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CLINICAL INVESTIGATION

Effect of Visibility of the Ciliary Body Processes on Ocular Biometric Parameters in Patients with Primary Angle Closure

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Abstract

Purpose To evaluate the differences in ocular biometric parameters between eyes with primary angle closure (PAC) with and without visible ciliary body processes (CBP) (PAC+CBP and PAC-CBP) and normal open-angle controls.

Study design Cross-sectional study.

Methods Eyes with PAC and normal open-angle controls underwent detailed ocular examinations and gonioscopy to determine the visibility of the CBP. The following ocular biometric parameters were determined using A-scan ultrasound biometry: axial length (AL), anterior chamber depth (ACD), lens thickness (LT), and vitreous length (VL). The lens–axial length factor (LAF) and relative lens position (RLP) were also calculated. Continuous variables were assessed by analysis of variance with Bonferroni correction. Multiple linear regression analysis was performed to adjust for confounding factors. Area under the receiver operating characteristic curves were calculated to determine the diagnostic capability of biometric parameters.

Results 84 PAC+CBP eyes, 57 PAC-CBP eyes, and 32 normal open angle control eyes were evaluated. The means of the ocular biometric values were significantly different among the three groups. AL, ACD, LT, VL, LAF, and RLP were also significantly different among the three groups in the multivariate regression analysis. AL, ACD, and VL were lower in the PAC+CBP group and LT, RLP, and LAF were greater in the PAC+CBP group than in the PAC-CBP and control groups. LAF $\geq$ 2.4 is the cutting point with the highest sensitivity and specificity to differentiate PAC+CBP from PAC-CBP.

Conclusions The ocular biometric parameters in the PAC+CBP group were more strongly associated with a crowded anterior segment than in the other groups. Visibility of CBP in PAC-affected eyes may serve as a surrogate for an anterior segment crowding mechanism and help to select the most appropriate treatment in individual cases.

Keywords Ciliary body processes · primary angle closure · biometry · mechanism

Introduction

Glaucoma is an optic neuropathy characterized by selective and progressive loss of retinal ganglion cells [1]. It clinically manifests as thinning of the neuroretinal rim and loss of the retinal nerve fiber layer with corresponding visual field defects. Although glaucoma isn't considered a leading causes of vision loss worldwide, the proportions of vision impairment caused by glaucoma is increasing [2]. The risks and subtypes of glaucoma may vary depending on ethnicity and country of origin. Although primary open-angle glaucoma appears to be more common than primary angle-closure glaucoma (PACG), Quigley and Broman demonstrate a higher prevalence of PACG in the Asian than Caucasian population [3].

Primary angle closure (PAC) can be caused by several mechanisms that are usually categorized into four anatomical levels [4]: the pupil, ciliary body, lens, and beyond-the-lens levels. Relative pupillary block is the most common and a very important mechanism leading to angle closure [5, 6]. In many cases, however, it is not the only mechanism of angle closure. More than one mechanism can coexist in an eye with PAC [7].

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Anterior segment crowding describes the anatomical characteristics of the anterior segment that produce the potential to develop a closed angle, including a shorter axial length (AL) [8], smaller corneal diameter [9], increased lens vault [10], increased lens thickness (LT) [8, 11, 12], and anterior-positioned lens [8, 11, 13, 15]. These characteristics are responsible for the crowded anterior segment in eyes with PAC [8, 16, 17]. Several previous studies involving A-scan ultrasound reveal the roles of ocular biometric parameters in determining the presence of anterior segment crowding [8, 9, 13, 14]. However, no consensus regarding the most appropriate ocular biometric values for this condition has been reached. Although several mechanisms can explain the development of PAC [7], anterior segment crowding appears to coexist with pupillary block in patients with PAC [18]. Anterior segment crowding plays a more prominent role in PAC development in the Asian than Caucasian population because of different anatomical features of the eyeball [7, 18].

