Dynamic Iris Changes as a Risk Factor in Primary Angle Closure Disease

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Purpose. We studied the association between dynamic iris changes and the spectrum of primary angle closure disease (PACD), using the anterior segment optical coherence tomography (ASOCT).

Methods. Eligible primary angle closure (PAC), primary angle closure glaucoma (PACG), age, and sex comparable primary angle closure suspects (PACS) and normal subjects from the 5-year follow-up of the Handan Eye Study underwent ASOCT testing in dark and light conditions. The right eye of each subject was analyzed and biometric parameters including iris cross-sectional area (IA), lens vault (LV), pupil diameter (PD), and centroid-to-centroid distance (CCD) were calculated using the Zhongshan Angle Assessment Program.

Results. Totals of 31 PACS, 31 PAC/PACG, and 31 normal eyes were eligible for analysis. Loss of IA per mm PD increase in the dark compared to light was 0.18 mm in PACS, 0.13 mm in PAC/PACG, and 0.24 mm in normal ($P = 0.015$ between groups) groups. Diagnoses of normal ($P = 0.001$) and a smaller PD in light ($P = 0.003$) were statistically significant determinants of a larger IA loss per mm PD increase in the dark compared to light. Logistic regression analysis showed that LV ($P = 0.002$) and IA loss per mm PD increase ($P = 0.017$) were risk factors for an occludable angle.

Conclusions. Significant differences in iris behavior in the dark compared to light in PACS, PACD, and normal eyes add to the evidence that dynamic iris change has a role in the pathogenesis of PAC in a rural Chinese population.

Keywords: primary angle closure suspect, primary angle closure disease, iris cross-sectional area, anterior segment optical coherence tomography, mydriasis

Primary angle closure glaucoma (PACG) is a major cause of visual morbidity in Asia, with the largest number of those affected resident in China.[1,2] Traditional known ocular risk factors of PACG include small eye, shallow central anterior chamber depth (ACD), short axial length (AL), and a thick and anteriorly positioned lens.[3–5] However, although PACG is more prevalent among Chinese than Caucasians, the mean ACD and AL is not significantly different between Chinese, Caucasian, or black populations.[6] This lack of difference suggests that other risk factors may contribute to the excess burden of PACG among Asians. Anterior chamber depth and AL do not have acceptable sensitivity or specificity to screen for angle closure, and these and other traditional risk factors do not predict which eyes might have angle closure.[7–10] The evidence suggests that primary angle closure (PAC) is a multifactorial disease caused by a combination of anatomical and dynamic components.[11–13]

The International Society of Geographical and Epidemiological Ophthalmology (ISGEO) classification for PAC includes primary angle closure suspect (PACS), PAC, and PACG.[10,14] However, PACS is not a disease state but a group at risk for PAC and PACG, which represents pathology. Furthermore, because use of the term "primary angle closure" to refer to PAC and PACG can lead to confusion, in this report we used the term primary angle closure disease (PACD) to refer to the disease states PAC and PACG, and labeled those with only the risk factor of occludable angles as PACS.[15] The three terms PACS, PAC, and PACG share the common characteristic of an occludable angle, defined as nonvisibility of posterior trabecular meshwork for at least 180°.[9]

Recent reports suggest that the main dynamic risk factors involved in PACD include changes in the iris and choroid.[16–26] As far as the iris is concerned, it has been hypothesized that since iris loses water with pupil dilation (because of the high fluid content of its stroma and the capacity for fluid movement), irides with more compact or water-retentive stroma (poor fluid conductivity) may be a dynamic factor that could predispose some anatomically susceptible eyes to PAC.[16]

Using anterior segment optical coherence tomography (ASOCT), PACS and PAC eyes of subjects of Caucasian ancestry showed a smaller loss of iris cross-sectional area (IA) following physiologic/pharmacologic dilation compared to those with

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open angles.[16] Similar findings have been reported in South Indians: IA and iris volume (IV) decreased with pupillary dilatation in normal and PAC eyes with the loss of IV lower in PAC.[17] In a French report, IVs in fellow eyes of patients with acute angle closure (AAC) increased following physiologic and pharmacologic mydriasis.[19,20] A study from Singapore also reported an increased IV following physiologic dilation of the fellow eyes of AAC.[21] The increase in IV is paradoxical and Quigley et al.[27] have shown that increased IV is an artifact caused by an increase of centroid-to-centroid distance (CCD) used in the formula to calculate IV from IA.[27]

Using data from the Handan Eye Study (HES), we have reported previously that PACS and normal eyes respond differently to physiologic and pharmacologic pupillary dilation, with the former showing a smaller reduction in IA and IV.[18] However, the formula used in that study suffered from the deficiency raised by Quigley et al.[27] and we now elect to use IA, rather than IV to represent iris dynamic change. In another study, we investigated the IA change after physiologic and pharmacologic mydriasis in PACS/PAC/PACG subjects with different dominant mechanisms for angle closure of the same population and reported that the smallest decrease of IA occurred in eyes with pupillary block as the dominant mechanism.[15]

The objective of this study was 3-fold: (1) quantify changes and differences in IA in the dark compared to light in normal, PACS, and PAC/PACG subjects; (2) study the association of such changes with demographic factors and previously reported ocular biometric measurements; and (3) investigate the possible risk factors (anatomical and dynamic) for PAC.

Methods

Subjects and Ophthalmic Examination

This observational, cross-sectional study was conducted on a sample of PACS, PAC/PACG, and normal subjects selected from the 5-year follow-up of the HES; the study has been described in detail previously.[8,15] Consecutive subjects aged $\geq$40 years old who participated in the follow-up examination between September 2012 and May 2013 and had an occludable angle (posterior trabecular meshwork not visible for at least 180° on gonioscopy) with peripheral anterior synechiae (PAS) and/or increased IOP, with or without glaucomatous optic neuropathy (GON), were included in the PAC/PACG group.[10,14] An equal number of age and sex comparable PACS and normal subjects were selected from a previous study, which was also conducted on the 5-year follow-up cohort of the HES.[8] Primary angle closure suspects (PACS) was defined as posterior trabecular meshwork not visible for at least 180° on static gonioscopy without PAS on indentation/manipulation, IOP $\leq$ 21 mm Hg, healthy optic nerves, and normal visual fields.[10,14] Normal was defined as IOP $\leq$ 21 mm Hg with open angles, healthy optic nerves, and normal visual fields, no previous surgery, and no family history of glaucoma.

