A Population-Based Assessment of 24-Hour Intraocular Pressure among Subjects with Primary Open-Angle Glaucoma: The Handan Eye Study

Ning Li Wang, David S. Friedman, Qiang Zhou, Lixia Guo, Dan Zhu, Yi Peng, Dolly Chang, Lan Ping Sun, and Yuan Bo Liang

PURPOSE. To describe the distribution of the 24-hour intraocular pressure (IOP) among subjects with primary open-angle glaucoma (POAG) in a population-based study in north China.

METHODS. All untreated POAG patients (n = 66) identified in the Handan Eye Study were invited to attend a follow-up study in which IOP was tested with a Goldmann applanation tonometer at 10 AM, 2 PM, 6 PM, 10 PM, 2 AM, and 6 AM.

RESULTS. Forty-seven subjects with untreated POAG (47/66; 71.2%) attended the study. Of them, 39 (85.0%) had a peak IOP of 21 mm Hg or less. The peak IOP (mean ± SD) was 18.4 ± 5.7 mm Hg. Peak IOP occurred in early morning in approximately 76.5% of the subjects (6 AM to 10 AM), and the trough occurred during night time in 70.2% of the subjects (10 PM to 2 AM). The 24-hour IOP (mean ± SD) was 15.4 ± 3.1 mm Hg and the mean fluctuation was 6.0 ± 2.2 mm Hg (range, 2–11 mm Hg). In the 22 persons with unilateral glaucoma, no significant differences were found in mean 24-hour IOP, peak IOP, trough IOP, or IOP fluctuation when comparing the glaucomatous eye with the nonglaucomatous eye (P > 0.05).

CONCLUSIONS. About 80% of Chinese persons with POAG identified in a population-based study had maximum IOPs of 21 mm Hg or less over a 24-hour period. Twenty-four-hour IOP was similar between glaucomatous and contralateral nonglaucomatous eyes suggesting that factors other than IOP may play a role in the development of glaucomatous optic neuropathy in these eyes. (Invest Ophthalmol Vis Sci. 2011;52:7817–7821) DOI: 10.1167/iovs.11-7528

Intraocular pressure (IOP) is the only known modifiable risk factor for primary open-angle glaucoma (POAG).1–4 Several population-based studies in Asia have reported that the majority of subjects with POAG have an IOP in the “normal” range. Ninety-two percent of those found to have POAG had IOP < 21 mm Hg in a large study from Japan.5 Similarly, 85% had IOP < 21 mm Hg in an urban Chinese population6 and in Singaporean Malay persons with glaucoma.7 These proportions appear to be substantially higher than has been seen in European and African derived populations. Among subjects with POAG, 55% had a screening IOP lower than 21 mm Hg in the Baltimore Eye Study,8 53% among Afro-Caribbeans in the Barbados Eyes Study,9 with an even higher rate in the Blue Mountains Eye Study (74%).10 However, all these population-based studies estimated this proportion based on a screening and/or a follow-up IOP measurement.

To characterize more precisely the IOP, among a population-based sample of Chinese persons with POAG, we conducted a 24-hour IOP measurement on persons diagnosed with POAG in the Handan Eye Study and report on the fluctuation range of 24-hour IOP.

METHODS

Study Design

The Handan Eye study is a randomized, clustered population-based study, consisting of self-identified Han Chinese, 30 years or older, living in a rural county of Handan, China. Details of the study design, sampling plan, and baseline data are reported elsewhere.11,12 In brief, the study adhered to the Declaration of Helsinki and ethics approval was obtained from the Beijing Tongren Hospital Ethical Committee and written informed consent was obtained from all participants. Residents of Yongnian County, Handan, Hebei province, aged 30 years and older were randomly selected using a clustered sampling technique with probabilities proportionate to the size of population in each cluster. In Yongnian County, 90% of the population are farmers, and 98% are Han. Per capita annual net income in this rural area is 3468 Yuan ($510) which is similar to the average income (3255 Yuan; $478) of those living in rural areas throughout mainland China.13

