Intraocular pressure and visual field loss in primary angle closure and primary open angle glaucomas

G Gazzard, P J Foster, J G Devereux, F Oen, P Chew, P T Khaw, S Seah

Aim: To compare the correlation between visual field loss and the pretreatment intraocular pressure (IOP) in primary angle closure glaucoma (PACG) and primary open angle glaucoma (POAG).

Methods: In a cross sectional observational study of 74 patients (43 PACG, 31 POAG), pretreatment IOP was measured at presentation, before treatment was initiated. Severe visual field loss was assessed by AGIS score, mean deviation (MD), pattern standard deviation (PSD), and corrected pattern standard deviation (CP-PSD). Glaucomatous optic neuropathy was assessed from simultaneous stereo disc photographs.

Results: There was a stronger correlation between pretreatment IOP and the extent of visual field loss in PACG subjects than in those with POAG for both MD (PACG: Pearson correlation coefficient ($r$) = 0.43, $p = 0.002$; $r'$ = 0.19), POAG: $r$ = 0.21, $p = 0.13$; $r'$ = 0.04) and AGIS score (PACG: $r$ = 0.41, $p = 0.003$; $r'$ = 0.17), POAG: $r$ = 0.23, $p = 0.19$; $r'$ = 0.05 respectively). No such associations were seen for pattern standard deviation (PSD) or corrected pattern standard deviation (CP-PSD) in either group ($p$ = 0.29). Both horizontal and vertical cup-disc ratio were well correlated with severity of field loss but not with presenting IOP for either diagnosis.

Conclusions: This is consistent with the hypothesis of a greater IOP dependence for optic nerve damage in PACG than POAG and, conversely, a greater importance of other, less pressure dependent mechanisms in POAG compared to PACG.

The aetiology of glaucomatous optic neuropathy (GON) is not fully understood. There are many implicated risk factors, the two most consistent of which appear to be intraocular pressure (IOP) and age. However, direct correlations between the extent of visual field loss (VFL) and the level of pretreatment IOP at presentation have been found to be weak for POAG. This probably reflects the multiple interacting risk factors for damage that modify the response of a particular nerve to a given IOP. The probability of developing glaucoma at a certain IOP may be different for different types of glaucoma. Stronger correlations between VFL and IOP have been seen in pseudexfoliative glaucoma, which has been thought to be a more pressure dependent disease, than in POAG. Primary angle closure glaucoma (PACG) may also be considered to be a more purely pressure dependent disease than POAG.

A strong correlation between pretreatment IOP and the amount of visual field damage present may be an indicator of the extent to which a disease can be considered pressure dependent. Such an association may support the belief that the pathogenetic mechanisms involved in PACG are more pressure dependent. This in turn might have implications for prognosis and the need for clinical trials to explore the extent to which pressure lowering alone may be successful in halting the progression of optic nerve damage and consequent VFL. We therefore set out to compare the association between pretreatment IOP at presentation and the degree of VFL in both PACG and POAG.

SUBJECTS AND METHODS

All subjects enrolled in a prospective, randomised, placebo controlled trial of the use of intraoperative 5-fluorouracil in glaucoma filtering surgery in south east Asia were considered for inclusion in this cross sectional observational study. These subjects were recruited from the clinics of a mixed secondary and tertiary referral centre. All glaucoma patients listed for trabeculectomy were considered for enrolment, and were enrolled if they met the stipulated criteria. The referral process was identical for the two diagnoses. This study was granted ethical approval by the ethics review committee of Singapore National Eye Centre, acting for the Ministry of Health of the Republic of Singapore. Written informed consent was obtained from all participants in their own language with an interpreter where necessary. We followed the tenets of the Declaration of Helsinki.

A thorough ocular examination was carried out on enrolment, and a diagnosis allocated on the basis of the findings. Subjects were included in this study if there was evidence of GON in conjunction with a reproducible visual field defect consisting of either two points reduced by >5 dB or one point reduced >10 dB below age specific threshold. GON was defined as reduction of the neuroretinal rim width to less than or equal to 0.1 of the vertical disc diameter, or glaucomatous damage in the opinion of a fellowship trained glaucoma specialist. PACG was diagnosed on the basis of an occludable angle and GON; POAG was diagnosed when the angle was not occludable. An occludable angle was defined as one in which the posterior (usually pigmented) trabecular meshwork was not seen over 270° or more of the angle without indentation.

