

Latent Asymmetric Intraocular Pressure as a Predictor of Visual Field Defects

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Objective: To investigate the association of latent asymmetric intraocular pressure (IOP) (IOP asymmetry between fellow eyes when patients were in the supine position but not when sitting) with visual field (VF) defects in patients with open-angle glaucoma.

Methods: Fifty-three patients with open-angle glaucoma, who were receiving the same topical medication in both eyes, were enrolled and were housed in a sleep laboratory for 24 hours. Intraocular pressures were measured when the patients with open-angle glaucoma were in the supine position or were sitting. A group of patients with latent asymmetric IOP was identified. Intraocular pressure asymmetry, monocular diurnal IOP fluctuation, and VF indexes were compared between the groups with and without latent asymmetric IOP.

Results: Among the study population, 16 patients had latent asymmetric IOP. Compared with fellow eyes, their hypertensive eyes demonstrated greater IOP fluctuations in the sitting and supine positions and had more aggressive VF defects. In addition, the eyes in patients having latent symmetric IOP showed significantly greater diurnal IOP fluctuations in the sitting and supine positions and more severe VF defects compared with the eyes in patients having symmetric sitting and supine position IOPs.

Conclusions: Patients with latent asymmetric IOP are at increased risk of VF deterioration. Latent asymmetric IOP may be a predictor of glaucomatous VF defects. Further investigation in a larger, more diverse group of patients is needed to assess the diagnostic implications of latent asymmetric IOP relative to glaucoma therapy.

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FOR SEVERAL DECADES, OPHTHALMOLOGISTS have recommended the lowering of intraocular pressure (IOP) to prevent further visual field (VF) deterioration in patients with glaucoma.¹⁻³ However, substantially lowering IOP does not always prevent progression,^{4,5} and many clinicians are interested in identifying other risk factors for glaucoma progression. Diurnal IOP fluctuation has been reported to be an important factor related to VF deterioration.⁶⁻⁹ However, other studies¹⁰⁻¹² have failed to demonstrate that large IOP fluctuation is an independent risk factor. Intraocular pressure asymmetry between fellow eyes has been identified as another risk factor for VF progression in patients with glaucoma, as well as a sign of undiagnosed glaucoma.¹³⁻¹⁶

Recent glaucoma studies¹⁷⁻²¹ have focused on diurnal IOP fluctuation. The precise patterns and characteristics of diurnal IOP fluctuation have not been well studied in patients with glaucoma, especially among those with asymmetric IOP.

In this article, we describe a group of patients who have IOP asymmetry while in the supine position but not while sitting. We refer to this unique pattern as la-

tent asymmetric IOP. Undiagnosed in routine clinical settings, latent asymmetric IOP places the patient at increased risk of glaucomatous damage. We investigated postural differences in IOP asymmetry, diurnal IOP fluctuation, and VF indexes in patients with medically controlled open-angle glaucoma (OAG). We evaluated the association between latent asymmetric IOP and asymmetric VF defects.

METHODS

After obtaining approval of our study by the institutional review board of Yonsei University College of Medicine, 70 consecutive patients who had bilateral well-controlled OAG were enrolled in the study. Of these, 53 patients receiving the same topical medication in fellow eyes were identified. Participants provided written informed consent, and all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the study. The subjects were housed in a sleep laboratory for 24 hours (from noon until noon of the next day). Intraocular pressures were measured every 2 hours when the patient was sitting (Goldmann applanation tonometer; Haag Streit, Koeniz, Switzerland) and when the patient was in the supine position (TonoPen XL; Mentor O & O Inc, Santa Barbara, California). Supine

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IOP was measured for the entire 24-hour period, while sitting IOP was not measured between 2:00 and 4:00 AM. The patients sat for 5 minutes before the sitting IOP measurements were obtained and then laid down for 5 minutes before the supine IOP measurements were taken. During sleeping hours, the patients were awakened if necessary, and the supine IOP was measured in dim light. Measurements were always obtained in the right eye first, and 3 IOP measurements were taken per eye. Intraocular pressure data in this article represent the mean values of these 3 measurements.