Clinical Data

All eligible individuals were invited and scheduled for a detailed eye examination and questionnaire interview, which were performed in a standardized manner at the Handan Eye Study (HES) centralized clinic (located in the Yongnian County Hospital). The examination included visual acuity, autorefraction, and subjective refraction; questionnaires, anterior segment examination with a slit lamp; intraocular pressure (IOP), gonioscopy, dilated examination, and photography of the fundus.
IOP was measured using Perkins handheld applanation tonometry (HA-2; Kowa, Tokyo, Japan) after topical anesthesia. IOP was measured twice, and a third measurement was performed if the difference between two measurements was > 2 mm Hg with the mean of the two closest results used as the IOP measurement. The tonometer was calibrated daily before examination.

Central corneal thickness (CCT) was obtained using ultrasound pachymetry (UP1000; Nidek, Inc., Tokyo, Japan), after instillation of 2 drops of 0.5% proparacaine for topical anesthesia (Alcon Laboratories, Inc., Fort Worth, TX). The pachymeter probe was placed on the center of the cornea, and the average of five readings was used. Axial length, anterior chamber depth, and lens thickness were measured using a 10 MHz A/B-mode ultrasound device (Cine Scan, Quantel Medical, Cedex, France), using a hard-tipped, corneal contact probe mounted on a slit-lamp. The optic disc was imaged with the a retinal tomography instrument (Heidelberg Retina Tomograph; HRT II; Heidelberg Engineering, Heidelberg, Germany) after cylinder lens correction was determined without pupil dilation. When the image quality was poor (SD > 30 μm), a repeat image was obtained after pupil dilation. All disc contours were drawn by a certified ophthalmologist (DZ).

Clinical Cup/Disc Ratio Grading and Glaucoma Determination

The optic nerve was evaluated using a 78 D or 90 D lens at ×16 magnification after pupil dilation. The vertical cup-to-disc ratio (VCDR) was used as the key index of structural glaucomatous change. Measurement of VCDR excluded peripapillary atrophy and the scleral ring of Elschnig. The margins of the cup were defined by stereoscopic view as the point of maximum inflection of the vessels crossing the neuroretinal rim. Standard photographs for VCDR from 0.1 to 1.0 in 0.1 increments were used in the grading process.6 While the final diagnosis was based on fundus photographs of the optic nerve, the clinical examination of the optic nerve head was one factor used to determine whether a subject was a glaucoma suspect and required additional testing (including gonioscopy and visual field testing).

Those with any of the following conditions were identified as glaucoma suspects: IOP ≥ 21 mm Hg, cup/disc ratio ≥ 0.6 (95 percentile of the Handan Eye Study population), cup/disc ratio asymmetry of ≥ 0.2, optic disc hemorrhage, a visible retinal nerve fiber layer defect, deposits at the pupil margin consistent with pseudoexfoliation syndrome, or pigment deposition on the cornea consistent with pigment dispersion syndrome. All glaucoma suspects were requested to come to the central clinic from August 2007 to October 2007 for a definitive examination including visual field testing; gonioscopy was performed among those who had missed gonioscopy during the initial examination.

Stereoscopic optic disc photographs were evaluated by two glaucoma specialists (YQJ and TCY; see Acknowledgments). The photographs were assessed using a stereoscopic viewer (Screen-Vu Stereoscope, PS Mfg., Portland, OR). The optic discs were categorized as "definite glaucoma," "probable glaucoma," "possible glaucoma," and "not glaucoma." Vertical cup/disc ratio, notchting of the neural rim, localized or diffuse loss of the neural rim, the presence of neural rim tissue of ≤ 0.1, as well as the presence of a nerve fiber layer defect were all documented. Those believed to have definite glaucoma, probable glaucoma, and possible glaucoma by either of the specialists were presented to a panel of glaucoma specialist to make the determination.

Visual Field Evaluation

Every 10th person examined as part of the HES was systematically sampled to undergo a visual field test using the 24-2-Swedish Interac-

Testing Algorithm (SITA) fast program with a visual field analyzer (Humphrey 750i; Carl Zeiss, Jena, Germany). In addition, all with suspect glaucoma were invited to have Swedish Interactive Testing Algorithm standard visual field tests during the definitive examinations.

