Novel Discoveries of the Relationship Between the Vitreous Zonule and the Anterior Segment Characteristics in Eyes With Primary Angle-Closure Disease

Kun Lv,[1,2] Zhiqiao Liang,[1,2] Kangyi Yang,[1,2] Xuanzhu Chen,[1,2] Yao Ma,[1,2] and Huijuan Wu[1,2]

[1]Department of Ophthalmology, Peking University People's Hospital, Beijing, China
[2]Eye Diseases and Optometry Institute, Beijing Key Laboratory of Diagnosis and Therapy of Retinal and Choroid Diseases, College of Optometry, Peking University Health Science Center, Beijing, China

Correspondence: Huijuan Wu, Department of Ophthalmology, Peking University People's Hospital, Eye Diseases and Optometry Institute, Beijing Key Laboratory of Diagnosis and Therapy of Retinal and Choroid Diseases, College of Optometry, Peking University Health Science Center, No. 11 Xizhimen South Street, Xicheng District, Beijing 100044, China; dr_wuhuijuan@126.com.

KL and ZL contributed equally to this study, and should be considered as co-first authors.

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Purpose. To investigate the presence of the vitreous zonule (VZ) in different subtypes of primary angle-closure disease (PACD) and to explore the relationship between VZ and anterior chamber angle characteristics.

Methods. Patients with clinical diagnoses of acute primary angle-closure (PAC)/PAC glaucoma (APAC[G]) or chronic PAC/PAC glaucoma (CPAC[G]) and healthy subjects were enrolled. A total of 300 eyes of 180 subjects were included. Anterior segment parameters and the presence of the VZ were assessed by ultrasound biomicroscopy. The presence of VZ was compared among different subtypes of PACD. Anterior segment parameters were compared between eyes in vitreous zonule group (VZG) and no vitreous zonule group (NVZG). Logistic regression analysis was conducted to identify factors associated with the presence of VZ.

Results. APAC(G) eyes had lower VZ presence compared to the fellow eyes of APAC(G) ($P < 0.001$). VZ was more likely to be seen in the eyes of healthy subjects and PAC suspect than in the eyes of PAC and PAC glaucoma (PACG) ($P < 0.05$). NVZG had shorter angle opening distance 500/750 ($P < 0.001$), smaller trabecular iris angle 500/750 ($P < 0.001$), smaller trabecular-iris space area 500/750 ($P < 0.001$), smaller trabecular–ciliary angle ($P = 0.009$), smaller iris area ($P = 0.010$), and greater lens vault ($P = 0.004$) compared to VZG. Greater lens vault (LV) was independently associated with absence of VZ (odds ratio = 0.253; 95% confidence interval, 0.109-0.586; $P = 0.001$).

Conclusions. VZ was less likely to be observed in PAC/PACG eyes. PACD eyes with less VZ had narrower angle, more anteriorly rotated ciliary body, and greater LV.

Keywords: vitreous zonule, primary angle-closure disease, ultrasound biomicroscopy

Primary angle-closure glaucoma (PACG) is a devastating disease, characterized by closure of the anterior chamber angle, causing irreversible visual loss and blindness worldwide.[1] Asia accounts for 87% of worldwide PACG cases and a large number of patients residing in China.[2]

Primary angle-closure disease (PACD) is defined as a series of diseases, including primary angle-closure suspect (PACS), primary angle-closure (PAC), as well as the aforementioned PACG.[3] The mechanisms of angle closure consist of pupillary block, plateaus iris, anterior position of ciliary body, increased thickness or subluxation of the lens, choroidal expansion, and aqueous misdirection.[4,5] In a previous study,[6] we identified thinner peripheral iris, smaller angle opening distance, and larger lens vault (LV) as anatomic factors in the acute attack of PAC. However, the intrinsic anatomic variations contributing to such differences between acute and chronic conditions remain poorly understood.

Although the presence of the vitreous zonule (VZ) was first observed in living humans by Coleman[7] and in monkeys by Glasser[8] using ultrasound biomicroscopy (UBM), the clinical role of this complex and novel structure was not fully understood. VZ is typically identified as the bridging bundles of zonular fibers running from the region of the zonular plexus in the valleys of the posterior pars plicata toward the vitreous membrane in the region of the ora serrata.[9] Previous studies demonstrated that the vitreous zonular system facilitates accommodative forward lens equator movement and lens thickening, and stiffening or loss of VZ may in turn contribute to age-related loss of accommodation.[9,10] Although Kaufman et al.[11] had postulated that dynamic changes of aqueous fluid flow caused by the contraction of VZ might play a role in the development of primary open-angle glaucoma, the association between VZ and PACD was not demonstrated. Recently, Shon et al.[12] described the relationship between VZ and anterior chamber angle characteristics in PAC and PACG patients and demonstrated that eyes without VZ appear to have a narrower angle than eyes with visible VZ. Unfortunately, in this pioneering study, VZ in age-matched normal subjects was not mentioned, and the

characteristics of VZ were not studied in different types of PACD. In this study, UBM was used to investigate the presence of VZ in eyes of healthy subjects and different subtypes of PACD to further explore the relationship between VZ and anterior chamber angle characteristics in UBM.

