

The Value of Intraocular Pressure Asymmetry in Diagnosing Glaucoma

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Purpose: To investigate the amount of intraocular pressure (IOP) asymmetry in a large group of ethnically diverse patients with and without glaucoma, and to delineate the risk for glaucoma which increasing amounts of IOP asymmetry confer upon the patient.

Patients and Methods: Collaborative retrospective study of 326 glaucoma patients and 326 controls. Former Wills Eye Institute fellows collected single pre-treatment measurements of IOP on patients diagnosed as having definite glaucoma based on characteristic optic nerve damage and confirmatory visual field damage. Patients with a normal eye examination who had normal-appearing optic discs and no apparent glaucoma, or who had a normal eye examination in association with refractive error or cataract, were used as controls.

Results: Intraocular pressure asymmetry is a significant risk factor for having glaucoma (odds ratio, 2.14; 95% confidence interval, 1.86-2.47; $P < 0.001$). Absence of IOP asymmetry between the fellow eyes is associated with a 1% probability of having glaucoma. A difference of 3 mm Hg is associated with a 6% probability of having glaucoma, and a difference of >6 mm Hg with a 57% probability of having glaucoma. The association between IOP asymmetry and glaucoma status is significant for subjects with both elevated IOP ($P = 0.014$) and statistically normal IOP (maximum IOP ≤ 21 mm Hg; $P < 0.001$).

Conclusions: Inter-eye asymmetry of IOP is a common finding in patients with glaucoma. There is a direct relationship between the amount of IOP asymmetry between the fellow eyes and the likelihood of having glaucoma.

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Asymmetric findings between the fellow eyes have long been considered a hallmark of glaucoma. The presence of asymmetries in patients with incipient or established glaucoma has been demonstrated for intraocular pressure (IOP),^{1–6} disc parameters,^{7–10} visual field thresholds,² contrast sensitivity,¹¹ visual evoked response,¹² retinal nerve fiber layer thickness,¹³ and blood velocity.¹⁴ Of these parameters, IOP is of special interest because it is an easily measured clinical characteristic and is directly related to the pathogenesis of glaucoma.^{15–17} Elucidation of the diagnostic implications of asymmetric IOP will aid clinicians in identifying patients who are at most risk of developing glaucoma and may also shed light on its pathogenesis.

Most early reports of asymmetric IOP focused on the importance of IOP in the pathogenesis of “low-pressure” glaucoma.^{4–6} These studies consistently demonstrated a correlation between asymmetric IOP and asymmetric visual field loss. More recently, 2 large population-based prospective studies have identified IOP asymmetry as a significant diagnostic indicator of primary open angle glaucoma (POAG).^{1,2} Notably, Levine et al² demonstrated that asymmetric IOP confers a risk, in addition to elevated IOP, of developing POAG.

The diagnostic implications of IOP asymmetry, however, are still not fully understood. In their study on low-pressure glaucoma, Greenfield et al¹⁸ found no relationship between IOP asymmetry and visual field loss. It has also been suggested that IOP asymmetry is indicative of glaucoma only in patients whose maximum pressures are ≤ 21 mm Hg.⁹ Furthermore, no study has considered the degree of IOP asymmetry, but only its absolute presence or absence, usually designating cut offs of ≥ 1 to 3 mm Hg IOP difference between the fellow eyes. The purpose of the current study is to investigate the amount of IOP asymmetry in a large group of ethnically diverse patients with and without glaucoma, and to delineate the risk for glaucoma with varying amounts of IOP asymmetry conferring upon the patient.

PATIENTS AND METHODS

The investigators are former clinical or research fellows in glaucoma at the Wills Eye Institute. Data were collected retrospectively from the medical records of their various

clinics around the world. Single recordings of pre-treatment IOP measured by Goldmann applanation tonometry were collected from patients who were diagnosed as having definite POAG. Investigators chose glaucoma patients whom they saw consecutively on a single or adjoining days.

For the purposes of our study, glaucoma was defined as an ocular condition with characteristic glaucomatous optic nerve damage and characteristic confirmatory glaucomatous visual field damage. Glaucomatous optic nerve damage was defined as a definite notch in the neuroretinal rim (a defect of at least 1 disc unit for a circumferential extent of < 2 h); or absence of neuroretinal rim, not because of optic neuritis, anterior ischemic optic neuropathy, giant cell arteritis, or other known cause; or a difference in cup/disc ratio of > 2 or in the Disc Damage Likelihood Scale > 1 , which could not be explained by anisometropia or other nonglaucomatous reason. The patient's disc damage had to correspond to a definite visual field defect, that is, a visual field that had at least a glaucoma hemifield test "outside normal limits" and/or a pattern standard deviation worse than the normal fifth percentile ($P < 0.05$).¹⁶ IOP was not used as a diagnostic consideration when classifying patients as having glaucoma.