According to Gullstrand's schematic eye and the physical properties of light, the ciliary body processes (CBP) cannot normally be seen on gonioscopy because of the effect of total internal reflection. In several conditions, however, the CBP can be seen: anterior or posterior lens subluxation, aphakia, anterior lens position, and an increased lens thickness [19]. The last two features are anatomical characteristics of a crowded anterior segment and can be confirmed by A-scan biometric data. Therefore, CBP visualization by gonioscopy in eyes with PAC may implicate the presence of an anterior segment crowding mechanism. In this study, we evaluated the differences in ocular biometric parameters between eyes with chronic PAC with or without visible CBP and open-angle controls.

Methods

This study was approved by the institutional review board of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. All patients who took part in this observational, cross-sectional study provided informed consent to participate in the research protocol. The study adhered to the Health Insurance Portability and Accountability Act and the tenets of the Declaration of Helsinki.

Consecutive patients with PAC aged 50 to 80 years were recruited from the outpatient Department of Ophthalmology, Ramathibodi Hospital, from August 2016 to April 2017. The diagnostic criteria for PAC in this study were taken from the classification of PAC described by Foster et al. [1]. These included three diagnostic categories: primary angle closure suspect (PACS), PAC, and PACG.

The exclusion criteria were the presence of the following conditions in one or both eyes: acute or subacute angle closure glaucoma, secondary glaucoma, phacodonesis, obvious or suspected lens subluxation, and any other diseases that may cause a closed angle such as central retinal vein occlusion, central retinal artery occlusion, uveitis, or any iris or corneal abnormalities. In addition, individuals with a history of trauma, intraocular surgery, or any kind of ophthalmic laser therapy; the presence of significant cataracts that diminish CBP visibility on gonioscopy in one or both eyes were excluded; limitations in completing the protocol examination; or a discrepancy in the visibility of CBP between eyes were also excluded.

Age-matched patients with a normal open angle were enrolled in the control group if they did not meet the exclusion criteria. Comprehensive ocular examination under slit-lamp biomicroscopy (Haag-Streit BQ-900; Haag-Streit International), Goldmann applanation tonometry, and gonioscopy under a nondilated pupil in dim light conditions were conducted in all patients. A single glaucoma specialist (W.S.) performed gonioscopy using a Zeiss-style four-mirror goniolens (Ocular Posner gonioprism; Ocular Instruments) with a narrow 1-mm beam of light and 16× magnification to evaluate angle structures. Upon completion of static gonioscopy, either the patient was asked to look away from the viewing mirror or the examiner could tilt the mirror away from an angle of interest without pressure exertion on the cornea and sclera. Then the slit beam was moved from the angle area to the pupillary zone. At this time, the focus of the slit-lamp should be behind the pupil through the lens equator. This technique made the pupil more constrict under photopic condition to determine visualization of the CBP. The CBP are characterized as small, brown-colored structures with a saw-tooth appearance (Fig. 1). Visible CBP in one mirror was deemed sufficient to confirm the diagnosis.

Eyes with PAC were categorized into two groups: those with visible CBP (PAC+CBP group) and those without visible CBP (PAC-CBP group). A-scan ultrasound biometry

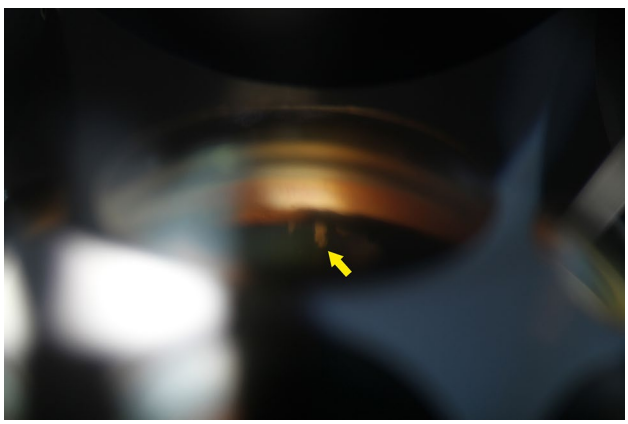

Fig. 1 Gonioscopic photograph shows the ciliary body processes (yellow arrow) on the superior mirror of the gonioprism

