What Are the Characteristics of Primary Angle Closure With Longer Axial Length?

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Purpose. To compare biometric parameters between primary angle closure with longer axial length (AL) and those with medium or shorter AL.

Methods. We prospectively recruited 138 primary angle-closure patients. Low-coherence interferometry and ultrasound biomicroscopy examinations were performed before laser peripheral iridotomy and pilocarpine treatment. AL was categorized as shorter (<22.5 mm), medium (≥22.5 to <23.5 mm), or longer (≥23.5 mm). Anterior chamber depth and width (ACD and ACW), lens vault (LV), anterior vault (AV), relative AV (AV/AL), relative lens position (RLP, [ACD + 1/2 lens thickness]/AL), trabecular-ciliary angle (TCA), keratometry, and other biometric parameters were compared among different AL groups.

Results. Among 138 angle-closure patients, 15 (10.9%) patients had longer ALs, of which 11 (73.3%) were male. These angle-closure eyes with longer AL had flatter cornea ($P = 0.006$ and 0.022 for flat and steep keratometry) and larger ACW ($P = 0.006$), but smaller RLP ($P = 0.019$) than those with medium AL; similarly, they had flatter cornea ($P < 0.001$ for both flat and steep keratometry), and larger ACW ($P < 0.001$), AV ($P = 0.004$), and TCA ($P = 0.024$), but smaller relative AV ($P = 0.040$) and RLP ($P = 0.005$) than those with shorter AL. No significant differences were found in the other parameters.

Conclusions. Primary angle closure with longer AL was uncommon. Causes of angle closure in these atypical patients were manifold. These patients were predominantly male; they had smaller relative dimension of the anterior segment, flatter cornea, and more anterior RLP and less anteriorly rotated ciliary body compared with those angle-closure patients with relatively shorter AL.

Keywords: myopia, primary angle closure, axial length, biometric parameters

Primary angle closure (PAC) with myopia has received increasing attention in recent years. This is not only because myopia, usually regarded as a protective effect against PAC, can still be observed in some angle-closure patients,[1–4] but also because this kind of PAC may significantly rise with the incremental rate of myopia in East Asia in the future.[5] Recent researchers have highlighted that there is a considerable proportion of myopia in the PAC population. A Singaporean study showed that almost one-quarter of PAC was myopic,[5] whereas a Malaysian investigation found that the distribution of myopia was approximately 37% in PAC patients.[6] Jin et al.[7] concluded that the increasing prevalence of myopia has minimal influence on the angle-closure prevalence. It seems that we are going to have more myopic PAC with the rise of myopia in the world, especially in East Asia.

However, myopia by the definition of the refractive status in angle-closure patients is often misleading. It is well known that PAC usually occurs in the population older than 40 years,[8] so the myopia formation in these patients might be due to an age-related increase in the refractive index of the lens. A population-based study revealed that myopia is related to nuclear cataract rather than axial length (AL) among people aged 40 to 80 years.[9] The Blue Mountains Eye Study also reported that the trend of a myopic shift after age 65 years was associated with development of nuclear cataract.[10] Nevertheless, "myopia as a protective effect against PAC" actually means axial myopia rather than lenticular myopia. Moreover, the recent myopia boom in the world also refers to axial myopia in teenagers and young adults rather than lenticular myopia. Therefore, lenticular myopia with short AL is not the focus of our study. Instead, clarifying the different characteristics of atypical angle closure with axial myopia could potentially help to better understand the mechanism of PAC glaucoma.

Thus, the purpose of this study was to compare biometric parameters of PAC patients quantitatively among different AL groups and to analyze the differences between PAC patients with longer AL and those with medium or shorter AL.

Methods

Participants and Procedures

The PAC patients were recruited from the Glaucoma Clinic of Eye and ENT Hospital of Fudan University from May 2015 to September 2017. The research followed the tenets of the Declaration of Helsinki, and all procedures were approved by the human subjects review committee of the Eye and ENT Hospital of Fudan University, Shanghai, China. All patients provided written informed consent.

