A Hierarchical Cluster Analysis of Primary Angle Closure Classification Using Anterior Segment Optical Coherence Tomography Parameters

Seunghee Baek,[1] Kyung Rim Sung,[2] Jae Hong Sun,[2] Jong Rak Lee,[2] Kyoung Sub Lee,[2] Chan Yun Kim,[3] and Kilhwan Shon[2]

Purpose. To investigate the possibility of classifying angle closure eyes in terms of features provided by anterior segment optical coherence tomography (AS OCT).

Methods. Angle closure (primary angle closure [PAC] or PAC glaucoma [PACG]) eyes diagnosed by gonioscopy were imaged using AS OCT under the same lighting conditions. Anterior chamber depth (ACD), anterior chamber width (ACW), iris cross-sectional area (IA), iris thickness at 750 μm from the scleral spur (IT750), iris curvature (IC), lens vault (LV), and anterior chamber area (ACA) were determined using Image J software (ver. 1.44). A hierarchical cluster analysis using Ward's method was performed using AS parameters obtained by AS OCT and axial length (AXL).

Results. A hierarchical cluster analysis was performed on 166 angle closure eyes and produced two clusters. The first cluster (84 eyes) was characterized by higher ACD (2.24 mm), higher ACA (12.5 mm^2), higher IT750 (0.44 mm), higher ACW (11.2 mm), lower LV (0.85 mm), and higher AXL (23.5 mm) compared with the second cluster (82 eyes, 1.82 mm, 9.5 mm^2, 0.38 mm, 10.8 mm, 1.1 mm, and 22.8 mm, respectively). The second cluster had essentially higher LV and lower ACA than the first cluster. Most parameters were significantly different between two clusters except IC ($P = 0.76$).

Conclusions. Our hierarchical cluster analysis indicated two clusters with quite different features existed in our total angle closure population. Our results suggest the possibility of subclassifying angle closure eyes according to AS OCT parameters. (*Invest Ophthalmol Vis Sci.* 2013;54:848–853) DOI:10.1167/iovs.12-10391

From the Departments of [1]Clinical Epidemiology and Biostatistics and [2]Ophthalmology, College of Medicine, University of Ulsan, Asan Medical Center, Seoul, Korea; and the [3]Department of Ophthalmology, Institute of Vision Research, Yonsei University College of Medicine, Seoul, Korea.

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Corresponding author: Kyung Rim Sung, Department of Ophthalmology, University of Ulsan, College of Medicine, Asan Medical Center, 388-1 Pungnap-2-dong, Songpa-gu, Seoul, Korea 138-736; sungeye@gmail.com.

Primary angle closure glaucoma (PACG) is a leading cause of blindness worldwide, especially in Asian countries.[1–3] Various factors, including age, shorter axial length (AXL), increased iris thickness, and shallow anterior chamber, have been reported to be related to PACG.[4–7] The principal mechanism of primary angle closure (PAC) is known as pupillary block (PB), which is defined as resistance of aqueous flow from the posterior chamber to the anterior chamber. Thus, laser peripheral iridotomy (LPI), which eliminates PB, has been considered the standard treatment for PAC. However, a considerable proportion of those PAC eyes have been reported to develop peripheral anterior synechiae (PAS) and show persistent angle closure and/or an increase in intraocular pressure (IOP) after LPI. Hence, some studies have reported that LPI might not be effective in treating all narrow angles.[8–12] Therefore, other pathogenic mechanisms, such as forward movement of the lens or a plateau iris configuration, have also been suggested to contribute to PAC.[13–16] Those outcomes suggest that PAC is not a single disease entity caused by single mechanism and thus may be classifiable into several categories with differing features.

Traditionally, the diagnosis of PAC has been entirely dependent on slit lamp and gonioscopic examinations. However, recent advances in imaging technology provide some quantifiable anterior segment (AS) features that have not been available before. Anterior segment optical coherence tomography (AS OCT) is an imaging technology that does not require contact, making it a noninvasive method for imaging the eye.

The purpose of the present study was to examine the possibility of classifying PAC in terms of features provided by AS OCT. We hypothesized that various AS and anterior chamber angle parameters measured by AS OCT may be related to each other. Thus, we performed a hierarchical cluster analysis to categorize PAC eyes into subgroups with differing characteristics.