Subjects with an axial length shorter than 19 mm or longer than 25 mm, previous intraocular surgery other than filtering surgery, previous eye injury, or corneal disorders preventing anterior chamber assessment, those on topical or systemic medication that could affect the iris or angle configuration, those who had suffered an episode of AAC or undergone laser iridoplasty, as well as subjects with a diagnosis of diabetic retinopathy or other fundus diseases were excluded.[15,18]

A comprehensive ophthalmic examination including presenting (PVA) and best corrected LogMAR visual acuity (BCVA), objective and subjective refraction, slit-lamp biomicroscopy, visual field examination, applanation tonometry, gonioscopy, A-scan ultrasound biometry, and fundus examination was performed on all participants.[15,18] A KR-8800 auto keratorefractometer (Topcon, Tokyo, Japan) was used to measure refraction of subjects, while the 24-2 Swedish Interactive Testing Algorithm (SITA) standard program on a visual field analyzer (Humphrey Visual Field Analyzer 740i or 750i; Carl Zeiss, Jena, Germany) was used for visual field testing. OcuScan RxP (Alcon, Inc., Fort Worth, TX, USA) was used for measurement of central corneal thickness (CCT), ACD, lens thickness (LT) and AL.[15,18]

The study adhered to the Declaration of Helsinki and was approved by the ethics committee of the Beijing Tongren Hospital. All subjects provided verbal and written informed consent.

ASOCT Image Acquisition

An ASOCT (Visante, Carl Zeiss Meditec, Inc., Dublin, CA, USA), a noncontact optical coherence tomographic system using 1310 nm wavelength light to capture high resolution cross-sectional images of ocular anterior segment, was used to image each eye of all subjects, first in the dark (approximately 3 lux, to induce physiologic mydriasis) and then after 3 minutes of exposure to approximately 200 lux of light.[28,29] The dark measurements were made after 3 minutes of dark adaptation.

All images were obtained in the ''anterior segment quadrant" mode at 0 to 180, 45 to 225, 90 to 270, and 135° to 315° meridians. The operator gently retracted the upper and lower lids as needed for a better vertical image acquisition, taking care to avoid inadvertent pressure on the globe. If scleral spur visibility was poor, the imaging was repeated and the best set of images selected.[15,18] As a small change in pupil diameter (PD) would not contribute to, or even mask information, eyes with a PD increase of less than 0.5 mm after physiologic mydriasis were excluded.[27]

Image Analysis

The Zhongshan Angle Assessment Program (ZAAP, Guangzhou, China) was used to measure and calculate the angle and anterior chamber configuration parameters. These included angle opening distance at 500 μm (AOD500), trabecular-iris space area at 500 μm (TISA500), angle recess area at 750 μm (ARA750), anterior chamber area (ACA), anterior chamber volume (ACV), and anterior chamber width (ACW); iris-related parameters, including iris thickness at 750 μm (IT750), iris curvature (IC) and IA, and lens vault (LV), CCD, and PD (see Fig.). The scleral spur was located manually on each side of the image.[30]

The AOD500 is the distance from the corneal endothelium to the iris surface as determined from a perpendicular to a line drawn at 500 μm from the scleral spur.[31] The TISA500 is the area bounded anteriorly by the AOD500, posteriorly by a line drawn from the scleral spur perpendicular to the plane of the inner scleral wall to the iris, superiorly by the inner corneoscleral wall and inferiorly by the iris surface.[32] The ARA750 is the area bordered by the anterior iris surface, corneal endothelium, and a line perpendicular to the corneal endothelium drawn to the iris surface from a point at 750 μm anterior to scleral spur.[33] The ACW is measured as the distance between the left and right scleral spur.[34] The ACA is defined as the cross-sectional area of the anterior segment bounded by the corneal endothelium, anterior surface of the iris, and anterior surface of the lens (within the pupil), and ACV is calculated by rotating the ACA 360° around the vertical axis which is through the midpoint (center) of the ACA.[35]

Table 1. Demographic Data and Ocular Biometric Measurements in Normal, PACS, and PAC/PACG Subjects

Parameter	Normal Subjects, $n = 31$	PACS Subjects, $n = 31$	PAC/PACG Subjects, $n = 31$	*P* Value	*P* Value, Normal vs. PACS	*P* Value, Normal vs. PAC/PACG	*P* Value, PACS vs. PAC/PACG
Age (SD), y	63.3 (8.5)	63.8 (6.5)	64.0 (6.4)	0.901*			
Male (%)	14 (45.2)	14 (45.2)	14 (45.2)	1.000†			
Female (%)	17 (54.8)	17 (54.8)	17 (54.8)				
PVA (IR)	0.20 (0.14, 0.40)	0.30 (0.18, 0.50)	0.28 (0.12, 0.40)	0.361*			
BCVA (IR)	0.00 (0.00, 0.20)	0.10 (0.00, 0.30)	0.00 (0.00, 0.20)	0.478‡			
SE (IR), diopter	0.00 (0.00, 0.75)	0.63 (0.00, 1.31)	0.44 (0.00, 1.13)	0.192‡			
IOP (SD), mm Hg	12.3 (2.6)	12.0 (2.4)	13.8 (5.3)	0.120‡			
CCT (SD), mm	534 (23)	536 (32)	540 (28)	0.737*			
Central ACD (SD), mm	2.75 (0.26)	2.52 (0.27)	2.65 (0.38)	0.014*	0.010§	0.426§	0.203§
LT (SD), mm	4.71 (0.50)	4.89 (0.39)	4.70 (0.56)	0.251*			
AL (SD), mm	22.87 (0.90)	22.19 (0.78)	22.53 (0.67)	0.005*	0.003§	0.209§	0.219§
MD	−3.99 (4.48) ($n = 21$)	−4.12 (2.68) ($n = 24$)	−7.01 (5.69) ($n = 25$)	0.036*	1.000||	0.078||	0.077||
PSD	3.22 (2.42) ($n = 21$)	3.74 (2.65) ($n = 24$)	5.31 (2.65) ($n = 25$)	0.021*	1.000||	0.026||	0.109||

IR, interquartile range.
* 1-way ANOVA.
† χ^2 test.
‡ Kruskal-Wallis test.
§ Tukey's Honestly Significant Difference (HSD).
|| Bonferroni test.