Method

Subjects

This prospective study of Chinese subjects was approved by the ethics committee of Peking University People's Hospital and followed the tenets of the Declaration of Helsinki. Institutional Review Board approval was obtained. Written informed consent was obtained from every subject. Patients diagnosed with acute PAC/acute PACG (APAC[G]) and chronic PAC/chronic PACG (CPAC[G]) were recruited from the glaucoma clinic of Peking University People's Hospital from March 2016 to January 2022. We enrolled patients who seek medical help due to refractive errors or mild cataracts as a healthy control group. A total of 300 eyes of 180 subjects (60 APAC[G] patients, 60 CPAC[G] patients, and 60 normal subjects) were included, of whom 39 eyes were excluded because of inadequate UBM image quality. Accordingly, 261 eyes of 163 subjects were enrolled in the final analysis.

According to International Society of Geography and Epidemiology of Ophthalmology classification system, all eyes of APAC(G) and CPAC(G) patients included in this study were classified as PACS, PAC, or PACG. An eye with possible appositional contact between the peripheral iris and the posterior trabecular meshwork was defined as PACS; an eye with iridotrabecular contact and an elevated intraocular pressure (IOP) or peripheral anterior synechia (PAS) lacking secondary cause for the PAS, and without glaucomatous optic neuropathy was defined as PAC. An eye with features of PAC, together with glaucomatous optic neuropathy was defined as PACG.

APAC(G) was diagnosed when the patient had no previous history of glaucoma, and their eyes presented any two of the following symptoms: headache, ocular or periocular pain, nausea and vomiting, and blurred vision with halos around lights. Additionally, to be diagnosed, these patients must have presented with an IOP greater than 30 mm Hg and shallow anterior chamber, as well as at least three of the following additional ophthalmologic signs: conjunctival hyperemia, corneal epithelial edema, keratic precipitates, glaucomatous fleck, iris atrophy, iris bombe, and mid-dilated pupil with or without glaucomatous optic neuropathy or visual field defect. The fellow eyes of APAC(G) (F-APAC[G]) were defined as the fellow eyes of patients with a recent unilateral APAC(G) that had not experienced an acute attack with no evidence of a prior acute attack.

CPAC(G) was diagnosed when eyes had no signs of a prior acute attack, including glaucomatous fleck, keratic precipitates, or iris atrophy. These eyes had more than three cumulative clock-hours of PAS observed by gonioscopy and a chronically elevated IOP (>21 mm Hg), with or without glaucomatous optic neuropathy or visual field defect. The fellow eyes of CPAC(G) (F-CPAC[G]) were defined as the less severe fellow eyes of CPAC(G) patients, and F-CPAC(G) were classified as PACS/PAC/PACG eyes as described above. If F-CPAC(G) was belonged to PACS, and the other eye of the same patient (CPAC[G]) was PAC or PACG, the CPAC(G) eye was definitely "more severe" than F-CPAC(G) eye. If F-CPAC(G) was belonged to PAC, and the other eye of the same patient (CPAC[G]) was PACG, the CPAC(G) eye was also "more severe" than F-CPAC(G). If two eyes of the same patient were classified as having chronic PAC, the eye with lower IOP and fewer degrees of PAS was F-CPAC(G). If two eyes of the same patient were classified as having chronic PACG, the eye with less severe glaucomatous optic neuropathy and visual field defect was diagnosed as F-CPAC(G).

Exclusion criteria were (1) Patients who had previous intraocular surgery or laser treatment (e.g., cataract surgery, laser trabeculoplasty, laser peripheral iridectomy, and laser iridoplasty), (2) Patients with a history of ocular diseases that may cause secondary angle closure (e.g., ocular trauma, iris neovascularization, tumor, uveitis, as well as lens intumescence and subluxation), (3) Patients using any medication that can affect the structure of the anterior chamber, such as the miotic agent, (4) Patients with crystalline lens opacity of Lens Opacity Classification System III (LOCSIII) grade over 1, (5) When it was difficult to make accurate diagnosis by history, symptoms, and signs, (6) Patients who were unable to finish gonioscopy or UBM examinations.

Ophthalmologic Examinations

All subjects underwent a comprehensive ocular examination, including best corrected visual acuity (BCVA), IOP measurement with Goldmann applanation tonometry (Haag-Streit, Koniz, Switzerland), detailed slit-lamp biomicroscopy, and stereoscopic evaluation of the optic disc using a 90-diopter lens (Volk Optical, Inc., Mentor, OH, USA). Gonioscopy was performed in a dimly lit room by a glaucoma specialist (H.J.W.) using a Zeiss-style four-mirror gonioscopy lens (Model G-4; Volk Optical, Inc.) at magnification ×16 with and without indentation, which was aimed to obtain the mean gonioscopic angle width (calculated by adding the Shaffer grade in each of four quadrants and dividing by four) and to assess for the presence of PAS. Five IOLMaster measurements were taken to determine axial length, the mean of which was used for analysis. Optical coherence tomography (Spectralis HRA+OCT; Heidelberg Engineering GmbH, Heidelberg, Germany) was used to test retinal nerve fiber layer defect, and a visual field test (Humphrey Field Analyzer; Carl Zeiss Meditec, Inc., Dublin, CA, USA) was performed to investigate a characteristic glaucomatous visual field defect.