All patients were examined using standard automated perimetry (Humphrey Field Analyzer II, 30-2 Swedish interactive threshold algorithm standard strategy; Carl Zeiss Meditec Inc, Dublin, California). Tests were always performed in the right eye first. The perimetric results were regarded as reliable if there were less than 20% fixation losses and less than 15% false-positive and false-negative responses. If the indexes met these reliability criteria, the first VF was analyzed. If not, a second VF test was performed. Central corneal thickness (CCT) was measured using ultrasonic pachymetry (DGH-1000; DGH Technology Inc, Frazer, Pennsylvania).

At each time point, IOP asymmetry between the more hypertensive (IOP_H) eye and the less hypertensive (IOP_L) eye was calculated for the sitting and supine positions as follows: IOP asymmetry = IOP_H eye minus IOP_L eye. Among the calculated IOP asymmetry values, the highest value during 24 hours was defined as the peak IOP asymmetry. Intraocular pressure fluctuation for each eye was derived by subtracting the highest IOP value from the lowest IOP value obtained for that eye regardless of measurement time.

For the sitting position, any subject having an asymmetric IOP of more than 3 mm Hg at any time during the 24-hour study

period was defined as having asymmetric sitting IOP. For the supine position, the cutoff value for asymmetric IOP was set at 5 mm Hg. In patients found to have symmetric sitting IOP, IOP symmetry was evaluated in the supine position using the same cutoff values (**Figure 1**).

Symmetric IOP in the sitting position concurrent with asymmetry in the supine position was defined as latent asymmetric IOP. To evaluate the effect of latent asymmetric IOP, we compared IOP fluctuations and VF indexes of IOP_H and IOP_L eyes between study groups.

Statistical comparisons between study groups were conducted using Mann-Whitney test, Kruskal-Wallis test, Pearson product moment correlation coefficient, and multiple backward regression analysis. $P < .05$ was considered statistically significant. Statistical analysis was performed using commercially available software (MedCalc for Windows, version 9.3.0.0; MedCalc Software, Mariakerke, Belgium).

RESULTS

Patient demographics are summarized in **Table 1**. No significant differences were noted among the study groups for age, sex, CCT, diagnosis, or medication use. Central corneal thickness was unrelated to IOP fluctuation in the sitting (Pearson product moment correlation coefficient, 0.081; $P = .54$) and supine (Pearson product moment correlation coefficient, 0.140; $P = .28$) positions. Sitting IOP symmetry was observed in 42 patients (79%). Of these 42 patients, 16 were found to have asymmetric supine IOP and were referred to as having latent asymmetric IOP.

The patient cohort was subdivided based on the presence of symmetric vs asymmetric IOP in the sitting position. Intraocular pressure variables and VF indexes were then compared between the groups (**Table 2**).

Regardless of the symmetry or asymmetry of sitting IOP, all participants had similar peak supine IOP asymmetry, sitting and supine IOP fluctuations, and VF indexes. Diurnal IOP fluctuation and IOP asymmetry curves in both positions are shown in **Figure 2**. There was a tendency for supine IOPs to be higher than sitting IOPs.

To investigate the significance of the finding of latent asymmetric IOP, we further analyzed IOP fluctuations and VF indexes in the symmetric sitting IOP group (**Figure 3** and **Table 3**). Among these patients, there was a trend for greater IOP fluctuations in the supine position compared with the sitting position ($P < .001$ for all). Compared with patients with bipostural symmetric IOP, pa-

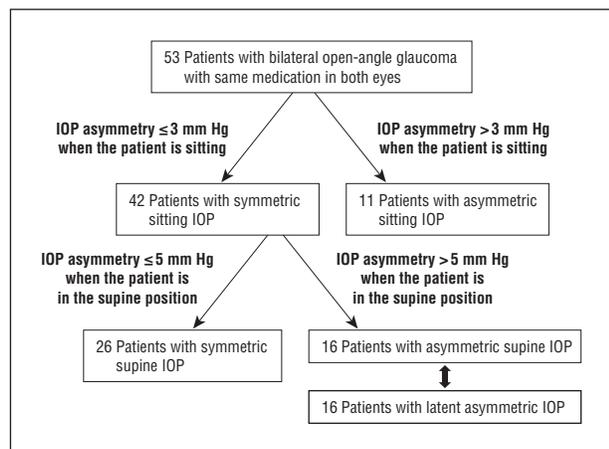


Figure 1. Diagram of the study design. IOP indicates intraocular pressure.

