Anterior Chamber Depth and the Risk of Primary Angle Closure in 2 East Asian Populations

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Objective: To evaluate the risk of peripheral anterior synchiae (PAS) and glaucomatous optic neuropathy attributable to primary angle closure at varying anterior chamber depths (ACDs) in two East Asian populations.

Methods: Participants 40 years and older were from 2 population-based glaucoma surveys in Mongolia and Singapore. Central ACD was measured by optical pachymetry. Presence of PAS was determined by dynamic gonioscopy. Cases with secondary PAS were excluded. Glaucomatous optic neuropathy was diagnosed in subjects with structural and functional evidence of glaucoma.

Results: A total of 2032 subjects, consisting of 942 Mongolians and 1090 Chinese Singaporeans, were included in this study. A logistic model of the relationship between ACD and PAS among Singaporeans showed a consistent, incremental increase in PAS across the entire range of ACD. In deeper anterior chambers the rate of PAS exceeded that seen in Mongolians. In Mongolians, there was a clear threshold for ACD (2.4 mm) at or above which PAS were very uncommon. With ACD less than 2.4 mm, the rate of PAS rose rapidly to overtake that seen in Singaporeans.

Conclusions: Shallow anterior chambers are a significant risk factor for angle closure in East Asians, although the nature of the association is specific to the individual population. There was a trend toward higher rates of glaucomatous optic neuropathy in people with the shallowest anterior chambers.


Primary glaucoma affects 67 million people worldwide, with Asians accounting for almost half of this number.1,2 Primary angle-closure glaucoma (PACG) is a major cause of visual morbidity in East Asia.3,5 Recent studies in southern India found that the prevalence of PACG in Indians is also higher than that seen in European people,6-8 with rates approaching those seen in Mongolia.6 The high prevalence of angle closure in China and India means that PACG may be at least as common as primary open-angle glaucoma and therefore a major form of glaucoma worldwide.

Eyes with primary angle closure tend to share certain biometric characteristics. These include shallow central anterior chamber depth (ACD), thick lens, anterior lens position, small corneal diameter and radius of curvature, and short axial length.9-11 Among these, shallow ACD is regarded as the cardinal risk factor in most ethnic groups, although comparative studies suggest that this may not be true for East Asian people, where the role of non-pupil-block angle closure in relatively deep anterior chambers has been debated.12,13

We have previously examined the performance of ACD measurement as a screening tool for primary angle closure and PACG.14 The results have been promising enough for a randomized trial of screening to be undertaken in Mongolia.15 In addition, we have studied the association between gonioscopic angle width and primary peripheral anterior synchiae (PAS) with the assumption that, in the majority of cases, PAS represent irrefutable proof of iridotrabecular contact from a “primary” mechanism. There is a clear association between narrower angles and higher rates of PAS.16 However, with the possible development of screening initiatives in Asian populations, the case for ACD as a risk factor for angle closure in East Asia must be made irrefutable. The risk of acute angle closure at different ACDs has been estimated previously in Europeans,17 although the robustness of the data may be open to question. It is not known whether there is a critical ACD below which the risks of angle closure and PACG become significantly greater.
The aim of this study was to evaluate the risk of PAS and glaucomatous optic neuropathy (GON) at varying ACDs in 2 East Asian populations: those of Mongolia and the Chinese people of Singapore, both with a high prevalence of PACG.

METHODS

STUDY POPULATION

The subjects for this study were from population surveys of glaucoma prevalence in East Asia. Ethical approval for these projects was obtained from the Mongolian Ministry of Health and the Ethical Review Board of Singapore National Eye Centre. The work was carried out in accordance with the World Medical Association’s Declaration of Helsinki. The methods of the examination in both Mongolia and Singapore have been described previously.4-14 A summary is given as follows.