Patients with a normal eye examination who had normal-appearing optic discs and no apparent glaucoma, or who had a normal eye examination in association with refractive error or cataract, were used as controls. Controls were matched with the glaucoma patients by sex, race, and age (within 2 y). All controls were enrolled from the investigators' general ophthalmology clinics.

Excluded from both groups were patients diagnosed with congenital glaucoma, angle closure glaucoma, pigmentary glaucoma, glaucoma in association with the exfoliation syndrome, or secondary glaucoma of any type (such as neovascular glaucoma, inflammatory glaucoma, or steroid-induced glaucoma). Patients with other ocular diseases (eg, uveitis, central retinal artery occlusion, central retinal vein occlusion, retinal detachment, and anisometropia with > 5 D difference between eyes) and all those who had trauma or surgery of any kind on either eye were also excluded from the study. Although there is no evidence that anisometropia should affect a patient's IOP or glaucoma status, patients with anisometropia > 5 D were excluded because such a marked asymmetry of ocular anatomy is suspicious for introducing a possible confounding factor in a study of IOP asymmetry. In addition, it is difficult to examine these patients reliably.

The amount of absolute asymmetry between the 2 eyes was calculated by subtracting the IOP in the eye with lower IOP from the IOP in the eye with higher IOP. The percent difference in IOP was calculated by dividing the absolute difference of the 2 IOP readings by the average of the 2 readings. Logistic regression was used to measure the association between glaucoma (the dependent variable) and asymmetry of IOP. The amount of IOP asymmetry was treated as a continuous independent variable with values of 0 to 7 mm Hg, where 7 equaled any difference > 6 mm Hg. As this was a case-control study, we could not directly estimate the probability of having glaucoma for a specific IOP difference. Using historical data to estimate the prevalence of glaucoma and the results of the logistic regression analysis, we can estimate these quantities indirectly as

$$\Pr(G = 1 \mid \Delta\text{IOP} = x) = \frac{\exp(\tilde{\beta}_0 + \beta_1 x)}{1 + \exp(\tilde{\beta}_0 + \beta_1 x)}$$

where

$$\tilde{\beta}_0 = \beta_0 - \log \left[\frac{[1 - \Pr(G = 1)]}{\Pr(G = 1)} \times \frac{\bar{y}}{(1 - \bar{y})} \right]$$

Here, β_0 and β_1 are the intercept and coefficient of IOP difference from the logistic regression and x is the particular value of IOP difference for which we would like to calculate the probability of a glaucoma diagnosis. $\Pr(G = 1)$ is estimated from historical data, and \bar{y} is the proportion of the sample with glaucoma. For this analysis we assumed that the worldwide prevalence of glaucoma was 2%.¹⁹ The same logistic regression technique was used to measure the association between percent difference in IOP and glaucoma.

RESULTS

Data were collected on 326 glaucoma patients and 326 controls. The mean age of glaucoma patients was 67.5 ± 14.3 years (range, 29 to 95 y) and the mean age of controls was 67.4 ± 14.3 years (range, 29 to 96 y). The sex distribution for both groups was 48% female and the racial distribution for both groups was 28% Asian, 21% Black, 28% European, 14% Latino, and 9% Middle Eastern/North African. The IOP parameters of glaucoma patients and controls are shown in Table 1. Mean IOP parameters were similar between the right and left eyes within each group. The distribution of study participants at each level of IOP asymmetry is shown in Figure 1, and at each level of percent difference in IOP in Figure 2.

Logistic regression analysis demonstrated that IOP asymmetry is a significant risk factor for having glaucoma [odds ratio (OR), 2.14; 95% confidence interval (CI), 1.86-2.47; $P < 0.001$]. There was a direct relationship between the amount of IOP asymmetry and the probability of having glaucoma (Fig. 3). The percent difference in IOP between the fellow eyes was also significantly associated with glaucoma status (OR, 2.52; 95% CI, 2.04-3.10; $P < 0.001$). There was a direct relationship between the percent difference in IOP and the probability of having glaucoma (Fig. 4).