Extensive peripheral anterior synechia (PAS) would affect the measurement of anatomic structures, especially iris parameters, so we studied relatively early stages of the diseases, including PAC suspect (PACS) eyes and PAC eyes that had no PAS or less than three cumulative clock-hours of PAS. All these eyes were examined before laser peripheral iridotomy or pilocarpine treatment (or discontinued for at least 1 week). If both eyes of a patient met the eligibility criteria, one eye was randomly selected as the study eye. The PACS eyes were defined as eyes with appositional contact between the peripheral iris and the posterior trabecular meshwork but without PAS, raised IOP, or glaucomatous optic neuropathy. The eyes with the presence of iridotrabecular contact and an elevated IOP or PAS with no secondary cause for the PAS, but without glaucomatous optic neuropathy were defined as PAC.[8]

We excluded eyes that had received pilocarpine treatment within a week at the time of the study; that had extensive PAS (more than three clock-hours) that could affect the iris and angle configuration; that had previous laser or intraocular surgery; and that had secondary angle closure, such as exfoliation syndrome, iris neovascularization, lens intumescence, or subluxation and uveitis.

All the participants underwent a comprehensive ophthalmic examination, including detailed silt-lamp examination of anterior segment, fundus examination, IOP measurement, gonioscopy, low-coherence interferometry, and ultrasound biomicroscopy (UBM) examination before therapeutic interventions. Gonioscopy was used with a four-mirror goniolens (Volk Optical, Inc., Mentor, OH, USA) with and without indentation under dark conditions. The angle was defined as closed if PAS existed when the posterior trabecular meshwork was not visible under cornea indentation.[11] Low-coherence interferometry (LenStar 900; Haag-Streit, Koeniz, Switzerland) was performed to measure biometric parameters, such as AL, lens thickness, central corneal thickness (CCT), and flat/steep keratometry. AL was categorized as shorter (<22.5 mm), medium (≥22.5 to <23.5 mm), or longer (≥23.5 mm).

The UBM (MD-300L; MEDA Co., Ltd., Tianjin, China) used in this research was equipped with a single-element mechanical linear scanner. The resolutions of the UBM were no less than 40 μm. The frequency of the probe transducer was 50 MHz. One of two experienced operators (ZJ and JC), who were masked to the clinical data, performed the UBM examinations with the participants lying in a supine position in a light room (illumination approximately 120 lux, measured with a luminance meter [model DT-1301, Everbest Machinery Industry Co., Ltd., Shenzhen, China]). An eye cup containing hydroxyethyl cellulose and physiologic saline was mounted on the globe after topical anesthesia was used, and the transducer was applied gently with care to avoid compression on the globe. Radial scans at the 12 (superior), 3 (nasal), 6 (inferior), and 9 (temporal) o'clock positions centered over the limbus and the horizontal perpendicular full-view scan at the nasal-temporal position centered over the pupil were obtained. If PAS was just at 3, 6, 9, and 12 o'clock, the position would be avoided for measurement and the picture next to the PAS position was used instead.