In Hovsgol province, Mongolia, 1000 subjects 40 years and older were chosen from the local government population register, representing 4.8% of the province’s population in this age group. The subjects were drawn from urban (400 people) and rural (600 people) areas, using a combination of clustered, random sampling and systematic sampling. The electoral register of Tanjong Pagar district in Singapore was used to identify 2000 Chinese subjects from this population (13.3% of the total), using a disproportionate, stratified, clustered, random sampling procedure. Subjects were drawn randomly, approximately 500 from each of 4 age strata: 40 to 49, 50 to 59, 60 to 69, and 70 to 79 years, residing in 50 area clusters defined by street name. The proportions of men and women were determined by the sex ratio of that age group in the district.

OPHTHALMIC ASSESSMENT

Central ACD (corneal epithelium to anterior lens epithelium) and central corneal thickness were measured with a slitlamp (model 900; Haag-Streit, Bern, Switzerland) by optical pachymetry (Depth Measuring Devices I and II; Haag-Streit). No cycloplegic agents were used before measurements were taken. “True” ACD (from corneal endothelium to the anterior lens surface) was calculated by subtracting central corneal thickness from the central ACD measurement. True ACD in the right eye was used in all further analysis. Single measurements were made for each eye in Mongolia, while 3 measurements per eye were made for each subject in Singapore. Ninety-five percent of measurements were made by 1 observer (P.J.F.).

Goldmann 2-mirror gonioscopy was performed on all subjects. A low level of ambient illumination was used throughout the examination. A 1-mm beam of light was reduced to a very narrow slit and was offset horizontally for assessing superior and inferior angles, and vertically for nasal and temporal angles. Care was taken to avoid letting light fall on the pupil during gonioscopy. The assessment was carried out at high magnification (×16 in Mongolia, ×25 in Singapore). Dynamic gonioscopy was used to establish presence or absence of PAS. Manipulative gonioscopy was performed using the rim of a Goldmann 2-mirror lens to indent the central cornea, while the subject looked toward the mirror. If sufficient corneal indentation could not be achieved, a Zeiss or Sussman 4-mirror lens was used.

In Mongolia, the vertical cup-disc ratio was estimated and the posterior pole was examined through an undilated pupil with a +90-dioptr lens (Volk Optical Inc, Mentor, Ohio). If there was a poor view or an inexplicable reduction of either visual acuity or field defect, the pupil was dilated with 0.5% tropicamide (Alcon Laboratories [UK] Ltd, Hemel Hempstead, England). In Singapore, the optic disc was examined through dilated pupils with a slitlamp by means of a fundus contact lens at ×40 magnification. The vertical dimensions of the disc and cup were measured by means of an eyepiece graticule etched in 0.1-mm units (Measuring Eyepiece; Haag-Streit). Visual field screening was carried out on all subjects by Henson field screener using the suprathreshold screening strategy. A suspect or abnormal outcome resulted in further threshold field testing (using the Henson field screener in Mongolia and a Humphrey Visual Field Analyzer, model 750 [Zeiss Humphrey, a division of Zeiss-Meditec, Dublin, Calif, in Singapore]). Glaucomatous optic neuropathy was defined as a combination of characteristic structural changes at the disc and a reproducible visual field defect, or, in the absence of reliable field tests, the presence of advanced structural damage to the disc. This definition of GON and the specific criteria used in each survey have been described in detail previously.4,9,10,18 These equated to International Society of Geographical and Epidemiological Ophthalmology categories 1 and 2 of glaucoma.

DATA ANALYSIS

Normality of distributions was checked with the 1-sample Kolmogorov-Smirnov test. Parametric t tests and analysis of variance were used if normality assumptions were satisfied; otherwise the Mann-Whitney test and Kruskal-Wallis test were applied. Univariate and multiple linear regression was used to explore the relationship between country of origin, sex, age, and ACD. Logistic regression was carried out to assess the relationship between GON and both PAS and occludable angles, while correcting for the effect of age and sex. Mean within-subject variance was used to calculate mean within-subject standard deviation (τWM). Repeatability was calculated as \( \frac{\sigma^2}{\frac{1}{n} \sum_{i=1}^{n} (Y_i - \bar{Y})^2} \).19

The expected relationship between proportion of PAS and group mean ACD was logistic. From the proportion (p) of people with PAS, the logit \( \log(p/(1-p)) \) was calculated and plotted against group mean ACD.20 All statistical tests were conducted at 5% level of significance, with the use of SPSS version 11.5 (SPSS Inc, Chicago, Ill). The 95% confidence intervals (CIs) and odd ratios (ORs) were calculated by means of Confidence Interval Analysis software (version 2.0; BMJ Books, London, England).