Table 1. Patient Demographics

Variable	Symmetric Sitting IOP Group (n=42)		Asymmetric Sitting IOP Group (n=11)		P Value
	Symmetric Supine IOP (n=26)	Asymmetric Supine IOP (n=16)	Symmetric Supine IOP (n=5)	Asymmetric Supine IOP (n=6)	
Age, mean (SD), y	47.27 (14.18)	46.69 (10.56)	41.80 (13.44)	43.83 (16.90)	.77
Male-female ratio	12:14	5:11	3:2	1:5	...
Normal-tension glaucoma–primary open-angle glaucoma diagnosis ratio	16:10	10:6	2:3	2:4	...
Central corneal thickness, mean (SD), μm	545.32 (35.53)	551.55 (28.64)	539.00 (58.99)	546.00 (20.41)	.93
Use of antiglaucoma eyedrops, mean (SD), No.	1.34 (0.69)	1.50 (0.63)	1.60 (0.89)	1.83 (0.75)	.35

Abbreviations: IOP, intraocular pressure; ellipses, not applicable.

Table 2. Intraocular Pressure (IOP) Variables and Visual Field (VF) Indexes According to the Presence of Sitting IOP Symmetry or Asymmetry

Variable	Mean (SD)		P Value
	Symmetric Sitting IOP Group (n=42)	Asymmetric Sitting IOP Group (n=11)	
IOP, mm Hg			
Sitting asymmetry			
IOP _H eye	13.37 (2.41)	14.35 (3.43)	.005 ^a
IOP _L eye	12.84 (2.31)	11.57 (4.37)	.004 ^a
Peak IOP asymmetry	1.52 (0.51)	4.45 (2.34)	<.001 ^a
Supine asymmetry			
IOP _H eye	17.12 (3.27)	17.58 (3.73)	.20
IOP _L eye	16.95 (3.21)	15.58 (4.69)	.002 ^a
Peak IOP asymmetry	4.33 (1.91)	5.55 (3.45)	.34
Sitting fluctuation			
IOP _H eye	3.21 (1.38)	4.00 (2.45)	.59
IOP _L eye	3.02 (1.07)	4.18 (3.06)	.44
Supine fluctuation			
IOP _H eye	6.95 (2.49)	8.36 (3.88)	.42
IOP _L eye	6.81 (2.55)	7.36 (3.67)	.76
VF, dB			
Mean deviation	-8.10 (8.45)	-7.43 (7.68)	.82
Pattern standard deviation	5.96 (4.53)	6.16 (4.79)	.97

Abbreviations: IOP_H, more hypertensive eye; IOP_L, less hypertensive eye.
^a $P < .05$.

tients in the latent asymmetric IOP group had greater IOP_H eye fluctuations in the sitting and supine positions ($P = .02$ for sitting and $P = .001$ for supine). Furthermore, the mean deviation and pattern standard deviation scores indicated worse VF deterioration in the IOP_H eyes ($P = .03$ for the mean deviation and $P = .04$ for the pattern standard deviation). Moreover, both VF indexes demonstrated worse values for the IOP_H eyes vs the IOP_L eyes in the latent asymmetric IOP group ($P < .001$ for both).