Methods

Subjects

Either PAC or PACG patients who visited the glaucoma clinic of Asan Medical Center, Seoul, Korea, and met the inclusion criteria were consecutively included from medical record review. We combined both PAC and PACG eyes and defined "angle closure" in our current analysis. The study was approved by the Institutional Review Board of Asan Medical Center, and we followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants.

All participants underwent a complete ophthalmic examination, including a review of their medical history, measurement of best-corrected visual acuity (to confirm that visual acuity was adequate for

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performance of automated perimetry), slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, fundoscopic examination using a 90- or 78-diopter lens, stereoscopic optic disc photography, retinal nerve fiber layer photography, central corneal thickness measurement (DGH-550 instrument; DGH Technology Inc., Exton, PA), a visual field (VF) test (Humphrey field analyzer, Swedish Interactive Threshold Algorithm [SITA] 24-2; Carl Zeiss Meditec, Dublin, CA), AXL measurement (IOL Master; Carl Zeiss Meditec), and AS OCT (Visante OCT, ver. 2.0; Carl Zeiss Meditec). If necessary, dilation was performed with careful IOP monitoring and gonioscopic examination for several hours afterwards at clinic. Patients were warned to visit an emergency room if acute angle closure–related symptoms occurred after they returned home.

PAC or PACG was diagnosed by gonioscopic examination. PAC was considered present when an eye had an occludable angle and exhibited features indicating that trabecular obstruction by the peripheral iris had occurred. Such features included elevated IOP, the presence of PAS, iris whorling (distortion of radially orientated iris fibers), "glaukomflecken" lens opacity, or excessive pigment deposition on the trabecular surface, but without the development of a glaucomatous optic disc or any VF change.[17] PAC eyes showing glaucomatous optic disc changes (neuroretinal rim thinning, disc excavation, and/or optic disc hemorrhage attributable to glaucoma) or a glaucomatous VF change (pattern standard deviation <5% and values outside normal limits in the glaucoma hemifield test) were considered to have PACG.[17] Only reliable VF test results (false-positive errors <15%, false-negative errors <15%, and fixation loss <20%) were included in the analysis). We excluded patients with a history or current use of topical or systemic medications that could affect the angle or the pupillary reflex; those with a history of previous intraocular surgery, including cataract surgery, laser trabeculoplasty, laser iridoplasty, and laser iridotomy; and those unable to fixate prior to conduct of the AS OCT examination. Those with a history of acute PAC, defined by the presence of ocular or periocular pain, nausea, or vomiting, and a history of intermittent blurring of vision with haloes; a presenting IOP of more than 30 mm Hg; and the presence of three or more of the symptoms conjunctival injection, corneal epithelial edema, mid-dilated unreactive pupil, and shallow anterior chamber were also excluded.[18] Eyes diagnosed with secondary angle closure, such as neovascular or uveitic glaucoma, were also excluded.

All eyes were newly diagnosed cases, and AS OCT imaging was performed before starting any glaucoma medication. If both eyes qualified in terms of the inclusion criteria, one eye was randomly selected for analysis.

Gonioscopy

Prior to AS OCT imaging, all patients underwent a slit-lamp examination and gonioscopy, conducted by an independent observer (KRS) who had extensive experience in the performance of such examinations. All eyes were examined using a Sussman lens in a darkened room (0.5 cd/m^2). Both static and dynamic gonioscopy were performed using a Sussman lens, with the eye in the primary gaze position. Indentation gonioscopy was performed to determine whether angle closure was attributable to apposition or to PAS. Care was taken to ensure that light did not fall on the pupil during examinations.