RESULTS

The study population consisted of a total of 2032 subjects 40 years and older, comprising 942 Mongolians and 1090 Chinese Singaporeans. The demographic data are summarized in Table 1.

ANTERIOR CHAMBER DEPTH

There was a highly significant correlation in the ACD of the right and left eyes (Pearson correlation coefficient: Singapore, 0.96, P < .001; Mongolia, 0.98, P < .001). The following analyses were based on the ACD of the right eye.

Table 2 shows the age-specific values for mean ACD in men and women by country of origin. Univariate linear regressions of ACD indicated that it was significantly shallower by 0.09 mm (95% CI, 0.06-0.12 mm; P < .001) in Mongolian people, was lower in women by 0.13 mm (95% CI, 0.10-0.16 mm; P < .001), and declined by 0.10 mm per decade (95% CI, 0.09-0.11 mm;
RISK OF PAS AT DIFFERENT ACD VALUES

After adjustment for age and sex, people with primary PAS had a shallower anterior chamber than people without (Mongolians: 0.31 mm, P < .001; Singaporeans: 0.19 mm, P < .001). Table 3 compares the rate of PAS at different ACDs in the 2 populations. There was a trend of increasing prevalence of PAS with decreasing ACD. In Mongolia, the PAS rate appeared to increase only below an ACD of 2.40 mm, whereas among Singaporeans, there appeared to be no threshold, but rather a stepwise increase in rate. Relative to an ACD of 2.8 mm or more, the odds of PAS with an ACD of 2.00 to 2.19 mm was 6 times higher among Singaporeans and 18 times greater among Mongolian people. With an ACD of 1.79 mm or less, the OR of PAS had increased to 16 in Singaporeans and 18 times greater than that among Mongolians (OR, 1.8; P < .001). For Mongolian people, there was a clear threshold of ACD above which the risk of PAS was very small. The Figure compares predicted values from these theoretical models with observed values.

Multiple logistic regression was used to investigate factors associated with the presence of primary PAS in right eyes. For Mongolian people, a shallower ACD was associated with higher odds of PAS (OR, 2.8 per 0.2-mm decrease in ACD; P < .001). Age and sex were not significantly associated (P = .16 and .70, respectively) with the presence of PAS. Similarly, in Chinese Singaporeans, shallower ACD was a significant risk factor for PAS (OR, 1.5 per 0.2-mm decrease in ACD; P < .001). In this model, female sex was also significantly, independently associated with PAS (OR, 2.0 vs men; P = .03), although age was not (P = .47). A strong correlation between ACD and gonioscopic angle width was identified in both populations (Mongolians: r = 0.69, P < .001; Singaporeans, r = 0.77, P < .001).

RISK OF GON AT DIFFERENT ACD VALUES

Table 4 illustrates the relationship between ACD and GON in Mongolians and Singaporeans. The highest rate