(OcuScan® RxP Ophthalmic Ultrasound; Alcon) was used to obtain the ocular parameters in all three study groups. Extra care was taken during the immersion technique to avoid exerting pressure on the globe. Measurements were taken three times in each eye by a well-trained, experienced ophthalmology resident (P.T.). This investigator was blinded to the gonioscopic findings. Both inter- and intra-operator reproducibility were assessed in 10 eyes. The most reliable biometric A-scan printout from each participant was chosen by another investigator (Y.S.) who was blinded to the patient's data. The ocular biometric parameters (AL, anterior chamber depth [ACD], LT, and vitreous length [VL]) were collected. Each collected biometric parameter was defined as the perpendicular distance between each amplitude spike as demonstrated in figure 2. These data were used to calculate the lens–axial length factor (LAF) by the following equation [20]: LAF = LT/AL × 10 and the relative lens position (RLP) by the following equation [11]: RLP = [ACD+(LT/2)]/AL × 10.

The data from the left eye of each patient were selected for subsequent analyses. The data from the right eye were selected instead if the A-scan biometric printouts from the left eye were not accurate. Upon completion of data collection, the patients received treatment modalities depending on their individual stages of PAC.

All statistical analyses were performed using STATA software version 14.2 (StataCorp). Baseline characteristics were compared by analysis of variance with Bonferroni correction and chi-square tests for continuous and categorical variables. Receiver operating characteristic curves were obtained and areas under the curves were calculated to determine the diagnostic capability of biometric parameters to differentiate between PAC+CBP and PAC-CBP. Multiple linear regression adjusted for age, gender, and stage was used to identify the differences among the groups. A *P*-value of <.050 was considered statistically significant.

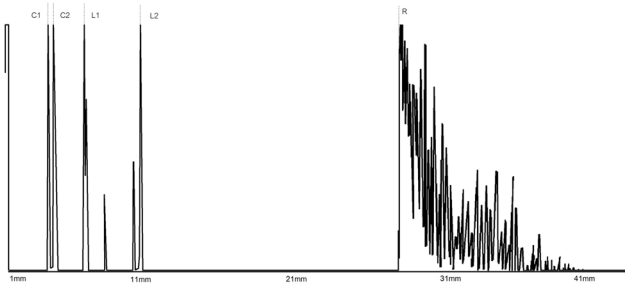

Fig. 2 Immersion technique A-mode image by A-scan ultrasound biometry shows the point of the front cornea (C1), rear cornea (C2), front lens (L1), rear lens (L2) and the retinal surface (R). The perpendicular distance from C1 → C2 = corneal thickness, C2 → L1 = ACD, L1 → L2 = LT, L2 → R = VL and C1 → R = AL

Results

In total, 141 eyes of 141 participants in various stages of PAC and 32 control eyes were recruited. The mean age of the patients was significantly higher in the PAC+CBP than control group (*P*=.030) (Table 1). The proportion of female patients was higher in the PAC+CBP than PAC-CBP group (*P*=.010). Most patients were PAC suspects (63.1% and 49.1% in PAC+CBP and PAC-CBP group, respectively). The CBP were not visualized in all control eyes. None of the acute PAC episodes presented within 2 weeks before LPI was performed.

Table 1 Demographic Characteristics of Patient in the PAC+CBP, PAC-CBP, and normal control

Characteristics	PAC+CBP 84 eyes	PAC-CBP 57 eyes	Normal controls 32 eyes	P value*	
				Between groups	Among 3 groups
Age (years) (MD±SD)	64.6±6.4	62.8±5.9	61.4±4.4	A vs B; 0.22	0.020
				A vs C; 0.03	
				B vs C; 0.87	
Female (%)	71 (84.5%)	37 (64.9%)	22 (68.8%)	A vs B; 0.01	0.020
				A vs C; 0.07	
				B vs C; 0.82	
Stage of PAC					0.005
PACS (%)	53 (63.1%)	28 (49.1%)			
PAC (%)	25 (29.8%)	13 (22.8%)			
PACG (%)	6 (7.1%)	16 (28.1%)			

A = PAC+CBP = PAC eyes with visible CBP, B = PAC-CBP = PAC eyes without visible CBP, C = normal controls

PACG primary angle-closure glaucoma, *PAC* primary angle closure, *PACS* primary angle-closure suspect

*P value; 1-way ANOVA for age, chi-square for gender, Fisher's exact for stage of PAC

The results of intra-operator reproducibility were 0.99 for AL, ACD and LT (all P-value<0.001) and inter-operator reproducibility were 0.99, 0.98 and 0.98 for AL, ACD and LT, respectively (all P-value<0.001).