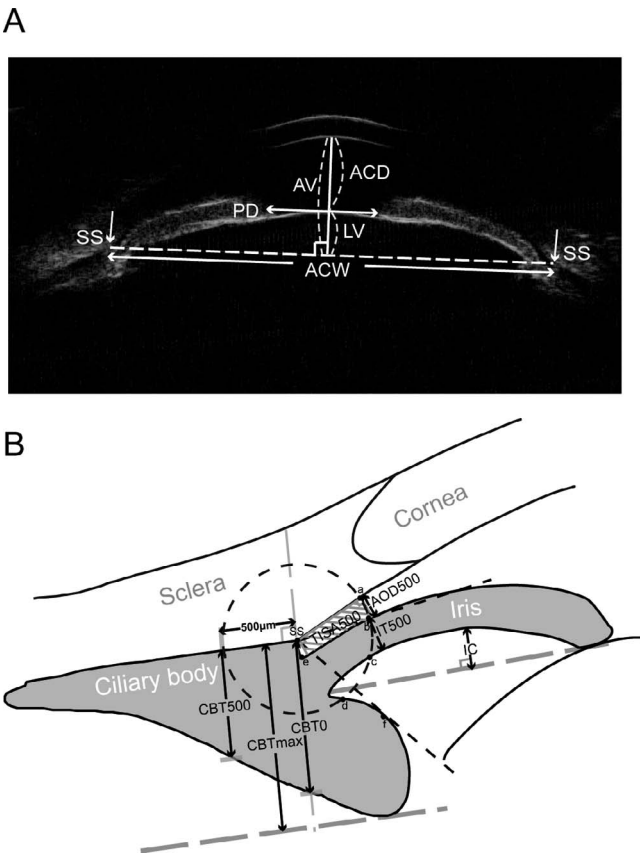

Figure 1. (A) The determination of the parameters on an ultrasound biomicroscopy image of the horizontal perpendicular full-view scans at the nasal-temporal position centered over the pupil. (B) The determination of the parameters on an ultrasound biomicroscopy diagram of the radial scans centered over the limbus. A circle with a radius of 500 μm centered on the scleral spur (SS) is drawn. ICPD, line of "cd"; IRD, line of "SS-e"; TCA, angle of "a-SS-f"; TCPD, line of "ad"; TIA, angle of "a-SS-b."

All captured UBM images we studied were analyzed using the built-in software in the machine. The following parameters were measured: anterior chamber depth (ACD), pupil diameter (PD), anterior chamber width (ACW), lens vault (LV), anterior vault (AV), angle-opening distance at 500 μm (AOD500), trabecular-iris space area at 500 μm (TISA500), trabecular-anterior iris surface angle (TIA), iris thickness at 500 μm (IT500), iris curvature (IC), iris root distance (IRD), trabecular-ciliary process distance (TCPD), iris-ciliary process distance (ICPD), trabecular-ciliary angle (TCA), ciliary body thickness at 0 μm and 500 μm (CBT0 and CBT500), and maximum ciliary body thickness (CBTmax). Then two relative parameters were calculated as follows: relative AV: AV/AL; and relative lens position (RLP): (ACD + 1/2 lens thickness)/AL. The definition[1,12–21] and diagram of these parameters are shown in Supplementary Table S1 and Figure 1. For each parameter, the mean of three measurements with the same image was used as the final value. The repeatability and reproducibility of all UBM parameters measured in this study were good (the intraobserver intraclass coefficients ranged from 0.948 to 0.999, whereas the interobserver intraclass coefficients ranged from 0.827 to 0.998, Supplementary Table S2).

Table 1. Demographic Data of PAC Subjects Among Three AL Groups

Parameters	Group 1, AL <22.5 mm	Group 2, 22.5 ≤ AL < 23.5 mm	Group 3, AL ≥23.5 mm	*P*
No. eyes	70	53	15	-
Age, y	62.7 ± 8.0	64.0 ± 10.8	69.3 ± 14.9	0.069*
Sex, male/female	13/57	23/30	11/4	**<0.001**†
IOP, mm Hg	16.48 ± 2.97	17.00 ± 4.58	18.00 ± 3.40	0.334*
Closed angles, clock-hours	1.16 ± 1.53	1.62 ± 1.46	1.73 ± 1.87	0.174*
Diagnosis, PACS/PAC	45/25	30/23	9/6	0.686†
AL, mm‡	22.00 (21.59, 22.25)	22.98 (22.73, 23.30)	23.80 (23.61, 25.30)	**<0.001**§

Continuous values are described as mean ± SD, except that AL is presented as median (interquartile range). *P* values < 0.05 are bold.
* One-way ANOVA.
† $\chi 2$ test.
‡ The distribution of AL among three groups is shown in Supplementary Figure S1.
§ Kruskal-Wallis test.

Statistical Analysis

Means and SDs or medians and interquartile ranges were calculated for continuous data, and the frequency distribution was used for categorical data. The means of the superior, nasal, inferior, and temporal AOD500, TISA500, TIA, IT500, IC, IRD, TCPD, ICPD, TCA, CBT0, CBTmax, and CBT500 were calculated and used for final analyses. One-way ANOVA or Kruskal-Wallis test was used to compare the continuous variables in the demographic data among three different AL groups, whereas χ^2 tests were used to compare the categorical variables. General linear model analysis was performed to compare the differences of anatomical parameters adjusted for sex and age among the three groups, with Bonferroni-adjusted post hoc comparisons. SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. A *P* value less than 0.05 was considered statistically significant.