Ultrasound Biomicroscopy

UBM (Aviso; Quantel Medical, Inc., Bozeman, MT, USA) measurements were performed using a 50-MHz transducer by a well-trained operator (Y.Y.W.) who was masked to the clinical data. All patients underwent UBM imaging in a supine position in a lit room. The measurements of both eyes were obtained in the superior, inferior, temporal, and nasal quadrants, and nasal-temporal scans were centered on the pupil to obtain full views of the anterior segment. During dynamic scanning, if VZ was shown on the monitor, the picture of VZ was stored. The strands change direction without passing in proximity to the zonular plexus to become the anterior zonule, which directly attach to the posterior lens equator, namely posterior VZ insertion zone and posterior lens equator (PVZ INS-LE),[9,13] were also categorized as VZ. (Fig. 1)

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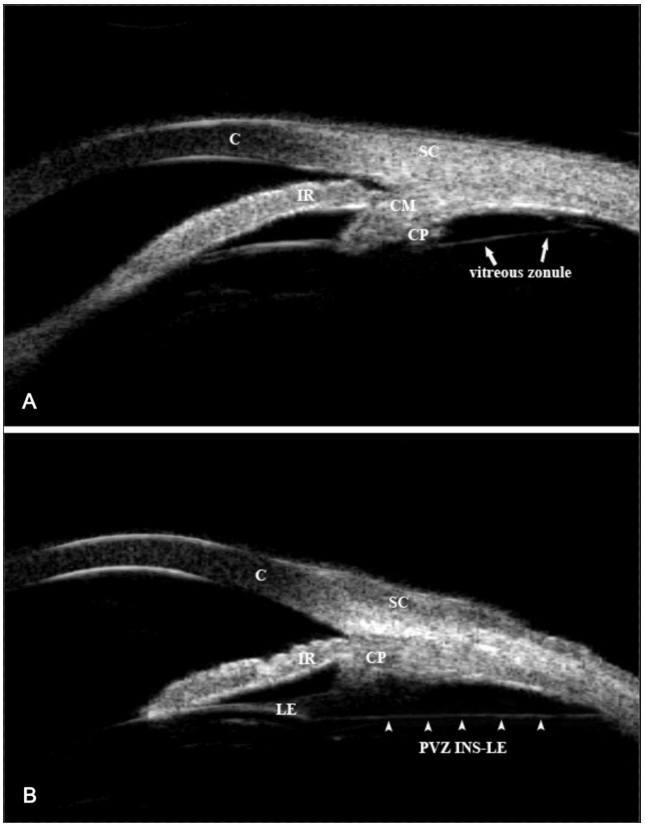

Figure 1. Vitreous zonule (*arrows*) visible in ultrasound biomicroscopy image of 76-year-old healthy male (**A**) and PVZ INS-LE visible in the fellow eye of 73-year-old female primary angle-closure patient (**B**). C, cornea; IR, iris; SC, sclera; CM, ciliary muscle; CP, ciliary process.

Images Analysis

UBM parameters were analyzed quantitatively in all the four quadrants using the in-built caliper by two examiners (K.L., K.Y.Y.), both of whom were masked to the clinical data. Eyes were classified into the vitreous zonule group (VZG) if VZ was clearly observed on at least one UBM image taken at the temporal, nasal, superior, and inferior quadrants (Fig. 1). The number of quadrants and the locations in which the VZ was visible were also recorded. The eyes with no visible linear structure behind the ciliary body on all four quadrants on UBM images were classified into the no vitreous zonule group (NVZG). Any image with poor-quality or insufficient information was excluded.

Scleral spur (SS) was shown to be a crucial anatomical mark in curvature of the inner surface of the angle wall, appearing as an inward extension of the sclera. The parameters we measured on full-view scans at the nasal-temporal position were as follows: (1) LV: the perpendicular distance from the anterior pole of the lens to the horizontal line between the SSs; (2) anterior chamber width: the distance between the two SSs[14]; and (3) anterior chamber depth (ACD): the axial distance between the corneal endothelium and the anterior lens surface.[15] Parameters measured on the radial scans at the superior, nasal, inferior, and temporal positions were as follows: (1) ciliary process area (CPA): the cross-sectional area of ciliary process bounded by a line connecting the insertion location of iris into the ciliary body and the cross-point of a line at 500 µm from the SS perpendicular to the plane of the inner scleral wall to the ciliary process, and internally by the ciliary process surface[6]; (2) trabecular–ciliary angle (TCA): the angle between the posterior corneal surface and the anterior surface of the ciliary body; (3) angle opening distance at 500 µm (AOD 500) and 750 µm (AOD 750): the distance between the posterior corneal surface and the anterior iris surface on a line perpendicular to the trabecular meshwork, 500 µm from the SS[16]; (4) trabecular-iris angle at 500 µm (TIA 500) and 750 µm (TIA 750): the angle between the line passing through a point on the trabecular meshwork at 500 µm and 750 µm from the SS, and the line from the SS to the point on the iris perpendicularly opposite; (5) trabecular–iris space area at 500 µm (TISA 500) and 750 µm (TISA 750): the surface area bounded by AOD 500 and AOD 750 anteriorly, a line drawn from the SS perpendicular to the plane of the inner scleral wall to the iris posteriorly, the inner corneoscleral wall superiorly, and the iris surface inferiorly[16]; and (6) iris area: the area bounded by the full length (from spur to pupil) of the iris (Figs. 2 and 3).