To evaluate whether the presence of latent asymmetric IOP may be an independent risk factor for worse VF deterioration in patients with glaucoma, multiple backward regression analysis was performed. The mean deviation of VF deterioration was significantly affected by sex ($\beta = 0.611$, $P < .001$), age ($\beta = -0.461$, $P < .001$), and latent asymmetric IOP ($\beta = 0.306$, $P = .003$) but not by CCT ($\beta = 0.109$, $P = .29$), type of glaucoma ($\beta = -0.006$, $P = .96$), number of medications used ($\beta = 0.103$, $P = .47$), IOP_H or IOP_L eye ($\beta = -0.024$, $P = .80$), mean sitting IOP ($\beta = 0.107$, $P = .90$), mean supine IOP ($\beta = 0.233$, $P = .10$), fluctuation of sitting IOP ($\beta = 0.189$, $P = .13$), or fluctuation of supine IOP ($\beta = 0.158$, $P = .14$). The regression equation was as follows: mean deviation = $-14.560 + (10.781 \times \text{sex}) - (0.267 \times \text{age}) + (5.281 \times \text{latent asymmetric IOP})$ (adjusted $R^2 = 0.67$, $F = 25.93$; $P < .001$).

COMMENT

Asymmetric IOP between fellow eyes has been implicated not only as a sign of undiagnosed OAG but also as an important risk factor for VF deterioration in patients with glaucoma.¹³⁻¹⁶ A 2006 report by Levine et al²² based

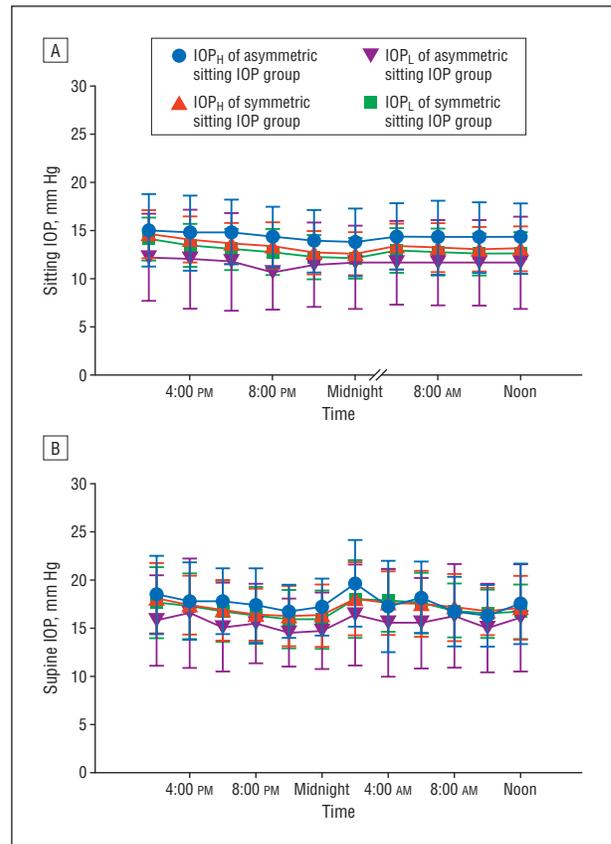


Figure 2. Diurnal intraocular pressure (IOP) fluctuation curves when the patient is sitting (A) and when the patient is in the supine position (B) according to the presence of sitting IOP symmetry or asymmetry. IOP_H indicates more hypertensive eye; IOP_L, less hypertensive eye; whiskers, SDs.

on data from the Ocular Hypertension Treatment Study found a significant association between VF defects and IOP asymmetry. Conflicting evidence exists. In the Low-Pressure Glaucoma Treatment Study, Greenfield et al²³ concluded that IOP asymmetry was unrelated to VF asymmetry. Gugleta et al²⁴ found a negative correlation between retinal nerve fiber layer thickness and IOP asymmetry. These data regarding asymmetric IOP as an independent risk factor for asymmetric glaucomatous damage are difficult to compare because subject selection criteria, statistical analyses, and methods of VF documentation and retinal nerve fiber layer thickness measurements differ among studies.

In the present study, the finding of latent asymmetric IOP demonstrated statistical significance for several noteworthy variables. Latent asymmetric IOP was identified in patients with symmetrically equal IOP between fellow eyes when the patient was sitting but with asymmetric IOP when the patient was in the supine position.