The IT750 is defined as the shortest distance between designated locations (at 750 μm from the scleral spur) at the anterior and posterior iris surface.[34] Iris curvature is determined by measuring the maximum distance between the posterior iris surface and a line from the iris root to the first point of contact between the iris and lens.[34] Iris cross-sectional area was defined as the cross-sectional area of the nasal and temporal sides.[36] The changes in ASOCT parameters were measured going from dark to light. To make the results easier to analyze and understand, the larger values minus the smaller values of each parameter were chosen to present the changes.

Lens vault is the perpendicular distance between the anterior pole of the lens and a horizontal line joining the two scleral spurs of the same cross-sectional image.[37] Centroid-to-centroid distance is the distance between the centers of the nasal and temporal iris masses.[27] Pupil diameter was automatically measured as the distance between the pupillary tips of the iris on both sides on the cross-sectional images.[34]

All images were analyzed by a single experienced observer (ZY). Each value represented the average of measurements from eight iris cross-sections as obtained from ASOCT scans.

Statistical Analysis

Data from the right eye were used for analysis. Variables demonstrating a normal distribution are presented as mean (SD), while variables failing to achieve a normal distribution are presented as median (percentiles). Analysis of variance, nonparametric tests, and the χ^2 test were used to compare differences between the normal, PACS, and PAC/PACG groups.

Multivariable linear regression was conducted with IA loss per millimeter (mm) PD increase as the dependent/predicted variable, and age, sex, spherical equivalent (SE), CCT, ACD, LT, AL, PD in light, PD in dark, CCD in light, CCD in dark, CCD change, and diagnosis (PACS versus normal, PAC/PACG versus normal) as independent/predictor variables.

Logistic regression models were used to determine the odds ratios (ORs) and 95% confidence intervals (CI) for putative risk factors associated with occludable angle (for both PACS and PAC/PACG), using a backward procedure in multivariable logistic regression analysis for all variables with $P < 0.05$ in a univariable analysis. Since age and sex were comparable between three groups, parameters including ACD, LT, AL, IT750 in light, IT750 in dark, IC in light, IC in dark, LV in light, LV in dark, and IA loss per mm PD increase were assessed as possible independent variables.

All analyses were performed using SPSS statistical software version 17.0 (SPSS, Inc., Chicago, IL, USA) for Windows. *P* values less than 0.05 were considered significant.

Results

Subjects Characteristics

There were 45 PAC/PACG subjects attending the 5-year HES follow-up during September 2012 to May 2013 eligible for inclusion. A total of 14 PAC/PACG eyes was excluded: five eyes (11.1%) due to poor image quality or inability to accurately identify the scleral spur and nine eyes with pupil diameter change less than 0.5 mm in the dark compared to light. There were no statistically significant differences in demographic or ocular features between the included and excluded PAC/PACG eyes/patients. A total of 93 eyes (31 PAC/PACG, 31 PACS, and 31 normal eyes) was available for final analysis.

Table 1 shows the demographic characteristics and ocular biometric data of subjects in the PACS, PAC/PACG, and normal groups. Reliable visual field examination results were available for 21 normal, 24 PACS, and 25 PAC/PACG subjects. There was no significant difference in age, sex, PVA, BCVA, SE, IOP, CCT, and LT among the three groups. There was a significant difference in ACD ($P = 0.014$), AL ($P = 0.005$), mean deviation (MD; $P = 0.036$), and pattern standard deviation (PSD; $P = 0.021$) among the three groups with the deepest ACD, longest AL, highest MD, and lowest PSD in the normal group.

The mean values and the absolute and relative changes when going from dark to light for ASOCT parameters in PACS, PAC/PACG, and normal groups along with the

Table 2. Anterior Chamber, Angle, and Lens Parameters Measured by ASOCT in Light and Dark Conditions

Conditions	Parameter	Normal Subjects, $n = 31$	PACS Subjects, $n = 31$	PAC/PACG Subjects, $n = 31$	*P* Value	*P* Value, Normal vs. PACS†	*P* Value, Normal vs. PAC/PACG†	*P* Value, PACS vs. PAC/PACG†
Light	AOD500; L (SD), mm	0.338 (0.084)	0.248 (0.078)	0.194 (0.083)	<0.001	<0.001	<0.001	0.029
	TISA500; L (SD), mm^2	0.140 (0.035)	0.103 (0.032)	0.068 (0.030)	<0.001	<0.001	<0.001	<0.001
	ARA750; L (SD), mm^2	0.357 (0.110)	0.269 (0.093)	0.176 (0.087)	<0.001	0.002	<0.001	0.001
	ACW; L (SD), mm	11.10 (0.30)	10.88 (0.36)	10.90 (0.46)	0.045	0.067	0.090	0.991
	ACA; L (SD), mm^2	17.97 (2.31)	15.96 (2.04)	14.69 (2.61)	<0.001	0.003	<0.001	0.089
	ACV; L (SD), mm^3	72.71 (12.21)	62.03 (10.51)	55.69 (13.61)	<0.001	0.002	<0.001	0.106
	IT750; L (SD), mm	0.46 (0.07)	0.47 (0.06)	0.47 (0.06)	0.630			
	IC; L (SD), mm	0.23 (0.06)	0.26 (0.06)	0.19 (0.12)	0.005	0.541	0.077	0.004
	LV; L (SD), μm	286.8 (157.6)	402.5 (129.9)	545.1 (232.3)	<0.001	0.033	<0.001	0.006
Dark	AOD500; D (SD), mm	0.293 (0.082)	0.203 (0.074)	0.107 (0.077)	<0.001	<0.001	<0.001	<0.001
	TISA500; D (SD), mm^2	0.117 (0.031)	0.079 (0.030)	0.038 (0.023)	<0.001	<0.001	<0.001	<0.001
	ARA750; D (SD), mm^2	0.299 (0.096)	0.207 (0.095)	0.108 (0.080)	<0.001	<0.001	<0.001	<0.001
	ACW; D (SD), mm	11.14 (0.29)	10.99 (0.42)	11.10 (0.42)	0.271			
	ACA; D (SD), mm^2	18.52 (2.28)	16.51 (2.15)	15.12 (2.61)	<0.001	0.003	<0.001	0.057
	ACV; D (SD), mm^3	74.85 (12.18)	64.53 (11.56)	57.69 (13.47)	<0.001	0.004	<0.001	0.083
	IT750; D (SD), mm	0.49 (0.06)	0.50 (0.06)	0.52 (0.06)	0.164			
	IC; D (SD), mm	0.24 (0.06)	0.26 (0.08)	0.23 (0.10)	0.248			
	LV; D (SD), μm	327.8 (163.4)	461.1 (173.7)	662.2 (225.3)	<0.001	0.018	<0.001	<0.001

L, light; D, dark.
* 1-way ANOVA.
† Tukey's Honestly Significant Difference (HSD).

differences among the three groups are summarized in Tables 2 and 3.