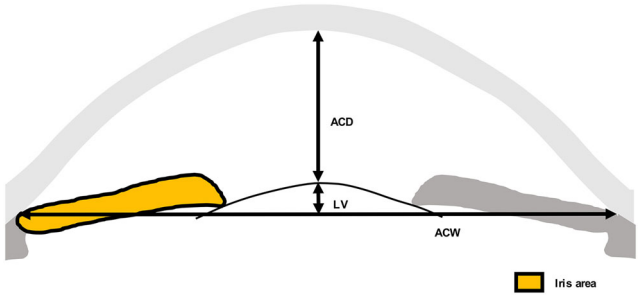

Figure 2. Overall image of anterior segment parameters measured by UBM (Illustrator: Kun Lv). ACW, anterior chamber width (the distance between the two scleral spurs); Iris area, the area bounded by the full length (from spur to pupil) of the iris.

Repeatability and Reproducibility

We performed repeatability and reproducibility analysis of the UBM parameters. Ten patients in each group were randomly selected for analysis. The first observer (K.L.) measured each parameter twice within two weeks to test intraobserver variability. A second observer (K.Y.Y.) measured the same images independently on a different day to determine interobserver variability. The intraobserver and interobserver variabilities were calculated using the coefficient of the intraclass correlation (ICC).

Statistical Analysis

The results were analyzed using SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA). All data were calculated to obtain a mean ± standard deviation. The distribution of the data was validated by the Kolmogorov-Smirnov test, which demonstrated that some quantitative parameters were normally distributed (age, AOD500/750, TISA500/750, iris area). Therefore parametric tests (Student's *t* test) were conducted for normally distributed data, and nonparametric tests (Mann-Whitney test) were applied to non-normally distributed data. Fisher's exact test was used to assess the gender and presence of VZ. We conducted Pearson tests to analyze the relationship between VZ and PAS in different

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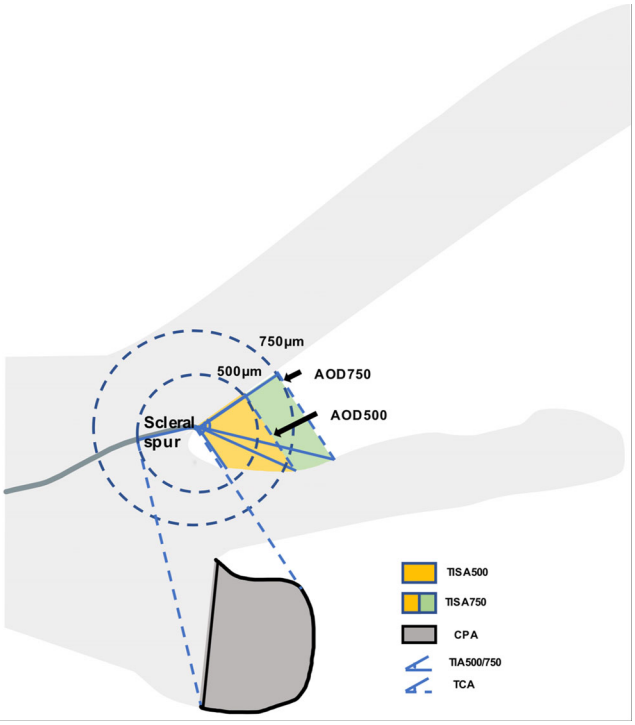

Figure 3. Anterior segment parameters measured by UBM (Illustrator: Kun Lv).

locations. Additionally, we performed univariate and multivariate logistic regression to determine which parameters of the anterior segment were associated with presence of the VZ. $P < 0.05$ was considered statistically significant.

Results

Table 1 provides the demographic data of all 163 patients (261 eyes), 55 APAC(G) eyes (20 eyes with PAC, 35 eyes with PACG), 55 F-APAC(G) eyes (42 eyes with PACS, 13 eyes with PAC), 50 CPAC(G) eyes (10 eyes with PAC, 40 eyes with PACG), 47 F-CPAC(G) eyes (6 eyes with PACS, 24 eyes with PAC, 17 eyes with PACG), and 54 normal eyes. Among all participants, the mean (± SD) age was 65.70 ± 9.33 including 49 males (30.1%) and 114 females (69.9%). No significant differences were identified between the five groups in age, and gender ($P > 0.05$). Patients with APAC(G) had significantly worse BCVA than that of other groups ($P < 0.001$). The mean spherical equivalent of refractive error was not significantly different between PACD groups ($P > 0.05$), but that of healthy eyes was significantly lower than the PACD groups ($P < 0.001$). The IOP in APAC(G) was significantly higher than that of other groups ($P < 0.001$). The axial lengths of APAC(G) and F-APAC(G) were significantly shorter than healthy eyes ($P < 0.019$). The extent of PAS observed by gonioscopy was 288.2° ± 104.1°, 94.9° ± 107.3°, 214.2° ± 127.1°, and 124.5° ± 122.4° in APAC(G), F-APAC(G), CPAC(G), and F-CPAC(G), respectively. Additionally, significant differences were found among different groups ($P < 0.001$), except between F-APAC(G) and F-CPAC(G), where no significant differences were found ($P = 0.168$) (Table 1).

In terms of the presence and the number of quadrants of VZ that could be recognized by UBM, there was no significant difference between CPAC(G) and F-CPAC(G) ($P > 0.05$), although there was a significant difference between APAC(G) and F-APAC(G) ($P < 0.001$). Compared to healthy eyes, no significant difference was shown in VZ in F-CPAC(G) or F-APAC(G) ($P > 0.05$). VZ was less likely to be observed in eyes with APAC(G) ($P < 0.001$) and CPAC(G) ($P < 0.001$) when compared to all other groups of eyes (Table 1). When classified eyes into PACS, PAC, and PACG, healthy eyes were similar to PACS ($P > 0.05$), and PAC were similar to PACG ($P > 0.05$) with respect to the presence and the number of quadrants of VZ. And the proportion of eyes with observable VZ in healthy eyes or eyes with PACS was significantly higher than that in eyes with PAC or PACG ($P < 0.05$). In general, the number of quadrants of VZ decreases in order from healthy eyes to PACS, PAC, and finally PACG (Table 2).