Results

A total of 138 consecutive angle-closure patients (84 PACS and 54 PAC) who met the required criteria were recruited for the study. Mean age (±SD) was 63.9 ± 10.2 years and 65.9% (n = 91) of the participants were female and 34.1% (n = 47) were male. There was no significant difference in AL between PACS (22.61 ± 1.40 mm, n = 84) and PAC (22.58 ± 0.95 mm, n = 54) eyes (P = 0.877). Among 138 angle-closure patients, 50.7% (n = 70) were in the shorter AL (< 22.5 mm) group, 38.4% (n = 53) were in the medium AL (≥ 22.5 to < 23.5 mm) group, and 10.9% (n = 15) were in the longer AL (≥ 23.5 mm) group. There were no significant differences in age, IOP, closed angles, and the proportions of PACS to PAC. However, a larger proportion of male participants presented in the longer AL group (73.3%) compared with the other two groups (18.6% in the shorter AL group and 43.4% in the median AL group) (P < 0.001) (Table 1).

Comparing the biometric parameters across the three AL groups after adjusting age and sex, the angle-closure eyes with longer AL had flatter cornea (P = 0.006 for flat keratometry; P = 0.022 for steep keratometry), and larger ACW (P = 0.006) but smaller RLP (P = 0.019) than those with medium AL. Also, the eyes with longer AL had flatter cornea (all P < 0.001 for flat and steep keratometry); larger ACW (P < 0.001), AV (P = 0.004), and TCA (P = 0.024); but smaller relative AV (P = 0.040) and RLP (P = 0.005) than those with shorter AL. No significant differences were found with regard to CCT, lens thickness, ACD, PD, LV, AOD500, TISA500, TIA, IT500, IC, IRD, TCPD, ICPD, CBT0, CBTmax, and CBT500 between the longer AL group and the other two groups (Table 2).

Table 3 summarizes five angle-closure patients with AL longer than 25 mm, of which four were male and one was female. The mechanisms of angle closure in these patients were different. For example, patient 1 had a greater IC with a shallower ACD, suggesting the pupillary block component might play a major role in angle closure for this patient (Table 3; Fig. 2A). Nonpupillary block mechanism might be the main reason for angle closure in patients 4 and 5. Patient 4 had flat iris, relatively deeper ACD, smaller LV, but more anteriorly rotated ciliary body pushing the root of iris forward, so the ciliary body element could be an important cause for angle closure in this patient (Table 3; Fig. 2D); patient 5 had a flat iris, extremely shallow ACD, but greater LV, indicating the lens element might be essential to angle closure in this patient (Table 3; Fig. 2E). For patients 2 and 3, both pupillary block and nonpupillary block mechanisms took part in the development of angle closure (Table 3; Figs. 2B, 2C).

Discussion

There are limited studies of PAC with myopia. Hagan and Lederer[3] first presented clinical descriptions of three PAC patients in a myopic kinship. Barkana et al.[2] then showed clinical characteristics of 20 angle-closure patients with high myopia (≤ −6.0 diopters [D]). Recently, a cross-sectional comparative study showed that almost one-quarter of PAC patients were myopic; compared with emmetropic and hyperopic counterparts, these patients had no significant differences in anterior segment parameters, such as ACD, corneal curvature, lens thickness, and LV.[5] However, in that study, 3 of 11 PAC patients with high myopia (≤ −5.0 D) had ALs even shorter than 22 mm,[5] which means axial myopia was mixed up with lenticular myopia. In addition, Mohamed-Noor and Abd-Salam et al.[6] reported that the AL between myopia and hyperopia groups (22.95 ± 0.98 vs. 22.73 ± 0.92 mm) was not different in 137 PAC subjects. Therefore, it seems that lenticular myopia is common in PAC patients and it is better to define myopia by AL instead of refractive status to clarify the characteristics of this atypical angle closure.