In the light condition, a significant difference in AOD500, TISA500, IC, ARA750, ACD, ACW, ACA, ACV, and LV was found among the three groups ($P < 0.05$). In the dark condition, AOD500, TISA500, ARA750, ACD, ACA, ACV, and LV showed significant differences among the three groups ($P < 0.05$).

IA Measurements

Mean IAs, CCDs, and PDs from eyes of the three groups measured in light and dark are summarized in Table 4. A significant difference in IA in dark condition ($P = 0.006$) existed among the three groups with the largest IA in the PAC/PACG group. There was no significant difference in CCD and

Table 3. Anterior Segment Optical Coherence Tomography: Changes in Anterior Chamber, Angle, and Lens Parameters from Dark to Light

Parameter	Normal Subjects, $n = 31$	PACS Subjects, $n = 31$	PAC/PACG Subjects, $n = 31$	*P* Value	*P* Value, Normal vs. PACS	*P* Value, Normal vs. PAC/PACG	*P* Value, PACS vs. PAC/PACG
AOD500; AC (SD), mm	0.045 (0.060)	0.045 (0.069)	0.087 (0.064)	0.017*	1.000†	0.034†	0.034†
TISA500; AC (SD), mm^2	0.024 (0.023)	0.024 (0.025)	0.030 (0.023)	0.437*			
ARA750; AC (SD), mm^2	0.059 (0.067)	0.062 (0.074)	0.068 (0.075)	0.861*			
ACW; AC (SD), mm	0.04 (0.15)	0.10 (0.20)	0.21 (0.21)	0.003*	0.374†	0.002†	0.091†
ACA; AC (SD), mm^2	0.55 (0.35)	0.56 (0.42)	0.43 (0.72)	0.537*			
ACV; AC (SD), mm^3	2.14 (2.65)	2.50 (3.17)	2.00 (3.22)	0.801*			
IT750; AC (SD), mm	0.03 (0.04)	0.03 (0.03)	0.05 (0.05)	0.313*			
IC; AC (SD), mm	0.002 (0.061)	0.002 (0.081)	0.040 (0.076)	0.067*			
LV; AC (SD), μm	41.0 (77.8)	58.7 (114.5)	117.1 (140.0)	0.026*	0.814†	0.027†	0.113†
AOD500; RC (SD)	0.144 (0.301)	0.144 (0.301)	0.470 (0.290)	<0.001*	0.967†	<0.001†	<0.001†
TISA500; RC (SD)	0.198 (0.295)	0.198 (0.295)	0.418 (0.312)	<0.001*	0.838†	0.001†	0.004†
ARA750; RC (SD)	0.204 (0.323)	0.204 (0.323)	0.350 (0.414)	0.044*	0.808†	0.042†	0.166†
ACW; RC (SD)	0.01 (0.02)	0.01 (0.02)	0.02 (0.02)	0.003*	0.385†	0.002†	0.075†
ACA; RC (SD)	0.04 (0.02)	0.04 (0.02)	0.03 (0.05)	0.860*			
ACV; RC (SD)	0.04 (0.05)	0.04 (0.05)	0.04 (0.06)	0.693*			
IT750; RC (SD)	0.07 (0.08)	0.07 (0.08)	0.11 (0.12)	0.329*			
IC; RC (IR)	−0.04 (−0.15, 0.09)	−0.04 (−0.15, 0.09)	0.17 (−0.06, 0.48)	0.042‡	0.751§	0.039§	0.024§
LV; RC (IR)	0.16 (−0.01, 0.39)	0.16 (−0.01, 0.39)	0.21 (0.05, 0.45)	0.581‡			

Changes in AOD500, TISA500, and ARA750: values measured in the light minus values measured in the dark. Changes in ACW, ACA, ACV, IT750, IC, and LV: values measured in the dark minus values measured in the light. AC, absolute change; RC, relative change.
* 1-way ANOVA.
† Tukey's Honestly Significant Difference (HSD).
‡ Kruskal-Wallis test.
§ Mann-Whitney *U* test (<0.05/3 = 0.017 = significant different).

Table 4. Anterior Segment Optical Coherence Tomography Data for IA, CCD, PD in Dark and Light Conditions

Parameter	Normal Subjects, $n = 31$	PACS Subjects, $n = 31$	PAC/PACG Subjects, $n = 31$	*P* Value	*P* Value, Normal vs. PACS†	*P* Value, Normal vs. PAC/PACG†	*P* Value, PACS vs. PAC/PACG†
IA; L (SD), mm^2	3.01 (0.36)	2.87 (0.26)	3.08 (0.40)	0.061			
CCD; L (SD), mm	7.55 (0.39)	7.50 (0.33)	7.42 (0.49)	0.431			
PD; L (SD), mm	3.82 (0.58)	3.84 (0.46)	3.69 (0.72)	0.559			
IA; D (SD), mm^2	2.77 (0.35)	2.70 (0.29)	2.95 (0.27)	0.006	0.956	0.008	0.003
CCD; D (SD), mm	8.07 (0.39)	8.03 (0.36)	8.02 (0.47)	0.874			
PD; D (SD), mm	4.83 (0.56)	4.79 (0.49)	4.65 (0.66)	0.437			
IA change (SD), mm^2	0.24 (0.16)	0.18 (0.15)	0.13 (0.26)	0.094			
IA loss per mm PD increase (SD), mm	0.24 (0.16)	0.18 (0.16)	0.08 (0.29)	0.015	0.492	0.011	0.174
PD change (SD), mm	1.01 (0.35)	0.95 (0.31)	0.96 (0.43)	0.792			
CCD change (SD), mm	0.52 (0.20)	0.53 (0.22)	0.60 (0.25)	0.333			
CCD increase per mm PD increase (SD)	0.51 (0.08)	0.56 (0.19)	0.64 (0.17)	0.005	0.475	0.004	0.087

Changes in IA and IA loss per mm PD increase: values measured in the light minus values measured in the dark. Changes in PD, CCD, and CCD increase per mm PD increase: values measured in the dark minus values measured in the light.