A further criterion for entry into the surgical trial was an intraocular pressure (IOP) greater than 21 mm Hg recorded on at least one occasion before surgery. Cases of normal pressure glaucoma (NPG) were therefore excluded. Only subjects for whom pretreatment IOP data at presentation were available and who first presented within 6 months of a qualifying visual field assessment are included in this analysis. Pretreatment IOP data were collected retrospectively from the case notes. “Presenting IOP” was defined as the first reading taken before pressure lowering treatment (medical or laser) was initiated. For four subjects with more than one available pretreatment IOP reading the mean value, up to a total of three, was used. IOP was also assessed at the time of visual field test.
Investigators conducting the slit lamp assessment (IOP gonioscopy, etc) and the technician conducting visual field examinations were initially masked to the underlying diagnosis. Standard practice was to measure IOP before gonioscopy to avoid measurement errors from ocular compression during indentation gonioscopy and from methylcellulose coupling fluid. This also prevented bias in IOP reading at first presentation and from methylcellulose coupling fluid. GTT was performed with a Goldmann two tonometer by a fellowship trained glaucoma subspecialist (SS, LT, Storz, St Louis, MO, USA). The mean of 16 individual measurements was taken (repeated up to three times or until standard deviation was less than or equal to 0.13 mm). The degree of lens opacity (nuclear opacity and colour, cortical, and posterior subcapsular opacities) was graded by clinical observation at a slit lamp using standard photographs of the LOCS III scheme. Visual field examination was carried out using static automated white on white perimetry (Model 750, Zeiss Humphrey, Dublin, Ireland) with appropriate refractive correction following subjective refraction by an optometrist. A minimum of two visual field tests were carried out on different days using the 24-2 test pattern. Tests were considered reliable and eligible for analysis if they were completed with <33% false positives, <33% false negatives, and <20% fixation losses. If the mean defect in the first two tests differed by more than 2 dB, further tests were carried out to ensure test results with a MD within 2 dB had been obtained. The second of the fields was used for analysis. When pupil diameter was less than 3 mm, the pupil was pharmacologically dilated. Pupil diameter, as measured by the field analyser, was recorded. Field analyses were conducted masked to the diagnosis and IOP. Fields were then scored for severity according to the AGIS system.

The cup-disc ratio (CDR) was independently estimated from simultaneous stereo disc photographs by two glaucoma specialists with good interobserver agreement.

Frequency histograms and the one sample Kolmogorov-Smirnov test were used to assess the distribution of numerical data for parametric characteristics. Differences in mean values of parametric data between study groups were examined using an independent samples t test. For non-parametric data, a Mann-Whitney U test was used to compare means and the Wilcoxon sign rank test for the distribution of two related samples.
variables, $\chi^2$ was used for the analysis of categorical variables. Linear regression analysis was used to assess the correlation between presenting IOP and VFL. Data are presented as mean (SD) and range where appropriate. The $p$ value and Pearson’s correlation coefficient ("$r$") is given for the linear regression analyses, together with the regression formula. Logistic regression analysis was used to further adjust for the potentially confounding effects of differences in severity, age, or sex between the two groups. Diagnosis was used as the dichotomous outcome variable and mean deviation, sex, and age as the independent variables with an interaction term where appropriate.

Statistical software, SPSS 9.05, (SPSS Inc Chicago, IL, USA) was used for analysis.