Univariate linear regression analysis revealed that gender was significantly associated with AL and VL, and age was significantly associated with LT. Both age and gender were significantly associated with ACD, LAF, and RLP (Table 2). These factors were further analyzed in the multivariate regression. After adjusting for age, gender, and stage, the multivariate regression analysis showed that AL, ACD, LT, VL, and LAF were significantly different among the three groups. The RLP was the only parameter without a statistically significant difference between the PAC+CBP and PAC-CBP groups (P=.460) (Table 3).

Among the 5 biometric parameters (AL, ACD, LT, VL, and LAF), LAF had the greatest area under the receiver operating characteristic (AUROC) curve for differentiating between PAC+CBP and PAC-CBP (Fig. 3). LAF ≥ 2.4 is the cut point with the highest sensitivity and specificity to diagnose PAC+CBP.

Discussion

Gonioscopy is the gold standard method with which to visualize angle structures and classify glaucoma types (open or closed angle). The two main gonioscopic techniques are static and dynamic. Looking behind the iris is a dynamic gonioscopic technique that provides helpful details for diagnosis of glaucoma and visualization of the CBP. Normally, the CBP cannot be seen on gonioscopy, but they can be found in eyes with specific conditions including an anterior lens position and an increased LT [19]. The role of crystalline lens-induced PAC has been investigated by several studies [11, 13, 15, 20, 21]. PAC-affected eyes with a more anterior lens position or thicker lens are considered to have a crowded anterior segment [11, 13].

Although there is no gold standard for diagnosis, most previous studies used ocular biometric parameters to indicate anterior segment crowding [6, 8, 9, 11, 15, 17, 22]. Visualizing the presence of CBP by gonioscopy is a cheaper and easier method than A-scan ultrasonography for determining whether an individual eye with PAC has an anterior segment crowding mechanism. To date, however, no study has specifically investigated the relationship between visualization of CBP and ocular biometric parameters.

Comparison of the demographic data among the groups in the present study showed statistically significant differences

Table 2 A-scan Biometric Parameters in the PAC+CBP, PAC-CBP, and Normal Control Groups

Biometric parameters	PAC+CBP (n=84)	PAC-CBP (n=57)	Normal controls (n=32)	P value*
Axial length (mm)	22.44±0.75	22.96±0.83	23.66±0.64	A vs B; <0.001
				A vs C; <0.001
				B vs C; <0.001
Anterior chamber depth (mm)	2.00±0.20	2.22±0.23	2.79±0.32	A vs B; <0.001
				A vs C; <0.001
				B vs C; <0.001
Lens thickness (mm)	5.26±0.23	4.95±0.28	4.56±0.25	A vs B; <0.001
				A vs C; <0.001
				B vs C; <0.001
Vitreous length (mm)	14.70±0.76	15.30±0.85	15.84±0.67	A vs B; <0.001
				A vs C; <0.001
				B vs C; 0.006
Lens/axial length factor	2.35±0.13	2.16±0.15	1.93±0.13	A vs B; <0.001
				A vs C; <0.001
				B vs C; <0.001
Relative lens position	2.07±0.09	2.05±0.11	2.14±0.12	A vs B; 1.000
				A vs C; 0.002
				B vs C; <0.001

A = PAC+CBP = PAC eyes with visible CBP, B = PAC-CBP = PAC eyes without visible CBP, C = normal controls

*P value between groups (ANOVA with Bonferroni correction)

Table 3 Multivariate Analysis of Ocular Biometric Parameters Adjusted for Age, Gender, and Stage Among the Three Groups