* 1-way ANOVA.

† Tukey's Honestly Significant Difference (HSD).

PD among the three groups under either light or dark conditions.

A summary of changes in IA, IA loss per mm PD increase, PD change, CCD change, and CCD increase per mm PD increase also is presented in Table 4. Iris cross-sectional area decreased in the dark compared to light in all eyes. Significant differences in the IA loss per mm PD increase in dark compared to light were observed among the three groups ($P = 0.015$); the smallest IA loss occurred in the PAC/PACG group. The CCD increase per mm PD increase ($P = 0.005$) was also significantly different among the three groups, with the largest increase in the PAC/PACG group. Tukey's HSD corrected comparisons showed significant differences in the IA loss per mm PD increase ($P = 0.011$) and CCD increase per mm PD increase ($P = 0.004$) between the normal and PAC/PACG groups.

Regression Analysis

Results of multivariable linear regression analysis of IA loss per mm PD increase are shown in Table 5. Two variables, CCD in light and PD in dark, were excluded because of collinearity with other independent variables. Diagnoses of normal eyes ($P = 0.001$) and a smaller PD in light ($P = 0.003$) were significant determinants of a larger IA loss per mm PD increase.

Table 5. Factors Associated With IA Loss per mm PD Increase

Variable	β	*P* Value	Direction
Age, y	−0.112	0.265	–
Sex	0.127	0.203	–
SE, D	−0.129	0.197	–
CCT, mm	0.173	0.082	–
ACD, mm	0.109	0.277	–
LT, mm	−0.130	0.194	–
AL, mm	−0.010	0.922	–
PACS subjects vs. normal	−0.117	0.302	–
PAC/PACG subjects vs. normal	−0.337	0.001	Normal eyes had more IA loss per mm PD increase
PD; L, mm	−0.308	0.003	Eyes with smaller PD (L) had more IA loss per mm PD increase
CCD; D, mm	−0.010	0.942	–
CCD change; L to D, mm	0.018	0.861	–

Change in CCD: values measured in the dark minus values measured in the light.

The results of the logistic regression analysis are presented in Table 6. A univariable analysis showed that ACD ($P = 0.025$), AL ($P = 0.007$), LV in light ($P < 0.001$), LV in dark ($P < 0.001$), and IA loss per mm PD increase ($P = 0.027$) were associated with an occludable angle. The multivariable logistic regression analysis included all parameters for which the *P* value of the association with an occludable angle was <0.05 in the univariable analysis. However, we could not include LV in light and LV in dark, since they were related. Accordingly, ACD, AL, LV in light, and IA loss per mm PD increase were included in the multivariable logistic regression analysis: risk factors independently associated with an occludable angle were greater LV ($P = 0.002$; OR, 1.006; 95% CI, 1.002–1.009) and less IA loss per mm PD increase ($P = 0.017$; OR, 0.015; 95% CI, <0.001–0.473).

Comparison Between Treated and Untreated PAC/PACG Subjects (Eyes)

Eight treated PAC/PACG eyes, three posttrabeculectomy and five with a laser peripheral iridotomy (LPI), were included in this study. There were no significant differences in age, sex, PVA, BVAR, SE, IOP, ACD, LT, LV (in light and dark), IA change, PD change, IA loss per mm PD increase, or CCD change between treated and untreated PAC/PACG eyes ($P = 0.585$, 1.000, 0.567, 0.256, 0.587, 0.463, 0.432, 0.517, 0.139, 0.325, 0.893, 0.315, 0.560, and 0.442, respectively). Treated eyes had longer AL, larger AOD500 in light, larger TISA500, ARA750, ACV, and smaller IC in light and dark ($P = 0.030$, 0.026, 0.007, 0.001, 0.048, 0.003, 0.012, 0.001, 0.042, and 0.001, respectively), compared to untreated ones (Table 7).

Discussion

The spectrum of primary angle closure "disease" includes three different stages, PACS, PAC, and PACG.[10,14] Primary angle closure subjects are those at risk for PAC and PACG. The presence of raised IOP (>21 mm Hg) and/or PAS in a PACS is termed PAC, and the presence of GON/visual field loss with PAC is considered PACG.

Table 6. Univariable and Multivariable Logistic Regression of Risk Factors for Occludable Angle

	Univariable		Multivariable	
Variable	**OR for Occludable Angle (95% CI)**	***P* Value**	**OR for Occludable Angle (95% CI)**	***P* Value**
ACD, mm	0.180 (0.040, 0.810)	0.025	–	0.594
LT, mm	1.424 (0.595, 3.406)	0.427	–	–
AL, mm	0.452 (0.254, 0.804)	0.007	0.553 (0.281, 1.090)	0.087
IT750; L, mm	29.763 (0.031, 28658.372)	0.333	–	–
IC; L, mm	0.205 (0.001, 28.579)	0.529	–	–
LV; L, μm	1.007 (1.003, 1.010)	<0.001	1.006 (1.002, 1.009)	0.002
IT750; D, mm	627.734 (0.294, 1341926.676)	0.100	–	–
IC; D, mm	2.939 (0.014, 631.126)	0.694	–	–
LV; D, μm	1.007 (1.003, 1.010)	<0.001	–	–
IA loss per mm PD increase, mm	0.046 (0.003, 0.702)	0.027	0.015 (<0.001, 0.473)	0.017

Changes in IA loss per mm PD increase: values measured in the light minus values measured in the dark.