In the present study, we grouped consecutive PAC patients by AL and found that only 15 (10.9%) of 138 patients had ALs longer than 23.5 mm. Interestingly, they were predominantly male (73.3%). These 15 patients with PAC with longer AL had larger absolute dimension of the anterior segment (larger ACW and AV), flatter cornea, and less anteriorly rotated ciliary body compared with those with relatively shorter AL. However, there were no differences in ACD, LV, iris parameters, and ciliary body thickness among patients with different AL groups. Our findings are in agreement with our previous retrospective study, in which PAC with longer AL had flatter corneal

Table 2. Comparison of Biometric Parameters in PAC Subjects Among Three AL Groups

Parameters	Group 1 AL <22.5 mm, $n = 70$	Group 2 22.5 ≤ AL < 23.5 mm, $n = 53$	Group 3 AL ≥23.5 mm, $n = 15$	*P* Value Adjusted for Sex and Age* Comparison of Three Groups	Group1 and Group 2	Group2 and Group 3	Group1 and Group 3
CCT, μm	537.4 ± 29.0	542.6 ± 33.5	556.1 ± 22.6	0.147	1.000	0.296	0.154
Lens thickness, mm	4.75 ± 0.43	4.71 ± 0.37	4.95 ± 0.36	0.319	0.679	0.680	1.000
Flat keratometry, D	44.90 ± 1.40	43.25 ± 0.96	42.02 ± 1.63	**<0.001**	**<0.001**	**0.006**	**<0.001**
Steep keratometry, D	45.72 ± 1.32	43.97 ± 1.00	42.95 ± 1.72	**<0.001**	**<0.001**	**0.022**	**<0.001**
ACD, mm	1.81 ± 0.20	2.01 ± 0.24	1.99 ± 0.27	**<0.001**	**<0.001**	1.000	0.051
PD, mm	3.39 ± 0.74	3.40 ± 0.80	3.33 ± 0.86	0.893	1.000	1.000	1.000
ACW, mm	11.10 ± 0.35	11.55 ± 0.44	11.93 ± 0.46	**<0.001**	**<0.001**	**0.006**	**<0.001**
LV, mm	1.05 ± 0.18	0.96 ± 0.18	1.08 ± 0.17	**0.009**	**0.017**	0.103	1.000
RLP†	0.192 ± 0.126	0.190 ± 0.011	0.181 ± 0.021	**0.007**	1.000	**0.019**	**0.005**
AV, mm	2.86 ± 0.18	2.97 ± 0.18	3.06 ± 0.17	**0.001**	**0.007**	0.501	**0.004**
Relative AV‡	0.131 ± 0.009	0.129 ± 0.008	0.124 ± 0.012	**0.046**	1.000	0.121	**0.040**
AOD500, mm	0.057 ± 0.035	0.067 ± 0.044	0.074 ± 0.054	0.522	1.000	1.000	1.000
TISA500, mm^2	0.025 ± 0.014	0.026 ± 0.017	0.030 ± 0.023	0.973	1.000	1.000	1.000
TIA, degree	7.06 ± 3.71	8.05 ± 4.55	9.16 ± 6.23	0.558	1.000	1.000	1.000
IT500, mm	0.356 ± 0.053	0.355 ± 0.049	0.359 ± 0.069	0.718	1.000	1.000	1.000
IC, mm	0.291 ± 0.075	0.280 ± 0.083	0.278 ± 0.105	0.113	0.368	1.000	0.190
IRD, mm	0.066 ± 0.046	0.060 ± 0.060	0.061 ± 0.059	0.582	1.000	1.000	1.000
TCPD, mm	0.527 ± 0.078	0.553 ± 0.086	0.604 ± 0.105	0.114	0.997	0.397	0.117
ICPD, mm	0.130 ± 0.084	0.155 ± 0.105	0.189 ± 0.139	0.103	0.673	0.531	0.116
TCA, degree	59.82 ± 11.06	62.75 ± 12.02	71.00 ± 14.35	**0.029**	0.957	0.108	**0.024**
CBT0, mm	0.905 ± 0.103	0.926 ± 0.108	0.949 ± 0.138	0.533	0.934	1.000	1.000
CBTmax, mm	1.002 ± 0.106	1.041 ± 0.107	1.046 ± 0.130	0.207	0.230	1.000	1.000
CBT500, mm	0.843 ± 0.101	0.893 ± 0.116	0.897 ± 0.121	0.087	0.083	1.000	1.000

Values are described as mean ± SD.

* General linear model analysis was used to compare the differences of biometric parameters adjusted for sex and age among the three groups, with Bonferroni-adjusted post hoc comparisons. *P* Values < 0.05 are bold.

† RLP = (ACD + 1/2 lens thickness)/AL.