In latent asymmetric IOP, the IOP_H eye seems to have greater diurnal fluctuation and, probably as a consequence, worse VF deterioration compared with the IOP_L eye (Table 3). Greater IOP fluctuation is observed when the patient was sitting and when he or she was in the supine position. This trend was more pronounced when the IOP_H eye in the latent asymmetric IOP group was compared with any eye in the bipostural symmetric IOP group. Visual field indexes showed differences of 6.38 dB for the

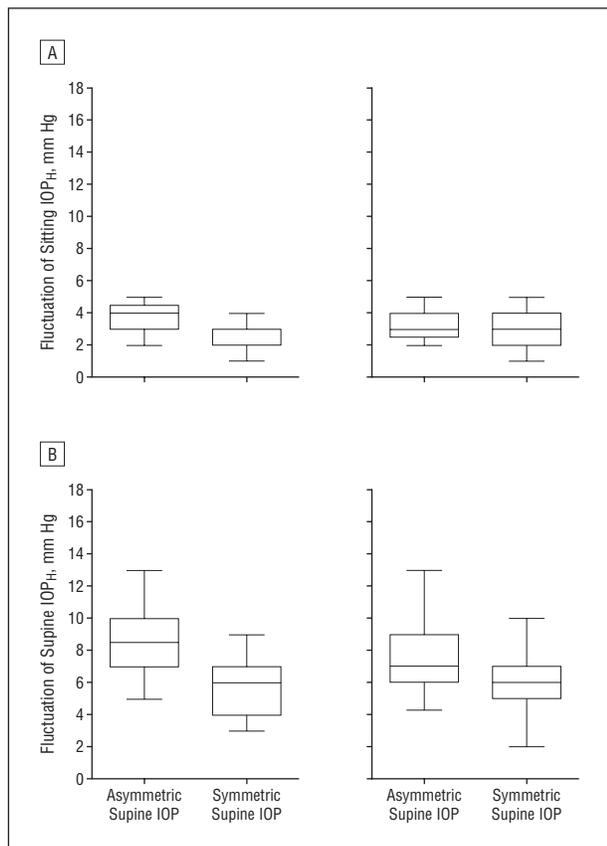


Figure 3. Intraocular pressure (IOP) fluctuations when the patient is sitting (A) and when the patient is in the supine position (B) according to the presence of supine IOP symmetry or asymmetry among patients with symmetric sitting IOP. IOP_H indicates more hypertensive eye; whiskers, SDs; line in the box, the median.

mean deviation and 1.84 dB for the pattern SD between fellow eyes in the latent asymmetric IOP group ($P < .001$ for both). The IOP_H eyes in the latent asymmetric IOP group had worse VF indexes (6.78 dB for the mean deviation [$P = .03$] and 3.64 dB for the pattern SD [$P = .04$]) compared with those in the bipostural symmetric IOP group. As described in the “Methods” section, IOP_H and IOP_L eyes were defined at each time point. Some patients in the symmetric IOP group demonstrated flip-flop IOP patterns, but the primary results were unaffected. Based on multiple regression analysis, the presence of latent asymmetric IOP may be an independent risk factor for worse VF deterioration in patients with glaucoma.

Latent asymmetric IOP is undetectable in routine clinical settings. Patients with latent asymmetric IOP are at increased risk of glaucomatous damage. For ophthalmologists, such patients represent diagnostic and management challenges relative not only to asymmetrically advanced glaucoma but also to early glaucoma and even to ocular hypertension.

The cause of latent asymmetric IOP is unknown. The most likely mechanism for postural IOP differences between fellow eyes is an incompetent IOP autoregulating system. An impaired autoregulating system has been reported to be associated with the pathogenesis of glaucoma, especially normal-tension glaucoma.²⁵⁻²⁷ This dam-

Table 3. Diurnal Fluctuations of Intraocular Pressure (IOP) Variables and Visual Field (VF) Indexes Among Patients With Symmetric Sitting IOP