Table 7. Comparison Between Treated and Untreated PAC/PACG Subjects

Parameter	**Treated PAC/PACG Subjects, *n* = 8**	**Untreated PAC/PACG Subjects, *n* = 23**	***P* Value**
Age (SD), y	65.1 (3.5)	63.7 (7.2)	0.585*
Male (%)	4 (50.0)	14 (45.2)	1.000†
Female (%)	4 (50.0)	17 (54.8)	
PVA (SD)	0.30 (0.22)	0.25 (0.19)	0.567*
BCVA (IR)	0.10 (0.00, 0.28)	0.00 (0.00, 0.20)	0.256‡
SE (SD), diopter	0.40 (0.82)	0.63 (0.95)	0.587*
IOP (SD), mm Hg	12.6 (2.5)	14.2 (5.9)	0.463*
Central ACD (SD), mm	2.75 (0.26)	2.62 (0.41)	0.432*
LT (SD), mm	4.59 (0.77)	4.74 (0.49)	0.517*
AL (SD), mm	22.96 (0.53)	22.37 (0.66)	0.030*
AOD500 (SD); L, mm	0.250 (0.076)	0.175 (0.078)	0.026*
TISA500 (SD); L, mm^2	0.092 (0.032)	0.060 (0.025)	0.007*
ARA750 (SD); L, mm^2	0.259 (0.097)	0.148 (0.063)	0.001*
ACV (SD); L, mm^3	63.80 (13.36)	52.86 (12.78)	0.048*
IC (SD); L, mm	0.08 (0.05)	0.22 (0.12)	0.003*
LV (SD); L, μm	650.3 (212.9)	508.5 (231.8)	0.139*
AOD500 (SD); D, mm	0.151 (0.074)	0.092 (0.073)	0.058*
TISA500 (SD); D, mm^2	0.055 (0.029)	0.032 (0.018)	0.012*
ARA750 (SD); D, mm^2	0.181 (0.116)	0.082 (0.043)	0.001*
ACV (SD); D, mm^3	65.93 (14.78)	54.82 (12.02)	0.042*
IC (SD); D, mm	0.14 (0.07)	0.26 (0.08)	0.001*
LV (SD); D, μm	730.8 (156.7)	638.3 (243.1)	0.325*
IA change (SD), mm^2	0.14 (0.39)	0.13 (0.21)	0.893*
PD change (SD), mm	1.09 (0.49)	0.91 (0.41)	0.315*
IA loss per mm PD Increase (SD)	0.03 (0.42)	0.10 (0.24)	0.560*
CCD change (SD), mm	0.66 (0.21)	0.58 (0.27)	0.442*

Changes in IA and IA loss per mm PD increase: values measured in the light minus values measured in the dark. Change in PD and CCD change: values measured in the dark minus values measured in the light.

* Independent *t*-test.

† χ^2 test.

‡ Mann-Whitney *U* test.

Population-based, prospective cohort studies have shown that a minority of PACS cases develop PAC/PACG. In south Indians aged 35 to 65 years, 22% of PACS cases progressed to PAC in 5 years (4.4% per year).[9] Of a cohort of Greenland Eskimos aged 30 and above with an occludable angle, 35% developed PACG over 10 years (3.5% per year).[38] Ye et al.[39] reported that over a follow-up period of 6 years, 4.1% of subjects aged 40 and older with an ACD ≤2.0 mm or peripheral anterior chamber depth ≤1/4 corneal thickness or ≤1/4 iris light band ratio on the nasal under flash light examination, suffered PACG.[39]

Evidence is accumulating that iris dynamic changes along with anatomical factors, may contribute to the progression.[16,17,19–21] Primary angle closure disease is a multifactorial disease for which the individual factors can be considered in the framework of a sufficient component causal model.[13] Our previous study of PACS and normal subjects suggested that the dynamic behavior of the iris is likely to be one of the component causes in sufficient component causal models for PAC/PACG.[18]

In this study, IA loss from the light to dark condition was used as the parameter for dynamic iris change. Iris cross-sectional area decreased in PACS, PAC/PACG, and normal eyes after physiologic dilation. Statistically significant differences existed among the three groups, with the smallest IA loss in the PAC/PACG group. Multivariable regression showed that normal eyes had more IA loss per mm PD increase, compared to PAC/PACG eyes. All these findings provide further support for the hypothesis that a diminished tendency to lose IA with dilation contributed to PAC.[16]

An interesting finding is the significant difference in the CCD increase per mm PD increase between PACS, PAC/PACG, and normal eyes, with the largest CCD increase per mm PD increase occurring in PAC/PACG eyes. The ratio of CCD increase to pupil dilation can be considered a measure of iris area redistribution peripherally.[27] Our results showed that following physiologic dilation of the pupil, PAC/PACG eyes had more peripheral redistribution of IA when compared to normal eyes; in eyes at risk this likely contributes to the narrowing or closing of the anterior chamber angle.

Equally interesting are the results of logistic regression analysis, which showed that only greater LV and less IA per mm PD increase were associated with occludable angles while traditionally described risk factors, including ACD, LT, and AL, were not significant. The A-scan ultrasound biometry results showed that PACS eyes had the smallest central ACD, largest LT, and smallest AL, compared to normal and PAC/PACG eyes, with significant differences in central ACD and AL. While it is possible that the small numbers may have been responsible for failure to achieve significance for some risk factors, we feel this is further

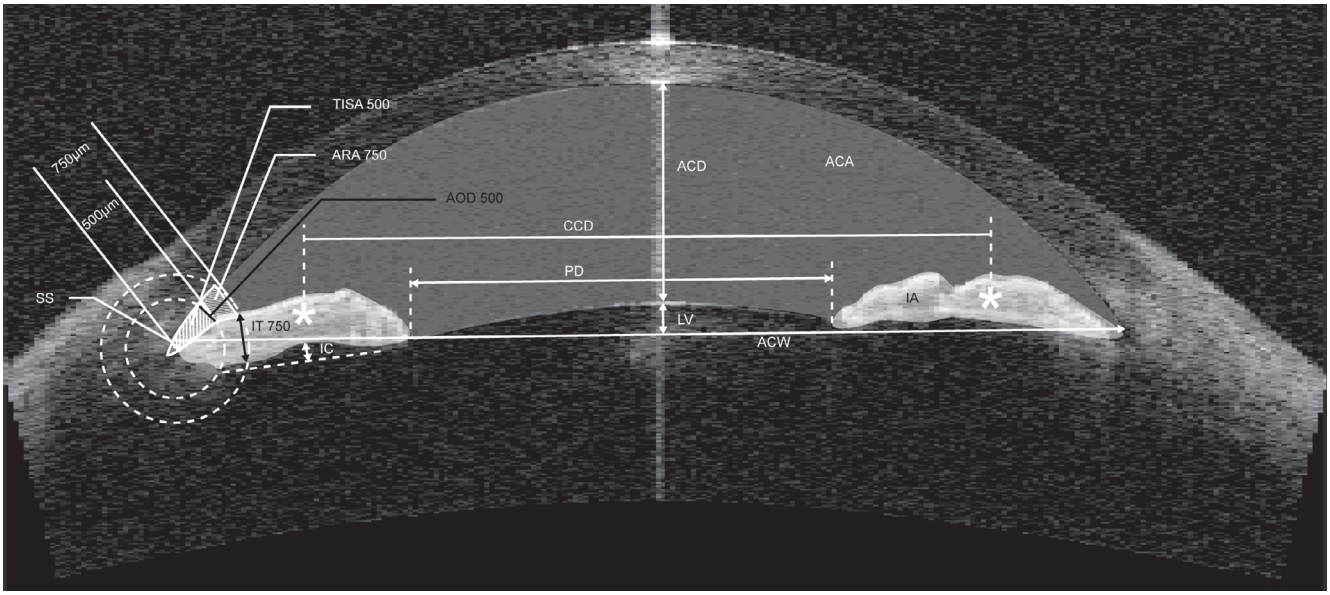

Figure. Anterior segment optical coherence tomography image showing measurements of main parameters.