We stratified subjects by whether IOP was statistically normal (≤ 21 mm Hg) in both eyes or not and tested for association of IOP asymmetry and glaucoma separately in each group. For subjects with normal IOP in both eyes, there was a significant association (OR, 1.66; 95% CI, 1.37-2.01; $P < 0.001$) between IOP asymmetry and glaucoma status. This association was also significant for subjects with elevated IOP in at least 1 eye (OR, 1.74; 95% CI, 1.12-2.70; $P = 0.014$).

From the logistic regression, we also estimated the area under the receiver operating characteristic curve, which tells us how accurate IOP asymmetry is in predicting glaucoma (0.5 = no predictive ability, 1 = perfect predictive ability). The area under the receiver operating characteristic

TABLE 1. Intraocular Pressure Parameters of Glaucoma Cases (n = 326) and Controls (n = 326)

	Glaucoma Cases	Controls
IOP of right eye	23.3 \pm 6.6 (9-57)	15.3 \pm 3.0 (8-26)
IOP of left eye	23.3 \pm 6.9 (9-60)	15.5 \pm 2.9 (8-24)
Absolute IOP asymmetry	3.7 \pm 4.6 (0-34)	0.8 \pm 1.0 (0-6)
Percent difference in IOP	14.9 \pm 16.2 (0-102)	5.2 \pm 7.1 (0-40)

Values presented as mean \pm SD (range) in mm Hg.
IOP indicates intraocular pressure.

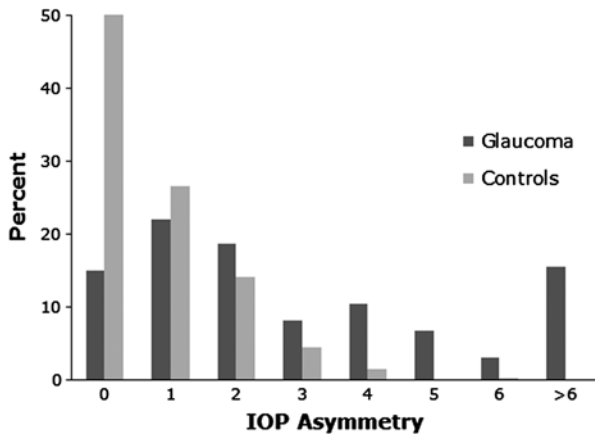


FIGURE 1. Distribution of glaucoma cases (n = 326) and controls (n = 326) at each level of absolute intraocular pressure (IOP) asymmetry between the fellow eyes.

curve value was 0.784, indicating that the apparent asymmetry of a single pre treatment measurement of IOP has diagnostic value.

DISCUSSION

The purpose of this study was to investigate the amount of IOP asymmetry in a large group of ethnically diverse POAG patients. These patients were compared with a set of sex, race, and age-matched controls to determine the probability of having POAG at each level of IOP asymmetry. Our results are consistent with previous studies, which have indicated that asymmetry of IOP is a common finding in patients with glaucoma.¹⁻⁶ We have further demonstrated that the likelihood of having POAG increases as intereye IOP asymmetry increases. This seems to be a definite finding, leading to the conclusion that patients with an IOP difference of ≥ 6 mm Hg should be considered as great risk for having glaucoma, whereas those with symmetric pressures are not likely to have the disease. In contrast to 1 previous study,¹ we found that IOP asymmetry was predictive of glaucoma status in subjects with both elevated and statistically normal levels of IOP.

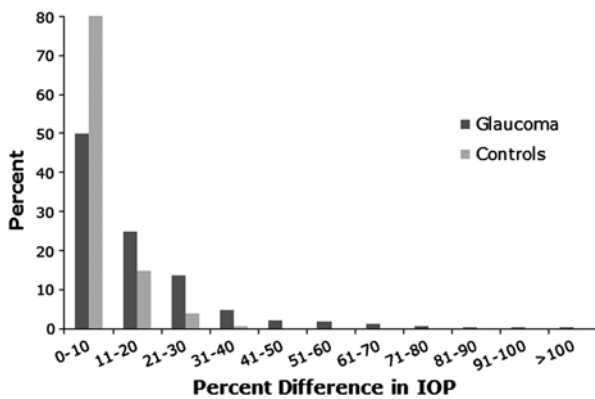


FIGURE 2. Distribution of glaucoma cases (n = 326) and controls (n = 326) at each level of percent difference in intraocular pressure (IOP) between the fellow eyes.