The visual field was repeated 20 minutes later if the glaucoma hemifield test (GHT) was outside normal limits, borderline, or if the test was unreliable (i.e., fixation losses > 20%, false positives > 35%, or false negatives > 35%).

Final Glaucoma Diagnosis

Three senior glaucoma specialists from China (NLW, ZQR, and MYL; see Acknowledgments) reviewed the examination results and categorized subjects as having definite, probable, possible, or not glaucoma based on consensus.

A second and independent review of the findings was carried out by a glaucoma specialist (DSP) who also classified the patients according to the same definitions. Where the two classifications differed, a final independent adjudication was carried out by another glaucoma specialist (HDJ; see Acknowledgments) and this final assignment was used to determine who had glaucoma. This approach was used due to the fact that other standardized criteria such as International Society for Geographical and Epidemiologic Ophthalmology methods (ISGEO) and World Glaucoma Association (WGA) recommended methods,14,15 require complete data (such as repeated, reliable visual fields) and 30% of the subjects either had no visual fields or they were unreliable. Glaucoma was also diagnosed as present in cases where the optic nerve was not visible due to media opacity and the visual acuity was <3 of 60 and the IOP was >99.5 percentile, or the visual acuity was <3 of 60 and the eye had evidence of prior glaucoma filtering surgery, or medical records were available confirming glaucomatous damage.

Those with "definite" and "probable" POAG were included in this study.36–39 POAG subjects had to have no secondary cause of glaucoma and open angles on gonioscopy.

Twenty-Four–Hour IOP Measurement

In April 2009, we recalled subjects to the Handan Eye Hospital for 24-hour IOP measurement. Although all subjects had been referred for treatment immediately after the initial screening examination, none had gone for treatment before this follow-up study, thus wash-out period was not arranged. IOP was recorded at 2 AM, 6 AM, 10 AM, 2 PM, 6 PM, and 10 PM. We encouraged patients to live and activities as usual; patients were allowed to sleep between measurements of IOP. IOP was measured with Goldmann applanation in an upright sitting position. Two measurements were obtained; if the measurement differed by 2 mm Hg or more, a third measurement was obtained and the two closest measurements were averaged to calculate the final IOP.

Statistical analysis

To describe the demographic characteristics, we used mean ± SD for continuous variables, and frequency for categorical variables. For comparisons, we used t-test or χ2 analysis. To compare the IOP parameters and clinical parameters between glaucoma eyes and contralateral non-glaucomatous eyes in the unilateral diagnosed patients, paired t-tests were used. P values < 0.05 were considered to be significant.

For peak IOP analysis, we used the eye with glaucoma if the person had unilateral glaucoma, and we used the eye with the higher peak IOP if the person had bilateral glaucoma. The other parameters of diurnal IOP, such as trough IOP, were calculated using the same eye. Fluctuation was defined as peak IOP minus trough IOP.

RESULTS

Sixty-seven patients were diagnosed with POAG. Ninety percent of them had an IOP less than or equal to 21 mm Hg in the original study. One was excluded because of previous glaucoma surgery. Forty-seven participants (47 of 66; 71.2%) attended the 24-hour IOP follow-up study. Participants were
TABLE 1. Characteristics of Participants and Nonparticipants for 24-Hour Intraocular Pressure Study

| Characteristics | Participants (n = 47) | Nonparticipants (n = 19) | P *
|-----------------|----------------------|--------------------------|-----
| Female          | 28 (59.6)            | 12 (63.20)               | 0.787 |
| Age, y          | 59.7 ± 10.6          | 66.1 ± 8.9               | 0.025 |
| Hypertension    | 33 (70.2)            | 16 (84.2)                | 0.239 |
| Diabetes        | 4 (8.5)              | 4 (21.1)                 | 0.159 |
| CCT, μm         | 533.5 ± 29.7         | 520.1 ± 34.4             | 0.159 |
| IOP, mm Hg      | 17.2 ± 3.1           | 16.9 ± 3.0               | 0.680 |
| VCDR            | 0.7 ± 0.2            | 0.7 ± 0.1                | 0.622 |
| MD, dB          | −9.9 ± 6.3*          | −8.2 ± 9.1               | 0.489 |

Data are given as mean ± SD or n (%). MD, mean deviation.