RESULTS

Tables 1 and 2 summarise the demographic and ophthalmological characteristics of the subjects for whom data are presented: 74 subjects were eligible for this analysis—31 with POAG and 43 with PACG. There were no significant differences between the groups in age ($p=0.74$) or ethnicity ($p=0.30$). There was an excess of males in both groups. There were no significant differences in any of the four LOCS III grades of lens opacity, pupil size during visual field testing, visual fields reliability indices, laterality, or use of antihypertensive medication ($p>0.2$). The PACG eyes had a significantly shorter AL (22.4 (1.0) v 23.6 (1.2) mm; $p=0.0001$) and thicker lenses (5.06 (0.53) v 4.74 (0.45) mm; $p=0.008$). The mean pretreatment IOP at presentation, was higher in the PACG group than the POAG (37.0 mm Hg, range 14–37 (4.9); PACG 26.8 mm Hg, range 12–56 (9.3); $p=0.004$). However, neither the mean IOP at the time of field testing (POAG 24.6 mm Hg, range 14–37 (4.9); PACG 26.8 mm Hg, range 12–56 (9.3); $p=0.003$; $r'=0.17$; Fig 1A), nor the percentage change in IOP between first presentation and field test ($p=0.17$) were significantly different between groups.

Linear regression demonstrated a moderate, significant, relation between higher presenting IOP and more negative MD for the PACG group ($r^2=0.19$; Fig 1A). The Pearson correlation coefficient ($r$) was 0.43, $p=0.002$. The correlation between pretreatment IOP and magnitude of MD for the POAG group was weaker and not statistically significant ($r=0.21, p=0.13; r'=0.04$; Fig 1B). Similarly, the AGIS score was significantly related to pretreatment IOP in PACG ($r=0.41, p=0.003; r=0.30, p=0.014$; Fig 2A), but this was not significant for POAG ($r=0.23, p=0.19; r'=0.05$ respectively; Fig 2B). No such association were seen for pattern standard deviation (PSD) or corrected pattern standard deviation (CPSD) in either group ($p>0.29$). It is known that the presence of “outliers” may influence the outcomes of regression and correlation analyses (“leverage”). The analysis was therefore repeated after excluding those cases with pretreatment IOP greater than 50 mm Hg, which might be considered as such (six cases of PACG, none for POAG). The significant relations between pretreatment IOP and both MD and AGIS score remained for the PACG group ($r=-0.41, p=0.006; r'=0.17$ and $r=0.3, p=0.014; r'=0.13$ respectively). This difference between the two groups in the relation between pretreatment IOP and MD was statistically significant, (multiple linear regression with MD and diagnosis as dependent variables, $p=0.002$). This relation remained when the additional potential confounder of lens opacity was also included in the model. There was no significant correlation between IOP at time of testing and MD or AGIS for either group, ($p>0.25$).

Figure 1  Scattergram showing simple regression analysis of the relation between untreated intraocular pressure at presentation and visual field mean deviation for primary angle closure glaucoma (PACG) [A] ($\beta = -0.54$ (95% CI $-0.89$ to $-0.19$)) and primary open angle glaucoma (POAG) [B] ($\beta = -0.15$ (95% CI $-0.42$ to $-0.12$)).

Figure 2  Scattergram showing a simple regression analysis of the relation between untreated intraocular pressure at presentation and visual field AGIS score for primary angle closure glaucoma (PACG) [A] ($\beta = +0.72$ (95% CI $+0.22$ to $+1.12$)) and primary open angle glaucoma (POAG) [B] ($\beta = +0.23$ (95% CI $-0.14$ to $+0.59$)).
There was a trend, though not statistically significant, towards a greater severity in the PACG subjects for both MD (19.8 (9.5) dB vs 16.0 (10.0) dB, p=0.12) and AGIS score (13.9 (6.8) vs 11.1 (7.4), p=0.1) (see Table 3). We therefore also used logistic regression analysis in an attempt to account for any differences in severity in the two groups. Using diagnosis as the binary outcome variable this revealed that after correcting for severity, pretreatment IOP at presentation was still a significant predictor of diagnosis (p=0.02, OR = 1.08 (95% CI: 1.01 to 1.15)). Thus, for a given level of MD there was a trend for the IOP to be higher in the PACG group. A further analysis conducted using a multiple linear regression model with severity of visual field as the dependent variable and an interaction term “diagnosis*pretreatment IOP” assessed as a covariate was not significant.