AS OCT imaging

For all participants, imaging was performed in terms of the nasal and temporal angle (0°–180°) using AS OCT (Visante OCT, ver. 2.0; Carl Zeiss Meditec), operating in the enhanced AS single mode (scan length 16 mm; 256 A-scans) under the same lighting condition (3.25 cd/m^2) by a single well-trained operator. AS parameters of each image were evaluated by an independent examiner (JHS) who was blinded to the other test results and clinical information of the participants. Anterior chamber depth (ACD), anterior chamber width (ACW), iris cross-sectional area (IA), iris thickness at 750 μm from the scleral spur (IT750), iris curvature (IC), lens vault (LV) and anterior chamber area (ACA), were determined using Image J software (ver. 1.44, National Institutes of Health, Bethesda, MD; Fig. 1). Image acquisition procedure and analysis method are described in detail elsewhere.[12,19,20]

ACD was defined as the distance from the corneal endothelium to the anterior surface of the lens. The scleral spur was defined as the point at which a change in curvature of the inner surface of the angle wall became apparent, and often presented as an inward protrusion of the sclera.[21] After determination of the scleral spur location, IT750 was measured.[19–23] IA was defined as the cross-sectional area of both the nasal and temporal sides. ACA was defined as the cross-sectional area bordered at corneal endothelium and anterior surface of lens and iris. IC was defined as the maximum perpendicular distance between the iris pigment epithelium and the line connecting the most peripheral to the most central point of the epithelium.[22] LV was defined as the perpendicular distance between the anterior pole of the crystalline lens and the horizontal line joining the two scleral spurs (ACW).[16,23] Three eyes were excluded due to inadequate visualization of the scleral spur in image acquisition. All AS parameters analyzed, including IA and ACA, are shown in Figure 1. Measurement variability was checked prior to full analysis by calculation of intraclass correlation coefficients (ICCs). Intra-examiner ICC values for various AS parameters ranged between 0.933 and 0.951.[19]

Statistical Analysis

Hierarchical cluster analysis, which has been widely applied in cluster analyses, was used to classify the angle closure eyes. Among the several options in determining the strategy for merging clusters, Ward's method was chosen. An agglomerative hierarchical cluster analysis was performed to identify similar groups with AS parameters obtained by AS OCT. It started with each case as a separate cluster (i.e., equal numbers of clusters and cases) and then combined clusters sequentially, reducing the number of clusters at each step until only one cluster remained. Before analysis, all parameters were standardized in order not to affect the squared Euclidean distances. This method was applied using the squared Euclidean distances as a similarity measure and Ward's method as the clustering algorithm; both are commonly used and known to be efficient in hierarchical clustering. To determine the optimal number of clusters, we used semipartial R^2 (SPR), pseudo F statistics (PSF), and pseudo t^2 statistics. We looked for peaks in the PSF value and chose cluster solutions corresponding to the peaks. Also, large values of SPR suggested that two heterogeneous clusters had been merged to form the new cluster. In general, a cluster solution with a low SPR is preferred because a high value for SPR implies that two heterogeneous clusters are being merged. PSF value in the peak combined with a small value of the pseudo t^2 statistic (PST2) was also considered. Clusters were compared in terms of the specified AS parameters to interpret the resulting clusters. Angle opening distance (AOD_{500}, linear distance between the point of the inner corneoscleral wall, which is 500 μm anterior to the scleral spur, and the iris) measured at temporal angle, which was provided by the manufacturer was also compared among clusters. Differences were tested by two-

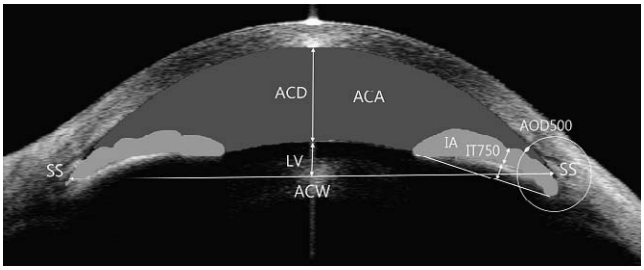

Figure 1. AS parameters measured by AS OCT and calculated using Image J software. SS, scleral spur.