evidence that risk factors other than those traditionally considered responsible contribute to the pathogenesis of PACD.

Lens vault is a recently described parameter that represents the height of the lens anterior to the scleral spur plane, and has been reported to be a significant predictor of angle closure disease.[11] Our study supported that finding. It would seem that a larger LV predisposes the eye to angle closure through at least two mechanisms. The larger area of the crystalline lens protruding anteriorly is expected to increase pupillary block via increased iridolenticular contact, while the greater the LV, the more the iris may be pushed anteriorly and aggravate angle narrowing.[40,41] However, while achieving statistical significance, the OR for LV (OR, 1.006; 95% CI, 1.002–1.009) was marginal and less impressive than that for IA loss per mm PD increase (OR 0.015; 95% CI, <0.001–0.473).

As far as IA loss per mm PD increase is concerned, the smaller the loss of iris area the narrower the angle becomes with dilatation. We suggest that what may matter most in angle closure is the relative location of the lens and the changes in the angle as the pupil dilates; both are explained by the two factors that we found to be significant. It seems logical that pupillary block (through any mechanism, including LV) and iris changes as the pupil dilates are keys to angle closure and this fits our understanding of a sufficient component causal model for PAC/PACG.[12,13]

The MD and PSD of visual fields were different between normal, PACS, and PACD. Advanced field defects can cause a change in pupillary reaction and could possibly affect the behavior of the iris.[42,43] However, it seems more plausible that dynamic iris changes lead to changes in IOP that then are followed by damage that manifests as visual field defects.

Iridotomy and trabeculectomy may change the dynamic response of iris during physiologic pupil dilation, particularly by eliminating pupillary block as well as a decrease in iris tension decreasing iris mobility; this may represent a potential bias in our study.[19] According to the reasoning for two major factors being involved as detailed above, it also is possible that inclusion of cases where pupillary block was eliminated may have led to the lower effect size for lens vault. While no significant difference was found in IA loss between treated and untreated eyes following physiologic mydriasis the numbers are too few to comment on the effect of iridotomy/trabeculectomy on iris dynamic changes.

The results of our study should be interpreted with its several limitations in mind. As all patients were of Chinese descent, the results may not be entirely applicable to other ethnic groups. The number of subjects included in this study is relatively small. While a larger sample size is desirable, the findings can be interpreted in the light of prior knowledge and biological plausibility: our results add to the existing evidence about lens vault and iris dynamic changes. As discussed above, the inclusion of treated eyes could have introduced a bias. The numbers were small but there were no differences between treated and untreated eyes, and we believe that such a bias would be expected to be toward the null. We grouped and analyzed PAC and PACG together as it is optic neuropathy that determines that classification and there is as yet no evidence for a difference in iris behavior or lens vault between PAC and PACG. Finally, as this was a cross-sectional study, a cause and effect relationship cannot be proven; the actual clinical risk factors for PACS and PAC/PACG remain to be confirmed in prospective, longitudinal studies.

In summary, this study provides further data on iris dynamic changes in PACS, PAC/PACG, and normal eyes as well as other risk factors associated with PACD. Our data suggested that the lens vault and iris dynamic change have a role in the pathogenesis of PAC, as demonstrated in a rural Chinese population. These findings emphasized the role of lens vault along with other factors in producing pupillary block and the need to evaluate the iris as a dynamic risk factor in PAC. We also highlight the need for longitudinal research into the role of iris dynamic changes and other risk factors in the pathogenesis of PAC and their possible use in predicting disease.