The glaucoma hemifield test was “outside normal limits” in 54 subjects (73%) and borderline in six (8%). The remaining 14 (27%), showed a “general reduction in sensitivity” (seven POAG and seven PACG) of which all showed advanced field loss with very profound disc cupping.

The vertical CDR (VCDR) and horizontal CDR (HCDR) were not significantly different between the two groups (p >0.9). VCDR and HCDR were significantly correlated with MD and AGIS for both diagnoses (p <0.006). However, there was no significant correlation between either measure of severity of GON and presenting IOP (p >0.6).

**DISCUSSION**

We have demonstrated a stronger correlation between pretreatment IOP at first presentation and the severity of VFL for PACG than POAG. This suggests that IOP may be more easily implicated as a causative factor for optic nerve damage in PACG than it is in POAG. Both MD and the more specific AGIS score showed this relation, implying that the VFL was indeed glaucomatous. These measures are based on parameters corrected for age related decreases in retinal sensitivity, so it is unlikely that any differences in age distribution have affected the result. There were no differences between groups in cataract grading or pupil size. This suggests differences in field severity are not attributable to lens opacity or miosis.

The Pearson correlation coefficient of $r = 0.43$ for the relation between MD and presenting IOP in PACG lies between reported values from other studies of 0.68 for pseudoxfoliative glaucoma and 0.26 for POAG, (using a different index of severity of field loss). However, a value of $r^2 = 0.19$ for PACG means that the measured pretreatment IOP accounts for only 19% of the variation in visual field loss in this model, implying the influence of other factors. Additionally, this might reflect the inherent diurnal lability of IOP in PACG and thus the inability of a single measurement to fully characterise it. It has also been suggested that diurnal fluctuation of IOP may itself be an independent risk factor for visual loss and this may further confound the results.

Furthermore, severity of VFL is not merely a function of a “snapshot” IOP alone, it is progressive and related to the duration of the insult. Thus, untreated IOP at presentation can only be part of the story—it is the “area under the curve” that is likely to give a truer measure of the pressure related component of damage. Although we cannot know the duration of disease before diagnosis, from which to derive this, the approximation afforded by the use of “presenting IOP” alone still suggests a significant difference between the two diseases.

We demonstrate a relation between VFL and presenting IOP but did not find a correlation between GON, as measured by cup-disc ratio determined from stereo disc photographs, and presenting IOP. This may be due to a lack of sensitivity to detect small differences in GON in the method of disc assessment used, a greater sensitivity in the measurement of VFL, or a non-linear relation between the two.

A stronger link between IOP and GON in PACG than POAG is biologically plausible given the existing body of knowledge but has not previously been confirmed for PACG. Similarly, this relation was also shown for psuedoxfoliative glaucoma. The weaker relation for POAG fits with the current pathophysiological model of optic neuropathy in which a number of other factors act to influence the susceptibility of a given nerve to the effects of IOP. Numerous studies have shown that factors such as race, sex, disorders of blood flow and vascular regulation, blood pressure, genetics, myopia, diabetes, or other factors may all influence the response of a nerve to IOP. Our findings that IOP alone was less able to explain the severity of VFL in POAG than in PACG may suggest that these or other modifying factors were more important in the POAG group.

PACG also had a higher mean IOP at presentation and, using logistic regression analysis, we found that IOP remained a better predictor of diagnosis even after accounting for differences in severity of VFL. This means that for a given severity of VFL PACG subjects tended to have a higher IOP. Conversely, for a given level of IOP PACG demonstrated less VFL. This in turn implies that subjects with POAG may have a lower tolerance to higher levels of IOP than do those with PACG. This again fits with the model of PACG in which numerous other factors act on the optic nerve head to increase its susceptibility to IOP, compared to the more purely pressure dependent PACG. One of these may be optic nerve head size. PACG eyes had shorter axial lengths and might therefore have smaller nerve heads. If smaller scleral canals are more resistant to deformation as has been suggested, then it might require a higher pressure to cause the same degree of optic nerve damage and thus visual field deficit.