The proportion of VZ and PAS in different locations of different groups is shown in Table 3. There was no significant correlation between VZ and PAS in almost all quadrants of the different groups except for the inferior quadrant of APAC(G) ($P = 0.021$), where there was a negative correlation between the presence of VZ and PAS.

Table 1. Comparison of Demographic, Clinical Characteristics, VZ Parameters Among Five Groups

	APAC(G)	F-APAC(G)	CPAC(G)	F-CPAC(G)	Healthy Eyes	*P* Value
Eyes	55	55	50	47	54	
PACS/PAC/PACG	0/20/35	42/13/0	0/10/40	6/24/17	—	<0.001*
Demographic and clinical characteristics						
Gender						0.676
Male	15	15	19	16	15	
Female	40	40	31	31	39	
Age (years)	66.04 ± 9.95	65.76 ± 9.57	67.34 ± 9.90	66.47 ± 9.97	64.15 ± 8.20	0.303
BCVA (decimal)	0.27 ± 0.24	0.54 ± 0.30	0.48 ± 0.35	0.59 ± 0.26	0.60 ± 0.25	<0.001*
SE (Dioptres)	0.62 ± 1.76	0.70 ± 1.50	0.78 ± 1.98	0.75 ± 1.87	0.05 ± 1.24	<0.001*
IOP (mm Hg)	27.59 ± 17.84	14.95 ± 3.18	16.24 ± 5.39	17.36 ± 8.81	12.95 ± 3.03	<0.001*
AL (mm)	22.64 ± 1.51	22.39 ± 1.24	23.18 ± 1.17	23.06 ± 1.28	23.66 ± 1.65	0.019*
Gonioscopy, grade	0.28 ± 0.35	0.69 ± 0.61	0.98 ± 0.96	1.15 ± 0.99	3.20 ± 0.41	<0.001*
Gonioscopy PAS	288.2° ± 104.1°	94.9° ± 107.3°	214.2° ± 127.1°	124.5° ± 122.4°	0	<0.001*
VZ on UBM						
Presence of VZ (with/without)	19/36	34/21	16/34	28/19	42/12	<0.001*
Number of quadrants of VZ on UBM	0.55 ± 0.86	1.01 ± 1.01	0.52 ± 0.86	1.06 ± 1.05	1.61 ± 1.34	<0.001*

AL, axial length; SE, spherical equivalent.
* $P < 0.05$.

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Table 2. The Presence and the Number of Quadrants of VZ Between PACS, PAC, PACG, and Control Groups

	PACS	PAC	PACG	Healthy Eyes	*P* Value
Eyes	48	67	92	54	—
Presence of VZ					<0.001
With	36	26	35	42	
Without	12	41	57	12	
Number of quadrants of VZ on UBM	1.29 ± 1.01	0.67 ± 0.98	0.60 ± 0.87	1.61 ± 1.34	<0.001

* $P < 0.05$.

Table 3. The Proportion of Presence of VZ and PAS in Different Locations in Each Group and the Association Between VZ and PAS

	APAC(G)	F-APAC(G)	CPAC(G)	F-CPAC(G)	Healthy Eyes
Superior quadrant					
VZ	18.2%	29.1%	12.0%	34.0%	46.3%
PAS	85.5%	18.2%	52.0%	19.1%	0
P value	0.659	0.945	0.919	0.416	—
Inferior quadrant					
VZ	10.9%	29.1%	16.0%	23.4%	46.3%
PAS	72.7%	23.6%	44.0%	27.7%	0
P value	0.021*	0.404	0.693	0.433	—
Nasal quadrant					
VZ	5.0%	29.1%	14.0%	23.4%	27.8%
PAS	90.9%	30.9%	74.0%	40.4%	0
P value	0.582	0.552	0.870	0.760	—
Temporal quadrant					
VZ	20.0%	16.4%	10.0%	25.5%	40.7%
PAS	80.0%	36.4%	68.0%	51.1%	0
P value	0.509	0.590	0.693	0.161	—

The comparison of demographic, clinical characteristics and anterior segment UBM parameters between VZG and NVZG are shown in Table 4. No significant difference in age and gender between VZG and NVZG ($P > 0.05$). The BCVA of NVZG was significantly worse than that of VZG ($P < 0.001$). Additionally, there was no significant difference between the two groups in ACD ($P = 0.067$), anterior chamber width ($P = 0.694$), and CPA ($P = 0.816$). NVZG had shorter AOD500 ($P < 0.001$) and AOD750 ($P < 0.001$), smaller TIA 500 ($P < 0.001$) and TIA 750 ($P < 0.001$), smaller TISA 500 ($P < 0.001$) and TISA 750 ($P < 0.001$), smaller TCA ($P = 0.009$), smaller iris area ($P = 0.010$), and greater LV ($P = 0.004$) compared to VZG.