Biometric parameters	Study groups	Coefficient	95% CI	P value
Axial length (mm)	A vs B	− 0.41	− 0.68, − 0.15	0.002
	A vs C	− 1.14	− 1.44, − 0.84	< 0.001
	B vs C	− 0.72	− 1.04, − 0.39	< 0.001
Anterior chamber depth (mm)	A vs B	− 0.21	− 0.28, − 0.13	< 0.001
	A vs C	− 0.76	− 0.86, − 0.66	< 0.001
	B vs C	− 0.56	− 0.67, − 0.46	< 0.001
Lens thickness (mm)	A vs B	0.29	0.21, 0.38	< 0.001
	A vs C	0.67	0.57, 0.78	< 0.001
	B vs C	0.38	0.27, 0.49	< 0.001
Vitreous length (mm)	A vs B	− 0.50	− 0.76, − 0.23	< 0.001
	A vs C	− 1.07	− 1.38, − 0.76	0.001
	B vs C	− 0.55	− 0.88, − 0.22	< 0.001
Lens/axial length factor (LAF)	A vs B	0.17	0.12, 0.22	< 0.001
	A vs C	0.40	0.35, 0.46	< 0.001
	B vs C	0.23	0.17, 0.29	< 0.001
Relative lens position (RLP)	A vs B	0.01	− 0.02, 0.05	0.460
	A vs C	− 0.07	− 0.12, − 0.03	< 0.001
	B vs C	− 0.09	− 0.14, − 0.04	0.001

A = PAC+CBP = PAC eyes with visible CBP, B = PAC-CBP = PAC eyes without visible CBP, C = normal controls

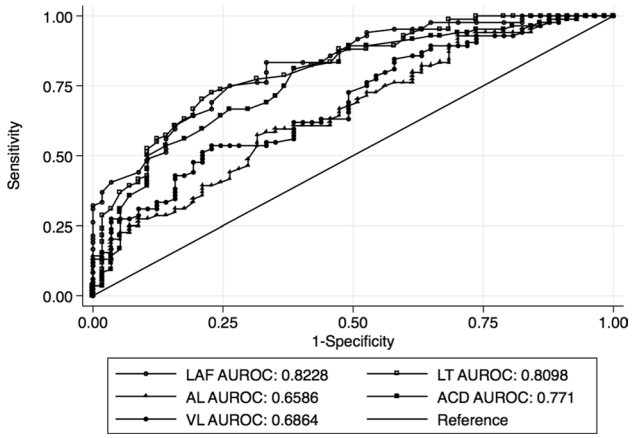

Fig. 3 The receiver operating characteristic curves for biometric parameters to differentiate between PAC+CBP from PAC-CBP. LAF= lens axial length factor, AL=axial length, VL= vitreous length, LT= lens thickness, ACD=anterior chamber depth, AUROC=area under the receiver operating characteristic

in age and gender between the PAC-affected eyes and normal control eyes (P=.02). However, age was not different between the PAC+CBP and PAC-CBP groups. Markowitz and Morin [20] demonstrate that an increased LT and decreased ACD are associated with increased age. Female gender is reportedly associated with shorter AL [17, 22] and shallower ACD [17, 23, 24]. Female patients are also more susceptible to PAC. In the present study, the univariate analysis of the association between age and gender with ocular biometric parameters revealed that gender was significantly associated with AL and VL, whereas age was also significantly associated with LT. Furthermore, both gender and age were significantly associated with ACD, LAF, and RLP. The multivariate regression analysis adjusted for age and gender demonstrated that AL, ACD, LT, VL, and LAF were significantly different among the three groups (all P≤.002).

These differences in ocular biometric parameters between the PAC-affected and normal control eyes were clear, as seen in previous studies [8, 14, 25]. We also observed significant discrepancies between eyes in the PAC+CBP and PAC-CBP groups. In brief, AL, ACD, and VL were smaller in the PAC+CBP than PAC-CBP group. Conversely, LT and LAF were greater in the PAC+CBP group. According to our results, a thicker lens and shorter AL, which lead to higher LAF in patients with PAC+CBP, can be explained by the anatomy of the eye because the lens is relatively large compared with the size of the eye in patients with PAC+CBP. These findings might also imply that a higher LAF is associated with an anterior segment crowding mechanism. Interestingly, our study also suggests that LAF ≥ 2.4 can be used to determine anterior segment crowding as an underlying mechanism in eyes with PAC. Moreover, there was a significantly higher percentage of female patients in the PAC+CBP than PAC-CBP group. This finding may indicate a higher proportion of anterior segment crowding mechanisms in female patients with PAC.