The POAG subjects in this study were defined as a high pressure group with at least one IOP greater than 21 mm Hg. One might speculate that had we included “normal pressure glaucoma” (NPG) in the study the difference between the two groups, and the effects of these modifying influences, might have been greater.

There will always be a question of limitations imposed by detection and selection biases in any study that is not purely population based (in this case both at disease detection and at entry into the trial). However, a study such as this would require very large numbers to be screened to obtain sufficient untreated cases for analysis which precluded the use a population based selection procedure on this occasion. This may

<table>
<thead>
<tr>
<th>Table 3 Field results (means (SD)); global indices, and AGIS score</th>
<th>All patients</th>
<th>POAG</th>
<th>PACG</th>
<th>PACG vs POAG p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>-17.6 (7.2)</td>
<td>-16.0 (10.0)</td>
<td>-19.6 (9.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>PSD</td>
<td>6.9 (3.8)</td>
<td>7.0 (3.7)</td>
<td>7.0 (3.9)</td>
<td>0.99</td>
</tr>
<tr>
<td>SF</td>
<td>2.1 (1.7)</td>
<td>2.0 (1.9)</td>
<td>2.2 (1.6)</td>
<td>0.56</td>
</tr>
<tr>
<td>CPSD</td>
<td>6.3 (4.0)</td>
<td>6.4 (4.0)</td>
<td>6.3 (4.1)</td>
<td>0.88</td>
</tr>
<tr>
<td>AGIS score</td>
<td>12.3 (7.2)</td>
<td>11.1 (7.4)</td>
<td>13.9 (6.8)</td>
<td>0.10</td>
</tr>
</tbody>
</table>
contribute to the ratio of PACG to POAG in this study, perhaps reflecting a greater need for surgical intervention in PACG than POAG, and to the excess of males to females. The best available data for the Sino-mongoloid races, from which race the majority of these subjects came, are from population based prevalence surveys of Foster et al.11–14 These found that while POAG (22 subjects, six blind in one eye) was more prevalent than PACG (14 people, seven blind in one eye) in the Tanjong Pagar survey subjects, PACG is much more visually destructive. With a 6:7 ratio of POAG:PACG for unilocular blindness (POAG 46%), the ratio of 31:43 cases (41% POAG) in the study would seem to fit well with the population based figures for severe disease. The sex distribution in PACG of 28 males to 15 females in this study compares to population based figures of 5:9 in Singaporean Chinese.11:14:15:16 1:1 in rural Mornagauri in urban southern India.17 The difference in sex ratios may reflect selection bias involved in recruitment to a surgical trial because, for example, of differences in willingness to undergo surgery. Although one study of acute PACG patients showed no difference in either knowledge about glaucoma nor time to seek medical advice,18 other work has suggested sex differences in attitudes to risk and treatment in this population.19

This study has positive implications for the treatment of PACG. Until a clinically significant “neuroprotectant” is devised IOP remains the sole modifiable risk factor for the development and progress of glaucomatous optic neuropathy.20 Large scale studies have demonstrated the protective effects of lowering intraocular pressure on the visual field in both high pressure POAG and NPG.1–4 No such longitudinal studies are yet available for PACG but if IOP is indeed a greater determinant of VFL in PACG then the protective effects of lowering IOP and the opportunities for arresting VFL may be even greater. The modern concept of defined therapeutic target pressures might be different in the two diseases with potential implications for the aggressiveness of treatment required and its risk/benefit analysis.

CONCLUSION
Severity of visual field loss in primary angle closure glaucoma was more closely related to the level of pretreatment intraocular pressure at presentation than in primary open angle glaucoma. This has implications for the treatment of PACG.

ACKNOWLEDGEMENTS
We would especially like to thank Dr Yiong-Hua Chan, senior statistician at the Singapore Clinical Trials and Epidemiology Research Unit (CTERU) for help and advice throughout the course of this study.

Funding: Singapore National Medical Research Council NMRC/0044/1994, Medical Research Council United Kingdom G9300070. Authors’ affiliations

REFERENCES