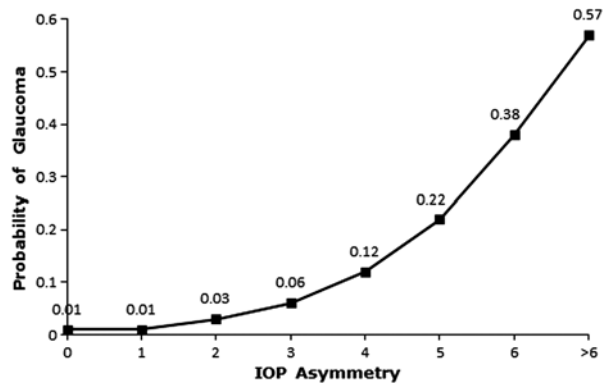


FIGURE 3. Probability of having glaucoma as a function of intraocular pressure (IOP) asymmetry between the fellow eyes. Probability of having glaucoma was calculated with a logistic regression analysis, assuming an overall worldwide prevalence of 2%.

Strengths of our study include a strict definition of POAG and exclusion of subjects with other ocular disorders. All IOP measurements were recorded before the initiation of glaucoma therapy or any surgical intervention on either eye. Our study group is also significantly larger than those of most previous studies, and our study participants represent an ethnically diverse group of patients.

An important limitation of this study is that IOP was measured only once in each subject. The ability to determine IOP accurately with applanation tonometry is limited because of the inevitable noise of any measurement, frank measurement error, and characteristics of the eye being measured that make it different from the eyes against which the tonometer was standardized. The retrospective and multicenter design of this study made it impossible to standardize the tonometers across all patients, and even single center studies have demonstrated a relatively low interobserver reliability of single IOP measurements using Goldmann applanation tonometry.²⁰

The stage of disease, though not addressed in this study, is another consideration which may influence the conclusions suggested by our data. Once glaucomatous damage is far advanced bilaterally, asymmetry of findings is

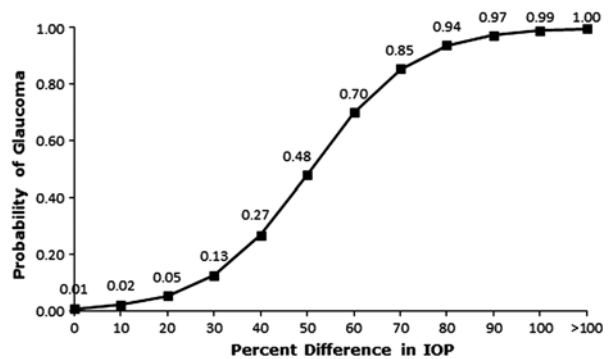


FIGURE 4. Probability of having glaucoma as a function of percent difference in intraocular pressure (IOP) between the fellow eyes. Probability of having glaucoma was calculated with a logistic regression analysis, assuming an overall worldwide prevalence of 2%.

difficult or impossible to detect. Furthermore, because atrophy of the ciliary body occurs in cases with far-advanced damage—as seen in the phenomenon of “burned out glaucoma,”—the untreated IOP of patients with far-advanced POAG is not necessarily a reflection of the level of IOP earlier in the disease. In addition, it is possible that asymmetry of IOP is among the initiating events for ocular damage. If this is the case, then there will of necessity be for some controls with IOP asymmetry who do not yet show glaucomatous optic atrophy or visual field changes.

Finally, it is well known that IOP measurements of a single eye vary significantly throughout the day and over more extended periods of time. Our study, however, deals not with measurements of IOP in a single eye, but with the difference in IOP between the fellow eyes. Reports on the symmetry of diurnal curves between the right and left eyes have been conflicting, but the most recent studies have found strong correlations of IOP fluctuations between the fellow eyes in patients with untreated glaucoma ($r = 0.84$) and ocular hypertensive patients ($r = 0.72$) using Goldmann applanation tonometry.^{21,22} Nevertheless, asymmetric fluctuations between the right and left eyes do occur in both untreated glaucoma patients and older healthy individuals, with estimates of the prevalence of this phenomenon varying widely.^{21–24} These variations may account for the fact that several controls in our study had asymmetric IOP, whereas many glaucoma patients were observed to have symmetrical IOP with only 1 measurement. The value of IOP asymmetry as a diagnostic consideration should be weighted heavily in patients who show consistent IOP asymmetry on repeat clinic visits, and especially if those measurements are recorded within 2 hours of the same time of the day as the baseline IOP.²²

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