Variable	Mean (SD)		P Value
	Symmetric Sitting and Supine IOP Group (n=26)	Latent Asymmetric IOP Group (n=16)	
IOP, mm Hg			
Sitting fluctuation			
IOP _H eye	2.92 (1.13)	3.69 (1.01)	.02 ^a
IOP _L eye	2.92 (1.16)	3.19 (0.91)	.45
Supine fluctuation			
IOP _H eye	6.00 (2.23)	8.50 (2.13)	.001 ^a
IOP _L eye	6.12 (1.88)	7.94 (3.11)	.07
VF, dB			
Mean deviation			
IOP _H eye	-2.84 (2.32)	-9.62 (9.17)	.03 ^a
IOP _L eye	-3.08 (2.38)	-3.24 (1.55)	.60
Pattern standard deviation			
IOP _H eye	2.55 (1.17)	6.19 (4.26)	.04 ^a
IOP _L eye	3.16 (2.53)	4.35 (2.44)	.20

Abbreviations: IOP_H, more hypertensive eye; IOP_L, less hypertensive eye.
^a $P < .05$.

aged autoregulating system is probably responsible for latent asymmetric IOP, which can pass undetected at a routine office visit, and leads to structural damage of the optic nerve head and to VF loss.

Medications may reduce IOP fluctuations among patients with OAG.^{28,29} Although the present study enrolled only patients receiving glaucoma medication, the large IOP fluctuation observed (approximately 9 mm Hg) among patients with latent asymmetric IOP is surprising. This is especially troublesome because latent asymmetric IOP would not have been diagnosed in routine clinical settings. Latent asymmetric IOP was found in 16 patients (30%) in our study population. It can reasonably be expected that such diurnal IOP variation would be greater in untreated eyes. However, our sample size was insufficient to draw definitive conclusions. Further investigation about this phenomenon in a larger and more diverse group of patients is needed to assess the diagnostic implications of latent asymmetry relative to glaucoma therapy.

As already noted, authors suggest that an impaired autoregulating mechanism is a primary pathogenesis of normal-tension glaucoma.²⁵⁻²⁷ Patterns of IOP asymmetry and fluctuation may differ between low-tension glaucoma and high-tension glaucoma. Because of the small number of patients enrolled in the present study, those with low-tension vs high-tension glaucoma could not be evaluated separately in the statistical analysis. We are interested in studying this further.

For the determination of IOP asymmetry in our study, we set cutoff IOP difference values of 3.0 and 5.0 mm Hg for the sitting and supine positions, respectively. These cutoff values were obtained by calculating 1 SD of IOP for each position in our study population (2.8 mm Hg for sitting and 4.5 mm Hg for the supine position). Other authors have adopted similar reference values for IOP asymmetry.¹⁶

This investigation is a pilot study to introduce a novel method of using latent asymmetric IOP as a diagnostic criterion for glaucoma therapy. Although our study was prospective, it has several limitations. We enrolled patients who had been previously diagnosed as having OAG and were receiving antiglaucoma medications, so their characteristics before medication use could not be evaluated. Our patients did not receive uniform antiglaucoma medications, they had various severities of VF defects, and the sample size was insufficient to make definitive conclusions about the associations among type of medication use, VF severity, and IOP fluctuation. Further investigation in a larger more diverse group of patients is needed to better understand the phenomenon of latent asymmetric IOP.

Monocular trials to assess the efficacy and possible adverse effects of antiglaucoma medication use in widely practice. These trials are based on the assumption that fellow eyes behave in a symmetric manner relative to IOP-lowering characteristics. If latent asymmetric IOP is confirmed in some patients with glaucoma, ophthalmologists would need to assess whether latent asymmetric IOP is present before the inclusion of these patients in monocular trials, especially the inclusion of patients with asymmetric VF defects.

In clinical practice, latent asymmetric IOP can be suspected if 1 eye shows worse VF indexes than the fellow eye, despite symmetric sitting IOP measurements. Practitioners should attempt to determine the presence of such a discrepancy. Glaucoma management strategies may differ in the presence of latent asymmetric IOP. A more aggressive treatment regimen should be instigated for the IOP_H eye. Although evaluation for latent asymmetric IOP when the patient is in the supine position may be difficult in an office setting and the condition may not manifest during daytime office hours, the high percentage of patients in our study found to have latent asymmetric IOP may warrant performance of such a procedure. Furthermore, evaluation for the presence of latent asymmetric IOP when the patient is in the supine position may be considered in all patients newly diagnosed as having OAG.

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