* n = 37; 10 cases had unreliable or no visual field test.

younger than nonparticipants (P < 0.05) but did not differ with regards to sex, IOP at the initial examination, central corneal thickness, VCDR, mean deviation on visual field testing, and prevalence of diabetes or hypertension (P > 0.05) (Table 1).

The mean of average IOP of the diurnal IOP was 15.4 ± 3.1 mm Hg, with the lowest average IOP recorded at 10 PM (14.5 mm Hg) and the highest at 10 AM (16.8 mm Hg) (Fig. 1). The mean peak IOP at any time point was 18.4 ± 3.7 mm Hg and the minimum was 12.4 ± 3.1 mm Hg. Eighty-three percent of the patients had a peak IOP less than or equal to 21 mm Hg, and 96.6% of the patients had a peak IOP ≤ 24 mm Hg (Fig. 2). Calculating the time of the peak IOP is complicated by the fact that seven patients had identical peak IOP at two different time points and three more patients had identical peak IOP at three different time points. Herein we counted all time points of peak IOP as the total number of peak IOP (n = 60). Peak IOP occurred in early morning in approximately 76.5% of the subjects (6 AM to 10 AM), and the trough occurred more during night time in 70.2% of the subjects (10 PM to 2 AM). The peak IOP occurred outside of office hours (8 AM to 5 PM) in 51.9% of the subjects and the trough occurred outside of office hours in 70.2% of subjects (Fig. 3).

The mean fluctuation in IOP was 6.0 ± 2.2 mm Hg (range, 2 to 11 mm Hg), and 72% of the patients had IOP fluctuation greater than or equal to 5 mm Hg. Fluctuation was strongly associated with peak IOP (r = 0.530, P < 0.001), but not significantly with average IOP (r = 0.244, P = 0.10). Among the seven patients with peak IOP greater than 21 mm Hg, the fluctuation was 7.3 ± 2.8 mm Hg, higher than among those with a peak IOP of 21 mm Hg or less (n = 39; 5.7 ± 2.0 mm Hg) but it was not statistically significant (P = 0.062).

Thirty-seven patients had a reliable visual field measurement. The mean deviation (MD) was −9.9 ± 6.3 dB. The MD was not significantly associated with peak IOP (r = −0.199, P = 0.232), average IOP (r = −0.20, P = 0.229), fluctuation (r = −0.166, P = 0.32), and trough IOP (r = −0.129, P = 0.44).

Of the 22 persons with unilateral POAG, 17 had IOP asymmetry of 1 mm Hg or more and seven (41.2%) of the eyes had lower average IOP were POAG eyes. The average IOP, SD of diurnal variation, peak IOP, and trough IOP were not different between glaucoma eyes and the contralateral nonglaucomatous eyes (paired t-test, P > 0.05). The fluctuation in IOP (5.8 ± 2.6 mm Hg) in glaucoma eyes, was similar to the fluctuation in contralateral nonglaucoma eyes (5.8 ± 1.7 mm Hg, paired t-test, P = 0.96; Table 2, Fig. 4).

The IOP at initial examination, spherical equivalent refractive error, axial length, central corneal thickness, and radius of corneal curvature in the glaucoma eyes were not significantly different from the fellow nonglaucoma eyes (P > 0.05). Disc size was larger in the glaucoma eyes, as was the vertical cup/disc ratio (P < 0.05; Table 2).

**DISCUSSION**

More than 80% of patients with POAG identified in a population-based prevalence survey from rural China had a peak IOP.
less than or equal to 21 mm Hg when IOP was measured during a 24-hour period. The peak IOP occurred during regular office hours in two-thirds of the patients with POAG, and both the mean IOP and fluctuation in IOP were similar in glaucoma eyes and contralateral nonglaucoma eyes in patients with unilateral glaucoma.