A multivariate logistic regression analysis was performed (Table 5) to identify which anterior segment parameters were associated with the presence of VZ. In univariate logistic regression analysis, greater AOD500, TIA500, TISA500, TCA were positive predictors for the presence of VZ, whereas greater LVs were identified as negative predictors for the presence of VZ. According to multivariate analysis incorporating variables with a $P < 0.1$, greater LV was independently associated with absence of the VZ (odds ratio = 0.253; 95% confidence interval, 0.109-0.586; $P = 0.001$]. The intraobserver ICC ranged from 0.850 to 0.976, and the interobserver ICC ranged from 0.849 to 0.995 (Table 6), which demonstrated good repeatability and reproducibility of all UBM parameters measured in this study.

Discussion

Although there were anatomic structural differences among subtypes of PACD (including PACS, PAC, and PACG) based on natural history[3] and between different clinical diagnoses of APAC(G) and CPAC(G) based on clinical presentation,[17–19] the intrinsic anatomic component contributing to these differences has not been clearly assessed. This study investigated the presence of VZ in eyes with different subtypes of PACD compared to healthy eyes, and their relationship with UBM parameters. VZ was less likely to be observed in eyes of PAC and PACG. PACD eyes with less VZ in general had a narrower anterior chamber angle, and greater LV was independently associated with absence of the VZ. To our knowledge, this is the first study to demonstrate the difference in VZ among subtypes of PACD and the age- and sex-matched controls.

Previous studies have shown that eyes with no VZ were more likely to have PACG than PAC.[12] However, our study did not replicate this difference between PACG and PAC. We demonstrated that healthy eyes were similar to PACS, and PAC are similar to PACG in terms of the presence of VZ and the number of quadrants of VZ. PAC and PACG are different clinical processes of PACD, and the differentiation between the two of them is predominantly related to the degree and duration of elevated IOP, which does or does not cause glaucomatous optic damage. Because of the similar pathogenesis, the similar frequency of presence of VZ in PAC and PACG groups is reasonable. In addition, we focused on a novel aspect, that is, the differences of VZ between eyes with APAC(G), CPAC(G), and the fellow eyes of APAC(G) and CPAC(G). These results provide a new explanation for the pathogenic mechanism of different clinical diagnoses. According to clinical course and presentation, PAC and PACG can be divided into APAC(G) and CPAC(G).[20] During the acute attack of PAC or PACG, the root of the

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Table 4. Comparison of Demographic, Clinical Characteristics, and Anterior Segment Parameters Between VZG and NVZG

Variables	VZG	NVZG	*P* Value
Demographic characteristics			
Age (y), mean ± SD	65.07 ± 8.43	66.88 ± 10.55	0.085
Gender (M/F)			0.106
Male	31	49	
Female	91	90	
BCVA (decimal)	0.58 ± 0.30	0.40 ± 0.30	<0.001*
IOP (mm Hg)	16.89 ± 10.07	19.52 ± 12.20	0.256
AL (mm)	22.27 ± 1.73	19.52 ± 12.20	0.674
UBM parameters			
LV (mm)	0.76 ± 0.33	0.92 ± 0.40	0.004*
ACW (mm)	11.21 ± 1.20	11.36 ± 0.60	0.694
ACD (mm)	2.13 ± 0.89	2.18 ± 1.90	0.067
CPA (mm^2)	0.55 ± 0.15	0.56 ± 0.17	0.816
TCA	59.64° ± 16.40°	54.86° ± 17.07°	0.009*
AOD 500 (mm)	0.16 ± 0.15	0.10 ± 0.14	<0.001*
AOD 750 (mm)	0.21 ± 0.20	0.13 ± 0.18	<0.001*
TIA 500	15.10° ± 12.41°	9.90° ± 11.78°	<0.001*
TIA 750	13.59° ± 11.92°	9.01° ± 10.93°	<0.001*
TISA 500 (mm^2)	0.06 ± 0.05	0.04 ± 0.05	<0.001*
TISA 750 (mm^2)	0.10 ± 0.10	0.06 ± 0.09	<0.001*
Iris area (mm^2)	2.02 ± 1.02	1.89 ± 0.37	0.010*

AL, axial length.
* $P < 0.05$.

Table 5. Logistic Regression Analysis of Determinants Associated with Presence of the VZ

	Univariate Logistic Regression			Multivariate Logistic Regression		
Parameters	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Demographic and clinical characteristics						
Age (y)	0.980	0.955-1.006	0.128			
Gender (female)	0.626	0.366-1.069	0.086			
Anterior segment parameters						
LV (mm)	0.289	0.130-0.643	0.002*	0.253	0.109-0.586	0.001*
CPA (mm^2)	0.862	0.185-4.008	0.850			
TCA (°)	1.018	1.002-1.033	0.026*			
AOD500 (mm)	20.582	2.853-148.450	0.003*			
TIA500 (°)	1.037	1.015-1.060	0.001*			
TISA500 (mm^2)	3675.438	12.663-1066801.25	0.005*			

OR, odds ratio; CI, confidence interval; ACW, anterior chamber width; CPA, ciliary process area.
* $P < 0.05$

Table 6. Intraobserver and Interobserver Intraclass Coefficients of the Ultrasound Biomicroscopy Parameters

	Intraclass Coefficients	
Parameters	Intraobserver	Interobserver
CPA	0.904	0.918
TCA	0.947	0.880
ACD	0.945	0.995
LV	0.881	0.897
ACW	0.850	0.849
TIA500	0.900	0.906
TIA750	0.941	0.914
AOD500	0.922	0.877
AOD750	0.951	0.844
TISA500	0.976	0.936
TISA750	0.863	0.849
Iris area	0.900	0.950