Table 3. Relationship Between Axial ACD and PAS*

<table>
<thead>
<tr>
<th>ACD, mm</th>
<th>No. With PAS</th>
<th>% With PAS (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
<th>No. With PAS</th>
<th>% With PAS (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2.80</td>
<td>1</td>
<td>1.0 (0.6-3.8)</td>
<td>1.0</td>
<td>1</td>
<td>0.6 (0.1-3.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>2.60-2.79</td>
<td>6</td>
<td>2.6 (1.2-5.6)</td>
<td>1.8 (0.5-6.4)</td>
<td>1</td>
<td>0.5 (0.1-3.0)</td>
<td>0.9 (0.06-15.0)</td>
</tr>
<tr>
<td>2.40-2.59</td>
<td>11</td>
<td>5.4 (3.0-9.4)</td>
<td>3.7 (1.2-11.9)</td>
<td>1</td>
<td>0.5 (0.1-2.7)</td>
<td>0.8 (0.05-13.5)</td>
</tr>
<tr>
<td>2.20-2.39</td>
<td>11</td>
<td>7.6 (4.3-13.1)</td>
<td>5.0 (1.7-17.3)</td>
<td>4</td>
<td>2.1 (0.8-5.3)</td>
<td>3.7 (0.4-33.6)</td>
</tr>
<tr>
<td>2.00-2.19</td>
<td>9</td>
<td>9.5 (5.1-17.0)</td>
<td>6.0 (2.1-23.0)</td>
<td>9</td>
<td>9.3 (5.0-16.7)</td>
<td>17.8 (2.2-142.7)</td>
</tr>
<tr>
<td>1.80-1.99</td>
<td>2</td>
<td>6.1 (1.7-19.6)</td>
<td>4.0 (0.75-24.2)</td>
<td>8</td>
<td>19.0 (10.0-33.3)</td>
<td>40.9 (4.9-338.1)</td>
</tr>
<tr>
<td>≤1.79</td>
<td>1</td>
<td>20.0 (3.6-62.4)</td>
<td>16.5 (1.5-182.0)</td>
<td>4</td>
<td>50.0 (21.5-78.5)</td>
<td>174.0 (15.7-1927.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ACD, anterior chamber depth; CI, confidence interval; PAS, peripheral anterior synechiae.
*The ACD was measured by optical pachymetry, with central corneal thickness subtracted.
†Ninety-five subjects with secondary PAS or incomplete gonioscopic data and 15 subjects with missing ACD data were excluded.
‡Three subjects with secondary PAS and 29 with incomplete gonioscopic or ACD data were excluded.

Figure. Anterior chamber depth (ACD) against rate of peripheral anterior synechiae (PAS) for Mongolian and Singaporean people. Observed proportion (p) of PAS is plotted as log(p/[1−p]) against weighted mean group ACD values: greater than or equal to 2.80 mm (mean, 2.995 mm), 2.60 to 2.79 mm (2.685 mm), 2.40 to 2.59 mm (2.49 mm), 2.20 to 2.39 mm (2.295 mm), 2.00 to 2.19 mm (2.11 mm), 1.80 to 1.99 mm (1.915 mm), and less than 1.80 mm (1.645 mm). The predicted relationship of a logistic relationship is shown by the solid line for Mongolians and the broken line for Singaporeans.

A shallow ACD has previously been identified as a risk factor for PACG, although the imprecise nature of the traditional classification of angle closure limits the inferences that can be drawn from these observations. Subsequently, measurement of axial ACD has been used in population screening for angle closure. Such measurements are noninvasive and are relatively quick and easy to perform on a large scale compared with gonioscopy. However, despite the acknowledged association between shallow ACD and angle closure, the precise nature of the association remains unclear and the risks remain unquantified.

In this study, we assessed the risk of angle closure (indicated by PAS) and GON among Chinese Singaporeans and Mongolians for different levels of ACD. The highest rate and risk of developing these 2 pathological entities, in both populations, occurred in the shallowest anterior chambers. In both Mongolia and Singapore, there appeared to be a dose-response relationship between shallower anterior chamber and higher rate of PAS. We recognize that there are weaknesses in the data supporting these observations, specifically that the number of cases in the important high-risk groups with shallower anterior chambers are small. This was especially problematic among Singaporean people, where ready access to ophthalmic services led to the detection and surgical treatment of 11 of 14 cases diagnosed as having angle closure with glaucoma, albeit using case definitions that were probably unduly stringent. We excluded all cases with possible explanations for secondary PAS, such as previous intraocular surgery, uveitis, or neovascularization. Consequently, the Singaporean population may not truly reflect the natural course of untreated angle closure.