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References

1. Cook C, Foster PJ. Epidemiology of glaucoma: what's new? *Can J Ophthalmol*. 2012;47:223–226.
2. Quiley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90:262–267.
3. Alsbirk PH. Anterior chamber depth and primary angle-closure glaucoma. I. An epidemiologic study in Greenland Eskimos. *Acta Ophthalmol (Copenh)*. 1975;53:89–104.
4. Rosengren B. Studies in depth of the anterior chamber of the eye in primary glaucoma. *Arch Ophthalmol*. 1950;44:523–538.
5. Lowe RF. Aetiology of the anatomical basis for primary angle closure glaucoma: biometrical comparisons between normal eyes and eyes with primary angle-closure glaucoma. *Br J Ophthalmol*. 1970;54:161–169.
6. Congdon NG, Youlin Q, Quigley H, et al. Biometry and primary angle-closure glaucoma among Chinese, white, and black populations. *Ophthalmology*. 1997;104:1489–1495.
7. Lavanya R, Foster PJ, Sakata LM, et al. Screening for narrow angles in the Singapore population: evaluation of new noncontact screening methods. *Ophthalmology*. 2008;115:1720–1727, 1727.e1.–1727.e2.
8. Zhang Y, Li SZ, Li L, Thomas R, Wang NL. The Handan Eye Study: comparison of screening methods for primary angle closure suspects in a rural Chinese population. *Ophthalmic Epidemiol*. 2014;21:268–275.
9. Thomas R, George R, Parikh R, Muliyil J, Jacob A. Five year risk of progression of primary angle closure suspects to primary angle closure: a population based study. *Br J Ophthalmol*. 2003;87:450–454.
10. Thomas R, Parikh R, Muliyil J, Kumar RS. Five-year risk of progression of primary angle closure to primary angle closure glaucoma: a population-based study. *Acta Ophthalmol Scand*. 2003;81:480–485.
11. Nongpiur ME, He M, Amerasinghe N, et al. Lens vault, thickness, and position in Chinese subjects with angle closure. *Ophthalmology*. 2011;118:474–479.
12. Thomas R, Walland MJ. Primary angle-closure glaucoma is a multifactorial disease. *Clin Exp Ophthalmol*. 2011;39:593–594.
13. Thomas R, Mengersen K, Thomas A, Walland MJ. Understanding the causation of primary angle closure disease using the sufficient component cause model. *Clin Exp Ophthalmol*. 2014;42:522–528.
14. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol*. 2002;86:238–242.
15. Zhang Y, Li SZ, Li L, et al. Quantitative analysis of iris changes following mydriasis in subjects with different mechanisms of angle closure. *Invest Ophthalmol Vis Sci*. 2015;56:563–570.
16. Quigley HA, Silver DM, Friedman DS, et al. Iris cross-sectional area decreases with pupil dilation and its dynamic behavior is a risk factor in angle closure. *J Glaucoma*. 2009;18:173–179.
17. Ganeshrao SB, Mani B, Ulganathan S, Shantha B, Vijaya L. Change in iris parameters with physiological mydriasis. *Optom Vis Sci*. 2012;89:483–488.
18. Zhang Y, Li SZ, Li L, et al. Quantitative analysis of iris changes after physiologic and pharmacologic mydriasis in a rural Chinese population. *Invest Ophthalmol Vis Sci*. 2014;55:4405–4412.
19. Aptel F, Denis P. Optical coherence tomography quantitative analysis of iris volume changes after pharmacologic mydriasis. *Ophthalmology*. 2010;117:3–10.
20. Aptel F, Chiquet C, Beccat S, Denis P. Biometric evaluation of anterior chamber changes after physiologic pupil dilation using Pentacam and anterior segment optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2012;53:4005–4010.
21. Narayanaswamy A, Zheng C, Perera SA, et al. Variations in iris volume with physiologic mydriasis in subtypes of primary angle closure glaucoma. *Invest Ophthalmol Vis Sci*. 2013;54:708–713.
22. Wang W, Zhou M, Huang W, Chen S, Ding X, Zhang X. Does acute primary angle-closure cause an increased choroidal thickness? *Invest Ophthalmol Vis Sci*. 2013;54:3538–3545.
23. Edwards RS. Behaviour of the fellow eye in acute angle-closure glaucoma. *Br J Ophthalmol*. 1982;66:576–579.
24. Zhou M, Wang W, Ding X, et al. Choroidal thickness in fellow eyes of patients with acute primary angle-closure measured by enhanced depth imaging spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2013;54:1971–1978.
25. Huang W, Wang W, Gao X, et al. Choroidal thickness in the subtypes of angle closure: an EDI-OCT study. *Invest Ophthalmol Vis Sci*. 2013;54:7849–7853.
26. Arora KS, Jefferys JL, Maul EA, Quigley HA. The choroid is thicker in angle closure than in open angle and control eyes. *Invest Ophthalmol Vis Sci*. 2012;53:7813–7818.
27. Seager FE, Jefferys JL, Quigley HA. Comparison of dynamic changes in anterior ocular structures examined with anterior segment optical coherence tomography in a cohort of various origins. *Invest Ophthalmol Vis Sci*. 2014;55:1672–1683.
28. Friedman DS, He M. Anterior chamber angle assessment techniques. *Surv Ophthalmol*. 2008;53:250–273.
29. Radhakrishnan S, Rollins AM, Roth JE, et al. Real time optical coherence tomography of the anterior segment at 1310 nm. *Arch Ophthalmol*. 2001;119:1179–1185.
30. Console JW, Sakata LM, Aung T, Friedman DS, He M. Quantitative analysis of anterior segment optical coherence tomography images: the Zhongshan Angle Assessment Program. *Br J Ophthalmol*. 2008;92:1612–1616.
31. Pavlin CJ, Harasiewicz K, Foster FS. Ultrasound biomicroscopy of anterior segment structures in normal and glaucomatous eyes. *Am J Ophthalmol*. 1992;113:381–389.
32. Radhakrishnan S, Huang D, Smith SD. Optical coherence tomography imaging of the anterior chamber angle. *Ophthalmol Clin North Am*. 2005;18:375–381.
33. Salim S. The role of anterior segment optical coherence tomography in glaucoma. *J Ophthalmol*. 2012;2012:476801.
34. Wang YE, Li Y, Wang D, He M, Lin S. Comparison of factors associated with occludable angle between American Caucasians and ethnic Chinese. *Invest Ophthalmol Vis Sci*. 2013;54:7717–7723.
35. Wang D, Qi M, He M, Wu L, Lin S. Ethnic difference of the anterior chamber area and volume and its association with angle width. *Invest Ophthalmol Vis Sci*. 2012;53:3139–3144.
36. Sun JH, Sung KR, Yun SC, et al. Factors associated with anterior chamber narrowing with age: an optical coherence tomography study. *Invest Ophthalmol Vis Sci*. 2012;53:2607–2610.
37. Ozaki M, Nongpiur ME, Aung T, He M, Mizoguchi T. Increased lens vault as a risk factor for angle closure: confirmation in a Japanese population. *Graefes Arch Clin Exp Ophthalmol*. 2012;250:1863–1868.
38. Alsbirk PH. Anatomical risk factors in primary angle-closure glaucoma. A ten year follow up survey based on limbal and axial anterior chamber depths in a high risk population. *Int Ophthalmol*. 1992;16:265–272.
39. Ye TC, Yu Q, Peng SX, Wang NL, Chen XQ. Six year of suspects of primary angle-closure glaucoma. *Chin J Ophthalmol*. 1998;34:167–169.

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40. Moghimi S, Vahedian Z, Zandvakil N, et al. Role of lens vault in subtypes of angle closure in Iranian subjects. *Eye (Lond)*. 2014;28:337–343.
41. Tarongoy P, Ho CL, Walton DS. Angle-closure glaucoma: the role of the lens in the pathogenesis, prevention, and treatment. *Survey Ophthalmol*. 2009;54:211–225.
42. Feigl B, Mattes D, Thomas R, Zele AJ. Intrinsically photosensitive (melanopsin) retinal ganglion cell function in glaucoma. *Invest Ophthalmol Vis Sci*. 2011;52:4362–4367.
43. Rukmini AV, Milea D, Baskaran M, et al. Pupillary responses to high-irradiance blue light correlate with glaucoma severity. *Ophthalmology*. 2015;122:1777–1785.

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