‡ Relative AV = AV/AL.

curvature than those with shorter AL.[22] Nevertheless, that research did find that PAC with longer AL had deeper ACD compared with those with relatively shorter AL.[22] The present study also showed that the tendency of ACD was deeper in angle-closure patients with longer AL compared with those with shorter AL, although there was no statistical significance with a marginal *P* value ($P = 0.051$). This discrepancy could be due to the small sample numbers of angle-closure patients with longer AL.

The differences of absolute dimension in the eyeball's anterior segment could be explained by AL elongation. In our study, angle-closure eyes with longer AL had flatter cornea, wider ACW, and larger AV than those with shorter AL. The flatter cornea could result from horizontal expansion of the eyeball in axial myopia, which is in agreement with the previous investigation demonstrating that eyes with axial elongation had a flatter cornea.[23] ACW, a known risk factor for PAC, is a parameter of horizontal dimension of anterior segment. As the AL gets longer, ACW becomes wider in both the healthy population and narrow-angle persons.[13] Meanwhile, AV is a novel parameter that represents the vertical dimension of the eyeball's anterior segment and could potentially predict the risk of a patient's angle closure.[15] Thus, our data showed that both vertical and horizontal dimension of the eyeball's anterior segment in the angle-closure eyes with longer AL were larger than those of angle-closure eyes with shorter AL. This might explain that the occurrence of PAC is evidently biased toward shorter AL.

However, why do these eyeballs with longer AL still have angle closures? A recent study demonstrated that although the healthy population had longer ALs than the PAC population, the relative dimensions of the eyeball's anterior segment (relative AV) in these two populations were quite similar.[15] Interestingly, our findings showed that the relative dimension of the eyeball's anterior segment (relative AV) was smaller in angle-closure patients with longer AL than those with shorter AL, suggesting that the anterior and posterior portions of the eyeball elongate disproportionately in angle-closure eyes with longer AL. Meanwhile, the RLP was smaller in angle-closure eyes with longer AL than in those with shorter AL, which reveals that the position of the lens is relatively more anterior in these atypical angle-closure eyes with longer AL. In the

Table 3. Summary of Five PAC Patients With AL Longer Than 25 mm

Patient No.	Sex	Age, y	Diagnosis	AL, mm	Spherical Equivalent, D	ACD, mm	LV, mm	Lens Thickness, mm	IC, mm
1	Male	86	PACS	25.09	−6.50	1.81	1.31	5.30	0.53
2	Male	65	PAC	25.30	−4.75	1.97	1.04	5.44	0.21
3	Male	83	PACS	25.47	−7.50	1.98	1.02	4.83	0.39
4	Male	64	PACS	29.55	−15.00	2.18	0.88	4.20	0.16
5	Female	26	PAC	29.68	−22.00	1.69	1.39	4.31	0.17