Unexpectedly, we found that the characteristics of the “dose-response” relationship between ACD and angle closure appears to differ between these 2 populations. The logistic model of relationship between ACD and PAS among Singaporeans showed a consistent, incremental increase in PAS across the entire range of ACD examined. In deeper anterior chambers (more numerous in the population at large) the rate of PAS exceeded that seen in the Mongolian people. In Mongolia, there was a clear threshold for ACD around 2.4 mm, above which PAS were very uncommon. With ACD less than 2.4 mm, the rate of PAS rose rapidly to overtake that seen in Singaporeans. The limitations in power discussed previously should be kept in mind when inferences are drawn from these

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observations. This difference may reflect the mechanisms responsible for angle closure in the 2 populations. A pronounced increase in angle width occurs in Mongolian people with narrow angles after laser iridotomy, indicating that pupil block is the predominant mechanism responsible for angle closure. It has been suggested that the situation may not be as clear-cut among Chinese people. A recent review suggested that only 40% of angle closure in Chinese people was attributable to pure pupil block, 8% resulted from non–pupil block (including plateau iris), and 55% was due to a combination of the 2 factors. It does hint that ACD may be less promising as a screening tool among Chinese people than was shown in the Mongolian population.

Our group previously suggested an inverse relationship between population mean ACD and the prevalence of angle closure. British, Australian, and American people of European ancestry, with a PACG prevalence of 0.04% to 0.6%, have deeper anterior chambers compared with Chinese and Mongolians, while Greenland Inuits with a PACG prevalence of 2.6% to 5.0% have the shallowest mean ACD of all. Congdon et al reported that, among Chinese people living in an industrialized country, there is no detectable difference in ACD distribution from that seen in European and African people. However, there is emerging evidence of significant differences in ocular biometric characteristics between East Asian people in affluent countries and those with less industrialization. Nonetheless, our current findings begin to reconcile these 2 points of view. We have shown that ACD is a risk factor for angle closure in Chinese people, but the magnitude of the risk at certain levels of ACD is specific to the population concerned.

Other significant findings in our study were that anterior chambers were significantly shallower in women than men of all ages, and anterior chamber depth decreased with age. These findings agree with previously published data. The shallower anterior chambers in both Singaporean and Mongolian populations were found in elderly women, and they are the subgroup most at risk of angle closure. Prevention programs for this disease may therefore adopt strategies targeting this subgroup at highest risk.

Our data have important implications for intervention for people with established angle closure and those with narrow drainage angle without conclusive evidence of closure, both at an individual and a population level. The ACD is a significant predictor of PAS. A greater extent of PAS is associated with poor intraocular pressure control and probability of needing drainage surgery. As PACG appears to be a predominantly pressure-dependent disease, this is in turn linked with the risk of subsequent GON. A prospective study of a cohort in India found that the 5-year incidence of established angle closure in people with narrow angles was 22%, and the 5-year incidence of GON was 29% in people with established angle closure, a proportion of whom had undergone laser peripheral iridotomy. Currently, most glaucoma specialists recommend laser peripheral iridectomy when any PAS or appositional closure is detected. We have shown that, especially for southern Chinese people, there is no level of ACD for which the risk profile of angle closure changes abruptly. This reinforces the importance of gonioscopy in the assessment of all glaucoma suspects. In the light of these findings, and the projected importance of angle-closure glaucoma as a cause of blindness in China, it could be strongly argued that gonioscopy should form part of the routine eye examination for Chinese people.

Our study has the advantage of being population based, thus giving a representative, cross-sectional depiction of Mongolian and, with some limitations we have already discussed, Singaporean communities. However, these findings are probably not applicable to whites or other racial groups. In addition, little is known about the long-term natural course of eyes with shallow anterior chambers. Large-scale, prospective studies are needed to assess the risks and benefits of prophylaxis by laser iridotomy, ideally powered to allow subgroup analysis at different levels of ACD. In addition, the optimal timing of intervention in the process of angle closure has yet to be determined. There is a critical need for further research into the detection and prevention of this major cause of blindness in Asia.

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