



24-hour IOP fluctuation: myth or reality?

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Abstract

Existing literature is divided on the importance of short-term intraocular pressure fluctuation as an independent factor for glaucoma development and progression. In this paper we present evidences in favor of and against the value of 24-hour intraocular pressure fluctuation in the evaluation and prognosis of patients with glaucoma. Potential directions for future studies and the role of new instruments for continuous intraocular pressure monitoring will be presented.

Intraocular pressure (IOP) is an important factor in diagnosing and managing glaucoma. Studies suggest that IOP tends to fluctuate throughout the day and over longer intervals.¹⁻⁴ Although mean IOP is known to correlate with glaucoma progression,⁵⁻⁸ actually no conclusive evidence can be drawn about IOP fluctuations.

The rationale for IOP measurements throughout the 24-hour cycle is that IOP exhibits time-dependent variation that can reach up to 6 mmHg over a 24-hour period in healthy eyes, even more in eyes with glaucoma.⁹⁻¹² Therefore, a single office-hour IOP measurement offers little information regarding the IOP profile of a patient. IOP variation could 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.

The traditional view is that IOP is generally higher in the morning. Konstas *et al.* found that although peak IOPs in up to 45% of untreated exfoliation glaucoma and 22.5% of untreated primary open-angle glaucoma (POAG) patients are outside office hours,¹³ mean peak IOP in 24-hour curves is generally between 6 AM and 10

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AM.¹⁴⁻¹⁶ Quaranta *et al.* found similar IOP profiles (Fig. 1),¹⁷⁻¹⁹ but other authors did not.²⁰⁻²² Discrepancies in the observed circadian IOP patterns among studies may be explained by differences in equipment (pneumotonometer vs Perkins or Goldmann tonometers) or study samples. The diagnosis of glaucoma and the use of topical IOP-lowering medication could per se influence 24-hour IOP rhythms. Moreover, age differences need to be taken into account when comparing IOP curves derived from different studies. Mansouri *et al.*²³ 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. Sleep lab conditions may also create an environment that affects biological rhythms. 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.

Different levels of evidence regarding the role of IOP characteristics in glaucoma can be found in several reports.²⁴⁻³⁰ Large, well-designed, prospective studies on the importance of circadian IOP fluctuation are currently lacking, and the existing literature has not produced consistent results. Moreover, actually there is no consensus about the way to define short-term IOP fluctuation: while it's generally defined as the difference between peak and trough,³ standard deviation (SD) of measurements has also been advocated.³¹

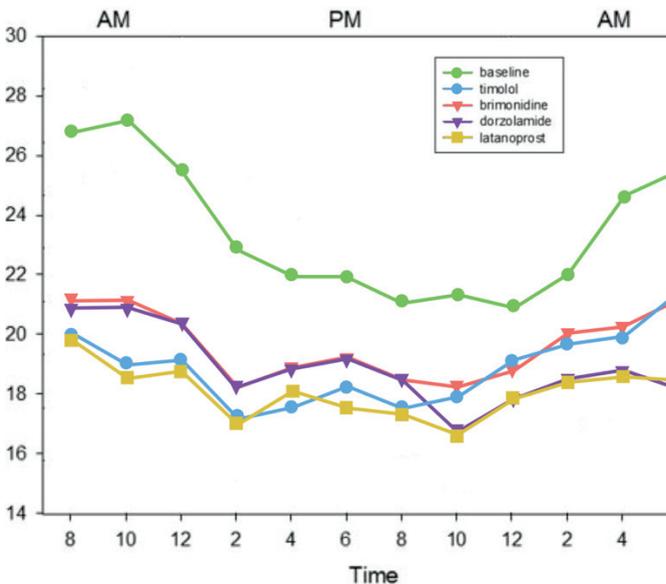


Fig. 1. 24-hour IOP profiles in treated POAG patients. (Adapted from Quaranta *et al.*¹⁷)

Several reports found an increased short-term IOP fluctuation in patients affected by glaucoma than in controls, prevalently during office-hour.³²⁻³⁴ Saccà *et al.* found that patients affected by POAG had a greater relative daily fluctuation (between -7 and +9.6%) than patients with normal-tension glaucoma (NTG, between -4.7 and +6.4%) or healthy eyes (between -3.4% and +6.9%).³⁵ On the other hand, following a cohort of 29 patients affected by ocular hypertension (OHT) for five years, Thomas *et al.* found that mean daily IOP fluctuation was 8.6 mmHg in patients progressed to POAG (n = 4), compared to 5.4 mmHg in patients not progressed.³⁶ In agreement with these results, Asrani *et al.* showed a strong association between diurnal fluctuation of IOP and disease progression in 105 eyes of 64 treated POAG patients using self-tonometry.³⁷ 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. Indeed, this study was largely criticized, due to the use of self-tonometry and no stringent criteria for visual field progression evaluation. Moreover, an abnormally high rate of visual field progression was found.

