly lowered mean 24-hour IOP, but did not affect BP and MOPP. They suggest that the lack of MOPP change could be attributed to the relatively small IOP reduction (12.5%) observed with latanoprost in this series of low-IOP patients (13.9 mm Hg at baseline). Sample size and study design may also account for these results, which were not confirmed by a crossover, investigator-masked study⁹⁵ on the effect of latanoprost 0.005% and bimatoprost 0.03% on 24-hour IOP and BP. In 40 newly diagnosed, previously untreated NTG patients, both medications had a similar ocular hypotensive effect over the mean 24-hour IOP (16% reduction from baseline) and at each time point. Following treatment with latanoprost, the circadian DOPP manifested a small (3%), but significant, increase compared to baseline ($p = 0.031$). The increase of circadian DOPP was not significant with bimatoprost (2%, $p = 0.21$). When treatments were compared directly, the DOPP was similar in both groups for the 24-hour curve and for all time-points.

In a crossover study of 60 eyes of 30 newly diagnosed NTG patients, Costagliola et al²¹ investigated the influence of latanoprost 0.005% and timolol 0.5% on 24-hour sitting IOP, BP, and MOPP (calculated as $2/3\text{MAP} - \text{IOP}$). Although both medications significantly reduced mean circadian IOP compared to baseline, there was a difference of 1.3 mm Hg in favor of latanoprost. Both 24-hour SBP and DBP were significantly reduced after treatment with timolol, but were not changed after treatment with latanoprost. Although latanoprost significantly raised 24-hour MOPP, timolol did not affect it. Compared with the reports previously mentioned, mean IOP at baseline was higher than in other studies with NTG patients (18.4 ± 2.3 mm

Hg) and single IOP measurements reached 27 mm Hg, with eight individual readings ≥ 24 mm Hg.

V. Conclusion

The currently available literature on the circadian IOP cycle fails to answer important questions about the optimal way of characterizing IOP fluctuation and the significance of such changes in glaucoma management. Although adequately powered, prospective trials are not available, the data from smaller studies suggest that high 24-hour fluctuation may have detrimental effects in eyes with glaucoma. As 24-hour IOP measurements are impractical for the majority of patients and clinicians, the identification of appropriate surrogate measures of circadian fluctuation is important. The currently emerging continuous IOP monitoring technologies^{22,44,78} may soon offer important contributions to the study of IOP rhythms. Once telemetric technologies become validated and widely available for clinical use, they may provide an invaluable tool towards a better understanding of long- and short-term IOP fluctuations during a patient's undisturbed daily routine. Some of the obvious benefits for research and clinical purposes include the elucidation of IOP and OPP rhythms in healthy and glaucomatous eyes, the response to medication, or the evaluation of IOP characteristics as predictors of disease progression.

A significant body of literature has highlighted the importance of 24-hour OPP in patients with glaucoma. Nonetheless, the precise relevance of these findings for clinical practice is not always clear. One of the problems with the application of such results to individual patients is related to the fact that the actual validity of calculated OPP measurements is limited. For example, brachial artery pressure is used, with or without correction, instead of ophthalmic or central retinal artery pressure. Additionally, a consensus on the equation that should be used to calculate the OPP in the supine position has yet to be reached. In fact, when the data set of a study by Costa et al²⁰ was analyzed with postured-adjusted OPP formulas, rather than the commonly used single-posture formula, an increase, rather than a decrease, in night-time DOPP was found for POAG patients.⁷⁶ Despite the fact that calculated OPP has proved to be a valuable surrogate of actual OPP, sources of error may still be introduced because the validation of blood perfusion and flow models at the level of the eye is practically unattainable. Additionally, the significance of perfusion pressure across the IOP spectrum may vary. For instance, low DOPP in the Rotterdam Study was associated positively with OAG in patients with IOP > 21 mm Hg treated for systemic

hypertension, but negatively with low-tension OAG patients.⁴⁰ As discussed previously, 24-hour BP measurements (and hence OPP values) performed in a hospital setting may not closely reflect a patient's usual daily rhythm.⁹¹

Although the relevance of OPP characteristics as risk factors in glaucoma has been highlighted by several studies, an important question that remains is whether increasing the OPP in glaucoma patients would actually be beneficial. Although such a course of action seems biologically plausible, evidence concerning the potential effects of such a strategy is currently lacking. In addition, ophthalmologists need to be aware that although nocturnal hypotension ("dipping") has been associated with glaucoma progression, its existence offers significant protection against cardiovascular mortality. For example, "non-dippers" have a 20% increased risk of death from stroke, heart attack, or heart failure.^{27,28,89} Based on the notion that low BP can be detrimental for some glaucoma patients, increasing salt intake might appear appealing, but increasing BP is associated with a higher risk of cardiovascular morbidity. Additionally, caution is needed when systemic medications that have been shown to exert beneficial vasoregulatory effects in experimental settings are used in clinical practice. For example, although systemic calcium channel blockers may enhance ocular blood flow,⁵⁹ there was an increased incidence of glaucoma in patients receiving these medications in the Rotterdam Eye Study.⁸⁶

Despite the recognition of circadian IOP and OPP as important factors in OAG, future research will need to address a number of issues. Because glaucoma represents a heterogeneous group of related optic neuropathies, there may be subgroups of patients in whom vascular factors are important. Consequently, an important direction for future research would be to identify and better characterize these subgroups so that more appropriate treatment strategies are used. Additionally, it will be important to quantify the potential changes in ocular blood flow resulting from changes in OPP. On the other hand, it has been shown that OPP and its circadian rhythm is influenced by the BP and the IOP rhythms. However, the influence of BP on intracranial pressure and its fluctuation, and the potential significance of such changes on the translaminal pressure, remains to be determined. This issue is further complicated by the effects of systemic and topical medication on IOP, BP, and intracranial pressure.

Although more research is needed to refine our current understanding of the role of perfusion pressure and its circadian fluctuation in glaucoma, an

appreciable body of evidence indicates that the introduction of OPP evaluation in clinical management may be valuable in a significant number of patients.

VI. Method of Literature Search

The Medline database was used for the literature search of this review. Although every effort was made to use the most recent references possible, articles irrespective of the year of publication were used if deemed appropriate. The key words searched included: *intraocular pressure, ocular perfusion pressure, glaucoma, circadian fluctuation, diurnal rhythm, risk factors*. Combinations of these terms with appropriate boolean operators were also used. After retrieving relevant articles using these key words, a search was conducted through the literature cited in these articles and additional papers were identified. Abstracts of papers in languages other than English were surveyed, too. Medical Subject Headings (MeSH) searches were also performed. Case reports and abstracts from meeting presentations were not used.

VII. Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Outline

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