The present study adds further evidence that there is no obvious cutoff of IOP where glaucoma begins. Over 90% of subjects from Handan had IOP below the cutoff of 21 mm Hg and even 80% after a full 24-hour assessment; four out of five had IOP in the “normal” range. A recent study conducted in white subjects reported that the rate of progression of visual field loss in persons with glaucoma at lower IOP was slower than in those with higher IOP, and the prevalence of juxtafoveal defect seems to be more common in those with lower IOP. While there may be differences in the manifestation of glaucoma in those with higher and lower IOP, there is no clear cutoff, and the dependence on the number 21 is not justified as documented in this study. IOP appears to be an inadequate screening tool in this population.

Although most of the POAG patients had a normal IOP, fluctuation of IOP among these subjects was still greater than what has been reported in persons without POAG. The normal range of fluctuation among Chinese was reported as 4.0 ± 1.45 mm Hg with Schiotz tonometer and 2.9 ± 0.7 in normal healthy Chinese with Goldmann applanation tonometry. This could in part be explained by a higher IOP in those with POAG (because fluctuation is greater in those with higher IOP). However, the reported fluctuation in persons without glaucoma was still lower than was found for those with IOP < 21 mm Hg in the present study.

Factors other than IOP may play a role in the pathogenesis of glaucoma in some of the POAG patients in this study. For patients presenting with unilateral glaucoma, IOP in the eye with glaucoma was not significantly higher than that of the eye without glaucoma in all diurnal IOP parameters, and approximately 40% of these eyes with glaucoma had a lower IOP. Several clinic-based studies of populations with glaucoma at low IOP have reported similar findings; severe visual field damage occurred in the eye with lower IOP in 14% to 78% of the patients. Two studies found no correlation with asymmetric IOP and asymmetrical visual defects. Ren et al. reported that among 23 unilateral glaucoma patients, mean IOP, peak IOP, and fluctuation were all similar between the presenting eye and the fellow eye. The level of IOP was not related to the magnitude of the visual field defects in those with bilateral visual field abnormalities. The Low-Pressure Glaucoma Study Group also did not find any significant difference in any diurnal IOP parameters between the eye with visual field loss and the normal visual field eye in unilateral cases, and the better visual field eye and worse visual field eye in bilateral cases. Larger disc size may play a role in the development of optic nerve damage in some glaucoma patients, which has been documented, although not confirmed in all studies.

In the present study, we found that the glaucoma eyes had larger size optic discs as measured by a retinal tomography instrument (HRT II; Heidelberg Engineering) than the fellow eyes in unilateral POAG cases (2.4 ± 0.4 mm² vs. 2.2 ± 0.4 mm²). Although this study was population-based and had standardized definitions and protocols, there are still some limitations that need to be recognized. First, 30% of POAG subjects did not attend the visit for diurnal IOP evaluation. Participants and nonparticipants were similar in overall and demographic aspects except for age. In the Handan Eye Study, IOP tended to decline with age, thus the fact that participants were younger would have resulted in a slight overestimate of the average and peak IOP over a 24-hour period, therefore we may have underestimated the proportion in the population of all those with glaucoma who had a maximum IOP < 21 mm Hg. Next, we tested the IOP in the sitting position, which is not the habitual position during sleeping hours. This likely resulted in lower measured nocturnal IOP. Third, the study population was enrolled from a single rural area of China and may not represent the entire Chinese population.
In conclusion, we demonstrated that the majority of persons with POAG had an IOP < 21 mm Hg in a population-based study of rural Chinese persons, and observed that IOP in the glaucomatous eye was similar to the IOP in the contralateral nonglaucomatous eye in unilateral cases. Factors other than IOP likely play an important role in the development of glaucomatous neuropathy.

Acknowledgments
The authors thank Mei Yu Li (Department of Ophthalmology, Peking University First Hospital), You Qin Jiang (Department of Ophthalmology, the 2nd Xiangya Hospital, Central South University), Tian Cai Ye (Zhongshan Ophthalmic Center, Zhongshan University), Ze Qin Ren (Department of Ophthalmology, Peking University People’s Hospital), and Henry D. Jampel (Department of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University), for evaluating the disc images and/or visual fields for glaucoma diagnosis.

References