In the Handan study, 47 Chinese patients affected by POAG underwent a 24-hour IOP curve, before starting any medication.³⁸ Mean IOP fluctuation was 6.0 ± 2.2 mmHg (range, 2-11 mmHg), and 72% of the patients had IOP fluctuation ≥ 5 mmHg. No correlation was found between 24-hour IOP fluctuation and Humphrey mean deviation (MD) ($r = -0.166$, $P = 0.32$). Interestingly, in patients with unilateral POAG, Authors found no difference in mean 24-hour IOP, peak IOP, trough IOP, or IOP fluctuation when comparing the glaucomatous eye with the nonglaucomatous eye ($P > 0.05$). Results from this study should be interpreted with caution, taking into account that all patients enrolled were from oriental ethnicity and that over 90% of subjects from Handan had IOP below the cut-off of 21 mmHg.

Jonas *et al.*³⁹ performed a retrospective chart review of 855 eyes from 458 treated patients with NTG, POAG, or OHT. They investigated the potential correlation between 24-hour IOP parameters and progression of the disease, after a mean follow-up time of 55.6 months (range 5.4–124.9 months). In a multiple Cox proportional hazards model, progression of the disease 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 recent study by Fogagnolo *et al.*, 52 patients affected by POAG under topical therapy were followed-up for two years, after a 24-hour IOP baseline curve.³¹ Authors registered visual field progression endpoint and investigated baseline IOP characteristics correlated with visual field progression. Regarding 24-hour IOP characteristics, only IOP peak was correlated to visual field progression, while 24-hour IOP fluctuation was not an independent risk factor. Indeed, 24-hour mean, peak

and fluctuation were associated with each other and a strong correlation was found between mean and peak IOP, and between fluctuation and peak IOP.

Twenty-four-hour IOP fluctuation could be a risk factor for glaucoma patients with low IOP and could influence ocular perfusion pressure. In a small cohort of 33 patients affected by NTG, Sakata *et al.* found that 24-hour IOP fluctuation was negatively correlated to visual field MD at baseline.⁴⁰ However, Choi *et al.* found opposite results in a retrospective study on 113 patients affected by NTG.⁴¹ In this study, no correlation was found at baseline between 24-hour IOP fluctuation, visual field functional variables (MD and pattern standard deviation (PSD)) and anatomical variables (scanning laser polarimetry, GDX-VCC). Only fluctuation of mean ocular perfusion pressure (MOPP) was significantly correlated with decreased MD, increased PSD, and increased Advanced Glaucoma Intervention Study scores. Besides the correlation with functional outcome variables, the model identified MOPP fluctuation as an important predictor of structural damage, such as a thinner retinal nerve fiber layer. Similarly, Sung *et al.* published a retrospective chart review of 101 NTG patients with at least four years of follow-up and 24-hour sitting IOP and MOPP tracings.⁴² Multivariate regression analysis identified baseline PSD and 24-hour MOPP fluctuations as significant predictors of visual field progression, but no correlation between VF progression and either 24-hour or follow-up IOP fluctuation was found. According to the model, each mmHg increase in MOPP fluctuation was associated with approximately 27% greater hazard ratio of glaucoma progression during follow-up.

As a result of all these studies, no conclusive evidences about the role of short-term IOP fluctuation in glaucoma can be drawn. Moreover, other points remain to be addressed. While 24-h IOP monitoring may provide the most accurate measurements, it is often limited by expense and doubts persist about stability of IOP patterns and IOP fluctuation from one day to the next, or between fellow eyes. Realini *et al.* found fair to good agreement of IOP values at each time-point in treated POAG patients who underwent two daytime IOP curves, one week apart (intraclass correlation coefficients (ICCS) ranging from 0.45 to 0.71 in right eyes and from 0.51 to 0.71 in left eyes).³⁰ However, poor agreement was found when IOP changes over time periods were considered (e.g., the change in IOP from 8 AM to 10 AM on visit 1 compared with the change in IOP from 8 AM to 10 AM on visit 2), with ICCS coefficients ranging from -0.08 to 0.38 in right eyes and from -0.11 to 0.36 in left eyes. These results show that IOP data collected on a single day could inadequately characterize diurnal or 24-hour IOP variability over time, making IOP curve repetition a new task to explore.

Another 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 could allow undisturbed tonometry of glaucoma patients at home⁴³ and may corroborate some of the existing evidence regarding the circadian IOP pattern found in sleep laboratory studies.²⁰⁻²² However, data provided by this instrument are not in mmHg and do not correlate with IOP values in mmHg.

In conclusion, further research is needed to establish the role of 24-hour IOP fluctuation in glaucoma, and to understand if 24-hour IOP fluctuation can influence our therapeutic decisions. Since current data suggest that repeatability of IOP change over time is uniformly poor, it's important to repeat diurnal IOP recordings in case a patient continues to deteriorate, in spite of an adequate diurnal IOP control, and in all patients with advanced disease. IOP is not a static number, but tends to fluctuate throughout the 24 hours. Mean IOP is a strong predictor of glaucomatous damage. A desired therapeutic target is therefore a uniform reduction of IOP throughout the 24 hours. A reliable method of continuous IOP measurement would be desirable, making 24-hour IOP phasing easier and opening new pathways for research.

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