ACW, anterior chamber width; CPA, ciliary process area.

iris completely covers the whole trabecular meshwork in sudden, namely acute angle closure, resulting in a sudden increase in IOP. The other eye of APAC(G) patients that has no acute attack is categorized as at a preclinical stage, with PACS being the most frequent diagnosis.[21] With respect to VZ, compared to F-APAC(G) and healthy eyes, eyes of APAC(G) have significantly less visible VZ. CPAC(G) is characterized by a less-crowded anterior segment compared to the APAC(G).[22] Lowe[23] postulated that the PAS gradually creep over the surface of the ciliary body band, SS, and reach the trabecular meshwork in eyes with CPAC(G) and F-CPAC(G) to a different degree. Furthermore, Wang et al.[24] did not uncover differences in ACD between CPAC(G) and F-CPAC(G). In terms of the presence of VZ or the number of quadrants of VZ, we demonstrated no significant difference between eyes of CPAC(G) and F-CPAC(G). The different degree of VZ deficiency may be the intrinsic factor in the development of different subtypes of PACD.

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Shon et al.[12] described VZ and its relationship to anterior chamber angle characteristics measured by anterior segment OCT and UBM in two clusters of PAC and PACG eyes and demonstrated that eyes lacking VZ appeared to have smaller anterior chamber area, AOD500, AOD750, angle recess area, TISA500, TISA750, TCA, and TCPD than eyes with visible VZ. We analyzed the anterior chamber angle from three aspects, including distance (AOD500 and AOD750), angle (TIA500 and TIA750), and area (TISA500 and TISA750). In agreement with the previous study,[12] the eyes lacking VZ on UBM were positively correlated with narrower angle parameters. A smaller TCA in NVZG implies that VZ plays a role in preventing excessive anterior rotation of ciliary body. An experimental study found the ciliary body moved forward an average of 0.256 mm, resulting in a narrower anterior chamber angle after using α-chymotrypsin to lyse the VZ in rhesus monkey eyes.[9] This phenomenon provides explanations for our discovery that NVZG has narrower angles independent to ACD and CPA. It suggested that the absence of VZ may be another factor causing PAC and PACG in addition to pupillary block, or an intrinsic factor resulting in pupillary block.

Contrary to a previous study,[12] we found that eyes with no VZ had greater LV compared to eyes with visible VZ on UBM. Furthermore, according to multivariate logistic analysis, greater LV was independently associated with absence of the VZ. The extent to which the crystalline lens protrudes into the anterior chamber can be quantified by LV, which has improved performance in evaluating the position of lens, compared to other parameters such as lens position (LP, calculated as ACD + 1/2 lens thickness) and relative lens position (calculated as LP/AL).[5] A possible reason for the difference from previous research was our categorization of PVZ INS-LE as VZ. There were few studies focusing on the role of this specific type of zonules in the position of the lens. A study attempted to elucidated the role of PVZ INS-LE in humans and rhesus monkeys and held the opinion that the PVZ INS-LE structure may act as a semi-rigid "strut" to the posterior lens equator, providing a direct drag against the lens forward movement and thereby act against lens thickening during accommodation.[10] Therefore lack of PVZ INS-LE may result in forward movement of lens. Other studies also suggested that PVZ INS-LE could create a posterior "drag" limiting the ability of the lens equator to move forward and of the lens to thicken.[13,25] These opinions are supported by the current study, in which the eyes with no VZ have reduced backward pull force on the lens and showed greater LV. Larger LV and narrower angle had been demonstrated to be important anatomic factors in the development of PAC and PACG.[5] Therefore it is worth considering that PACS eyes with less or no VZ are more likely to progress to PAC and PACG. In the current study, no significant correlation between VZ and PAS had been found in almost all quadrants of the PACD groups except for the inferior quadrant of APAC(G) (negative correlation, $P = 0.021$). These results and the findings of "PACD eyes with less VZ had narrower angle, more anteriorly rotated ciliary body and greater LV" may indicate that the absence of VZ may affect the anterior segment structure of the eyes in whole (i.e., the position of iris, ciliary processes and lens), but it may not be directly related to the certain area of PAS.

Although the current study has several important results and outcomes, the following study limitations should be considered. First, the sample size was relatively small, and further larger-scale trials will provide stronger evidence of the relationship between VZ and anterior chamber angle characteristics in PACD. Second, although the intraobserver and interobserver ICCs were good, the subjective evaluation of UBM images may influence the measurement of parameters because of the inherent nature of UBM examination. A three-dimensional imaging technique using ultrasonography or other advanced technology may provide better VZ images in the future. Third, this study was cross-sectional, and further longitudinal studies are needed to investigate whether "without VZ" was an indicator of more-severe forms of PACD. Finally, although patients who used miotics before UBM examination were excluded from this study, some subjects used other antiglaucoma drugs. The potential impact of these drugs on anterior segment structure is not clear.

In conclusion, VZ was less likely to be observed in APAC(G) eyes than in F-APAC(G), although there was no significant difference between eyes of CPAC(G) and F-CPAC(G) in terms of the presence of VZ or the number of quadrants of VZ. In addition, PAC and PACG eyes had a lower proportion of VZ than PACS and healthy eyes. PACD eyes with less or no VZ appeared to have a narrower angle and more anterior rotation of ciliary body, and greater LV was independently associated with absence of the VZ, which may play an important role in the development of PACD. The function and clinical significance of VZ is interesting and important, and it is worthy of further exploration.