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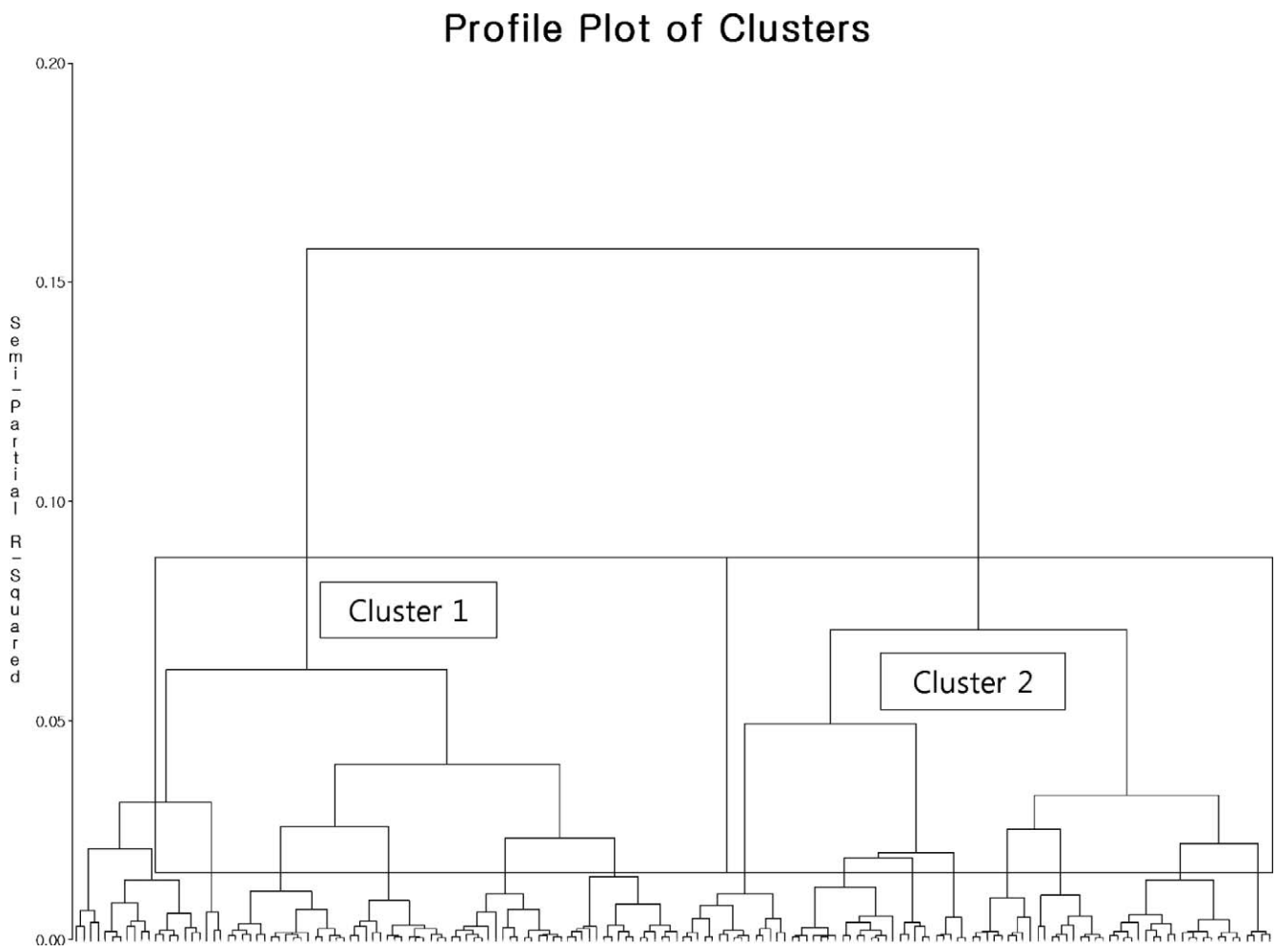

Figure 2. Dendrogram that shows two clusters classified by hierarchical cluster analysis.

sample *t*-test. Statistical analyses were performed using the SAS 9.2 software (SAS Institute, Inc., Cary, NC).

Results

Among 166 angle closure eyes, 98 eyes were PAC and 68 eyes were PACG. A hierarchical cluster analysis with Ward's method was performed on 166 cases with seven prespecified AS parameters obtained by AS OCT and AXL. The Pearson correlation coefficient between ACD and ACA was 0.83, which was highly correlated. Therefore, we remove ACD from the AC parameters to avoid confounding effect in the hierarchical cluster analysis. Iris parameters did not show strong correlation among them (correlation coefficient, IC versus IT750, 0.142; IC versus IA, 0.239, IA versus IT750, 0.054), thus all those three iris parameters were included in the hierarchical cluster analysis.