Several reports indicate that a decreased RLP (a more anterior lens position) contributes to the manifestation of

PAC and development of appositional closure [26], synechial closure, and eventually to angle-closure glaucoma [8, 15, 27]. Marchini et al. [8]. report that acute PACG was associated with a decreased RLP (a more anterior lens position) more often than chronic PACG [8]. A retrospective study by Chen et al. [27]. shows that PACG was associated with a more anteriorly positioned lens (decreased RLP) than PAC and control eyes, while PAC revealed the lens position similar to control eyes. An anterior lens position reflects a decrease in ACD. In a recent study, multivariate regression analysis also showed a significantly decreased RLP in PAC+CBP and PAC-CBP eyes than in control eyes (all $P \leq .001$). In the present study, PAC-affected eyes had a more anteriorly positioned lens than normal open angle eyes.

However, in the comparison between the two PAC groups (PAC+CBP and PAC-CBP), the RLP (mean ± SD) was not significantly different (2.07±0.09 vs. 2.05±0.11, respectively; $P=.46$). According to Lowe's formula for RLP calculation [11], the RLP value depends on changes in various ocular biometric parameters including the ACD, LT, and AL. The interactions between these parameters are complex as individual factors can affect one another. It is difficult to determine exactly which biometric parameters play a major role in determination of the RLP. In the present study, the decreased RLP in the PAC-CBP group could have been due to the longer AL in this group. Thus, whether the RLP is a comprehensive indicator for anatomical assessment of anterior segment crowding in PAC-affected eyes remains unclear. However, the presence of the CBP in PAC-affected eyes has a stronger association with LAF than RLP. Analysis of AUROC also confirmed this finding.

This study has several advantages. First, all participants were Asian, a population with a high prevalence of PAC [3] and a higher proportion of PAC induced by non-pupillary block mechanisms than Western populations [28, 29]. Therefore, the data from this study may be useful for routine ophthalmic healthcare, especially among Southeast Asian countries. Second, none of the patients had undergone LPI before recruitment. This provided a more accurate physiologic status of the eye compared with iridotomized eyes, in which the relative pupillary block mechanism might be eliminated. Finally, this study compared ocular biometric parameters between two different types of PAC-affected eyes, PAC+CBP and PAC-CBP, which has not been previously performed. Based on this group of Thai patients, the visibility of the CBP using gonioscopy could potentially be used to determine the presence of an anterior segment crowding mechanism without need for A-scan ultrasonography.

This study also has some limitations. The number of patients in each PAC group might not have been large enough for the subgroup analysis, and only patients with chronic manifestations were enrolled. The visibility of the CBP may be diminished by lens opacity. This study also excluded patients with limited CBP visualization by cataracts in one or both eyes. The data from these eyes have been lost. Finally, all patients in this study were of a single race. The results might not apply to patients with PAC worldwide.

At present, the data regarding CBP visibility in PAC-affected eyes are still limited. Further studies would be useful to determine whether our observational results hold true in other Asian or Western populations. Larger sample sizes, especially with respect to the number of eyes with each stage of PAC and the differences in gonioscopic findings and biometric parameters between PAC+CBP and CBP-CBP eyes in the long term after iridotomy, would be of great interest and should provide a better understanding of the impact of CBP visibility on PAC mechanisms.

In conclusion, gonioscopy is a routine and simple tool in daily ophthalmic practice, and the visibility of CBP by gonioscopy in PAC-affected eyes may implicate the presence of anterior segment crowding.

Conflicts of interest W. Supakontanasan, None; P. Thunwiriya, None; Y. Suwan, None; S. Nilphatanakorn, None; S. Arunmongkol, None; C. Teekhasaenee, None.

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