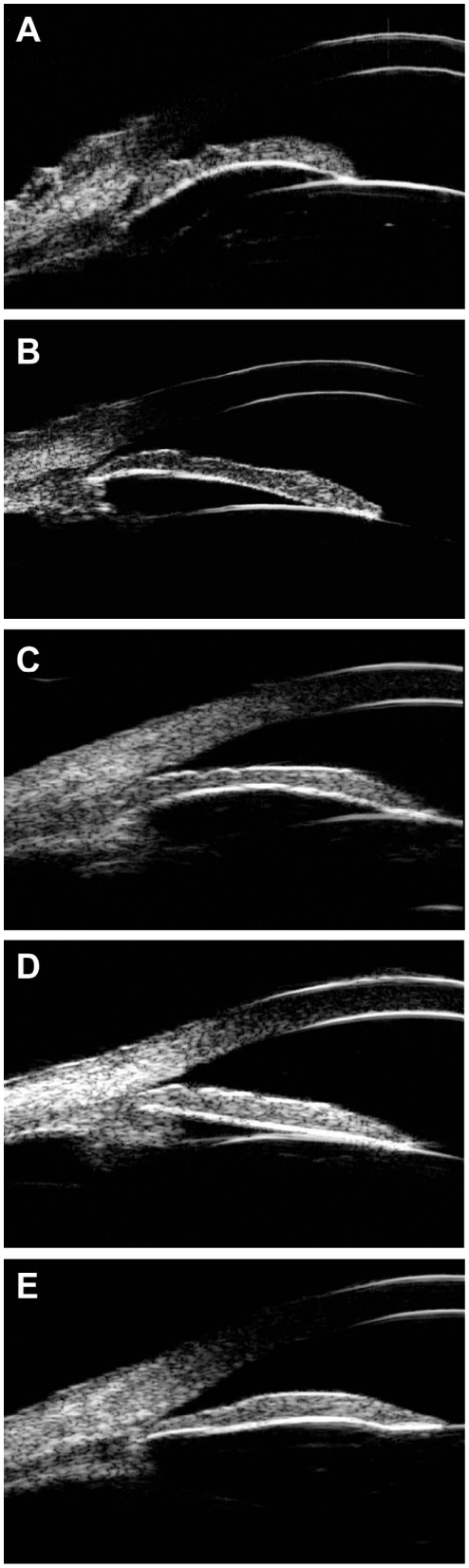

FIGURE 2. Ultrasound biomicroscopy features of five PAC patients with axial length longer than 25 mm (patients 1–5). (**A**) Patient 1 had evident iris bombe. (**B**) Patient 2 had iris bombe and anterior iris insertion. (**C**) Patient 3 had iris bombe, thick iris root, anterior iris insertion, and anteriorly rotated ciliary body. (**D**) Patient 4 had flat iris, deep ACD, and anteriorly rotated ciliary body. (**E**) Patient 5 had flat iris but shallow ACD, and anterior iris insertion.

present study, most of the risk of biometric factors had no significant differences across different AL groups, such as ACD and LV. Therefore, relative crowded anterior chamber angle still exists in this subtype of patients.

On analyzing five PAC patients with AL longer than 25 mm, we noted that the mechanism of angle closure in these patients was quite diversified. Therefore, although there were no statistical differences in ACD, LV, iris parameters, and ciliary body thickness between angle-closure patients with longer AL and those with medium or shorter AL, it did not mean that each angle-closure patient with longer AL shared the same cause for angle closure. In the general angle-closure population, several studies identified distinct subgroups of PAC subjects with different mechanisms.[24,25] Thus, in angle-closure patients with longer AL, there might also exist various types of angle closure, including pupillary block and nonpupillary block. A previous case series reported that nonpupillary block mechanism was more common in angle closure with high myopia than in the general angle-closure population.[2] However, in the present study, ICs were quite similar among different AL groups, indicating that the proportion of pupillary block to nonpupillary block might not make a big difference among different AL groups. Interestingly, less anteriorly rotated ciliary body was found in the angle closure with longer AL on average, which might suggest that an anteriorly positioned ciliary body could play a more essential role in typical angle-closure patients.

Our investigation showed that longer AL was still uncommon in the PAC population. The considerable prevalence of myopia in the PAC population reported in the existing literature might be overestimated owing to failure to exclude lenticular myopia. Nevertheless, axial myopia can occur in PAC patients. With the increasing rise of adolescent axial myopia in East Asia, we speculate that the prevalence of PAC may reduce in the overall population, but there might be more PAC cases with longer AL in the future.

One limitation of our cross-sectional research was the relatively small sample size, especially for the angle-closure patients with longer AL. It is actually not easy to recruit this kind of patient due to the low prevalence of PAC eyes with longer AL. A larger sample size will be needed to clarify the effect of AL on the occurrence of PAC. Second, we performed UBM examinations only in the ambient lighting condition, not in the dark condition, so we were not able to compare dynamic change of iris parameters between PAC with longer AL and those with medium or shorter AL. Third, previous studies found that there still existed significant differences in some anterior segment parameters (like TCPD) between PAS-positive and PAS-negative eyes.[26,27] Although no significant difference was found in the number of closed angles among the three AL groups, it could not be excluded that mild PAS might affect the comparison of the biometric parameters in the present study.

In conclusion, we found that PAC with longer AL was still uncommon. The mechanisms of angle closure in these patients were manifold. These atypical PAC patients were predominantly male. They had larger absolute but smaller relative dimension of the eyeball's segment, flatter cornea, more anteriorly RLP, and less anteriorly rotated ciliary body, but had similar ACD, LV, iris parameters, and ciliary body thickness compared with those with relatively shorter AL.

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