This analysis produced three clusters, between which the variables were significantly different overall. The number of clusters was determined given a semipartial R^2 value, PSF, and PST2. We chose two cluster solution corresponding to the peaks in the PSF value with small value of the PST2 (Fig. 2). Also, semipartial r^2 suggested cluster 2 was the best option since it increased relatively a lot when merging into one. The mean age and sex proportions were not significantly different between the two clusters (Table 1). The proportion of PAC/PACG was not different between the two clusters (Table 1). The descriptive statistics of the AS parameters in each cluster are presented in Table 2. The first cluster was characterized by higher ACD, higher ACA, higher IT750, higher ACW, lower LV, higher IA, and higher AXL than the second cluster. The second cluster had essentially lower ACD, lower ACA, lower IT750, lower ACW, higher LV, lower IA, and lower AXL than the first cluster (Table 2). From two-sample *t*-test, between-groups means of most parameters were significantly different (Table 2). However, IC parameter showed no significant difference between two clusters. AOD_{500}, which is the indicator of angle closure, was not different two clusters. Figure 3 shows representative cases belonging to the first and second cluster, respectively. All analyzed parameters did not show significant difference between PAC and PACG (Table 3). Figure 3A shows an AS OCT image of an eye that belonged to the first cluster with relatively higher ACD, higher ACA, lower LV, and higher

Table 1. Demographics of Two Clusters Obtained by Hierarchical Cluster Analysis

Variables	Cluster 1 (84 Eyes)	Cluster 2 (82 Eyes)	*P* Value
Age, mean ± SD	62.4 ± 8.6	64.9 ± 10.6	0.105
Sex, female/male	65/19	63/19	0.933
PAC/PACG	33/51	35/47	0.387

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Table 2. Comparison of AS OCT Parameters and AXL in Each Cluster

Parameters (Mean ± SD)	Cluster 1 (84 Eyes)	Cluster 2 (82 Eyes)	*P* Value
ACA, mm^2	12.5 ± 2.1	9.5 ± 1.7	<0.001
ACD, mm	2.24 ± 0.27	1.82 ± 0.38	<0.001
IT750, mm	0.44 ± 0.10	0.38 ± 0.07	<0.001
IC, mm	0.26 ± 0.06	0.26 ± 0.08	0.756
ACW, mm	11.2 ± 0.47	10.8 ± 0.51	<0.001
LV, mm	0.85 ± 0.26	1.10 ± 0.29	<0.001
IA, mm^2	2.45 ± 0.45	2.14 ± 0.39	<0.001
AXL, mm	23.5 ± 0.82	22.8 ± 1.02	<0.001
AOD_{500}, mm	0.16 ± 0.08	0.15 ± 0.08	0.303

ACW. Figure 3B shows an image of an eye with lower ACD, lower ACA, higher LV, and lower ACW, which was classified as belonging in the second cluster.

Discussion

PAC is defined as a closed anterior chamber angle, viewed on gonioscopy, with no secondary cause, such as neovascularization or inflammation. "Closed angle" includes both appositional and synechial closure between the TM and peripheral iris. Obviously, persistent apposition of two structures could result in permanent synechial closure. Various reasons for this closed angle have been suggested. A demographic predisposition, such as Asian race, female sex, and short stature, which may be related to anatomical characteristics, has been reported. Anatomical characteristics included short AXL, ACD, narrow angle, and ACW.[1–7] Because not all eyes with such predisposing conditions develop angle closure, dynamic conditions have also been proposed.[24–29] Dynamic features are not well appreciated in static clinical exams. For example, PB is, in a sense, one of the possible predicting factors for dynamic causes for angle closure. Such dynamic features may not be observed in ordinary condition. Thus, there have been efforts to provoke PB using various stimuli.[30–32]