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References

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014;121:2081–2090.
2. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90:262–267.
3. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol*. 2002;86:238–242.
4. Quigley HA. Angle-closure glaucoma-simpler answers to complex mechanisms: LXVI Edward Jackson Memorial Lecture. *Am J Ophthalmol*. 2009;148:657–669.e1.
5. Sun X, Dai Y, Chen Y, et al. Primary angle closure glaucoma: What we know and what we don't know. *Prog Retin Eye Res*. 2017;57:26–45.
6. You S, Liang Z, Yang K, et al. Novel discoveries of anterior segment parameters in fellow eyes of acute primary angle closure and chronic primary angle closure glaucoma. *Invest Ophthalmol Vis Sci*. 2021;62(14):6.

7. Coleman DJ, Silverman RH, Lizzi FL, et al. *Ultrasonography of the Eye and Orbit*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2006.
8. Glasser A, Croft MA, Brumback L, Kaufman PL. Ultrasound biomicroscopy of the aging rhesus monkey ciliary region. *Optom Vis Sci*. 2001;78:417–424.
9. Lütjen-Drecoll E, Kaufman PL, Wasielewski R, Ting-Li L, Croft MA. Morphology and accommodative function of the vitreous zonule in human and monkey eyes. *Invest Ophthalmol Vis Sci*. 2010;51:1554–1564.
10. Croft MA, Heatley G, McDonald JP, Katz A, Kaufman PL. Accommodative movements of the lens/capsule and the strand that extends between the posterior vitreous zonule insertion zone & the lens equator, in relation to the vitreous face and aging. *Ophthalmic Physiol Opt*. 2016;36:21–32.
11. Kaufman PL, Lütjen Drecoll E, Croft MA. Presbyopia and glaucoma: two diseases, one pathophysiology? The 2017 Friedenwald Lecture. *Invest Ophthalmol Vis Sci*. 2019;60:1801–1812.
12. Shon K, Sung KR, Kwon J, Hye Jo Y. Vitreous zonule and its relation to anterior chamber angle characteristics in primary angle closure. *J Glaucoma*. 2019;28:1048–1053.
13. Croft MA, McDonald JP, Katz A, Lin TL, Lütjen-Drecoll E, Kaufman PL. Extralenticular and lenticular aspects of accommodation and presbyopia in human versus monkey eyes. *Invest Ophthalmol Vis Sci*. 2013;54:5035–5048.
14. Nongpiur ME, Sakata LM, Friedman DS, et al. Novel association of smaller anterior chamber width with angle closure in Singaporeans. *Ophthalmology*. 2010;117:1967–1973.
15. Shabana N, Aquino MC, See J, et al. Quantitative evaluation of anterior chamber parameters using anterior segment optical coherence tomography in primary angle closure mechanisms. *Clin Exp Ophthalmol*. 2012;40:792–801.
16. Moghimi S, Vahedian Z, Fakhraie G, et al. Ocular biometry in the subtypes of angle closure: an anterior segment optical coherence tomography study. *Am J Ophthalmol*. 2013;155(4):664–673, 673 e1.
17. Mochizuki H, Takenaka J, Sugimoto Y, Takamatsu M, Kiuchi Y. Comparison of the prevalence of plateau iris configurations between angle-closure glaucoma and open-angle glaucoma using ultrasound biomicroscopy. *J Glaucoma*. 2011;20:315–318.
18. Chen HJ, Wang X, Yan YJ, Wu LL. Postiridotomy ultrasound biomicroscopy features in the fellow eye of Chinese patients with acute primary angle-closure and chronic primary angle-closure glaucoma. *J Glaucoma*. 2015;24:233–237.
19. Li M, Chen Y, Chen X, et al. Differences between fellow eyes of acute and chronic primary angle closure (glaucoma): An ultrasound biomicroscopy quantitative study. *PLoS One*. 2018;13(2):e0193006.
20. Salmon JF, Mermoud A, Ivey A, Swanevelder SA, Hoffman M. The prevalence of primary angle closure glaucoma and open angle glaucoma in Mamre, western Cape, South Africa. *Arch Ophthalmol*. 1993;111:1263–1269.
21. Lee JR, Sung KR, Han S. Comparison of anterior segment parameters between the acute primary angle closure eye and the fellow eye. *Invest Ophthalmol Vis Sci*. 2014;55:3646–3650.
22. Marchini G, Pagliarusco A, Toscano A, Tosi R, Brunelli C, Bonomi L. Ultrasound biomicroscopic and conventional ultrasonographic study of ocular dimensions in primary angle-closure glaucoma. *Ophthalmology*. 1998;105:2091–2098.
23. Lowe RF. Primary creeping angle-closure glaucoma. *Br J Ophthalmol*. 1964;48:544–550.
24. Wang W, Li X, Chen S, Huang W, Zhang X. Biometric Differences between Unilateral Chronic Primary Angle Closure Glaucoma and Fellow Non-Glaucomatous Eyes. *Semin Ophthalmol*. 2018;33(5):595–601.
25. Croft MA, Nork TM, McDonald JP, Katz A, Lütjen-Drecoll E, Kaufman PL. Accommodative movements of the vitreous membrane, choroid, and sclera in young and presbyopic human and nonhuman primate eyes. *Invest Ophthalmol Vis Sci*. 2013;54:5049–5058.