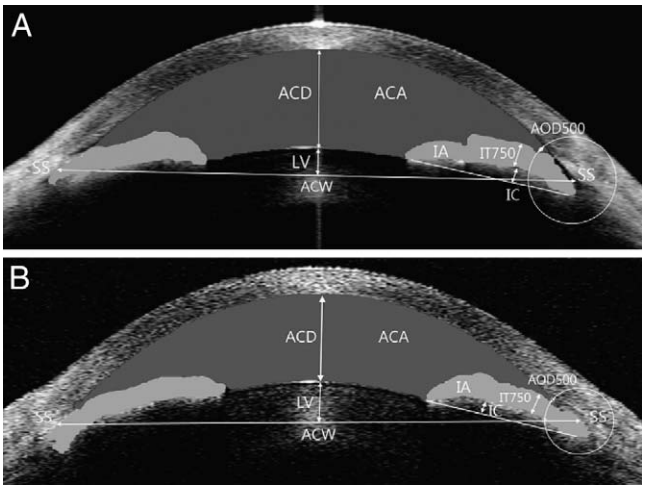

Figure 3. Representative cases belonging to the first and second cluster. (**A**) AS OCT image of the eye that belonged to the first cluster with relatively higher ACA, lower LV, and higher ACW. (**B**) An image of an eye with lower ACA, higher LV, and lower ACW that classified as belonging to the second cluster.

Table 3. Comparison of AS OCT Parameters and AXL between PAC and PACG

Parameters (Mean ± SD)	PAC (98 Eyes)	PACG (68 Eyes)	*P* Value
ACA, mm^2	11.3 ± 2.5	10.6 ± 2.3	0.069
ACD, mm	2.05 ± 0.34	2.00 ± 0.36	0.325
IT750, mm	0.42 ± 0.09	0.39 ± 0.09	0.067
IC, mm	0.26 ± 0.08	0.24 ± 0.06	0.083
ACW, mm	11.0 ± 0.57	10.9 ± 0.47	0.213
LV, mm	0.97 ± 0.26	0.97 ± 0.35	0.934
IA, mm^2	2.31 ± 0.45	2.27 ± 0.44	0.544
AXL, mm	23.1 ± 0.99	23.3 ± 0.97	0.085
AOD_{500}, mm	0.16 ± 0.09	0.15 ± 0.07	0.289

Currently, the consensus is that angle closure is not a single disease entity caused by a simple anatomical condition or a single mechanism; rather, it may be a group of diseases, composed of different entities. Categorization of angle closure eyes according to differing features is potentially important because the primary treatment modality may vary in different types of angle closure. For example, PB should be resolved by peripheral laser iridotomy in the first place if it is the main cause of angle closure. If forward movement of the lens or lens swelling is the main cause of angle closure, it should be handled by eventual removal of the lens. A plateau iris configuration may not be completely resolved by peripheral laser iridotomy.

Because AS imaging can more objectively show features that are not available by slit lamp or gonioscopic examinations, it is expected to play an important role in terms both of diagnosis and exploration of the pathogenic mechanisms of angle closure. If AS OCT can categorize angle closure eyes using various parameters, it may be possible to devise a new classification for angle closure eyes. We assessed this possibility in the current study.

Our analysis indicated two different clusters from the total angle closure population, between which variables were significantly different overall. The first cluster included 50.6% of the total eyes (84 eyes) and was characterized by relatively higher ACD and ACA, lower LV, thicker peripheral iris, and higher ACW. Plateau iris configuration or thick peripheral iris may be contributing factors for angle closure in the first cluster. The first cluster showed significantly higher IT750 than the second cluster. Thick peripheral iris has been suggested as risk factor for angle closure.[22,33] Regarding plateau iris configuration, no widely accepted definition is yet available. Some reports have indicated that plateau iris configuration has a deep central ACD, an anteriorly directed ciliary body, the absence of a ciliary sulcus, and flat iris plane.[15] However, some of these features cannot be diagnosed by standard methods such as slip lamp and gonioscopy. Since AS OCT also does not show all relevant features, it would seem far-fetched that all eyes in the first cluster have characteristics of the plateau iris configuration. However, it would be an interesting finding that a considerable proportion of our angle closure eyes could be categorized with similar features, principally the relatively deeper anterior chamber and higher ACA.

The second cluster had quite different features from the first one, and a similar number of eyes (82 eyes) was categorized into this group. The second cluster was most typically characterized by high LV, smaller AXL, and smaller ACW. These features induced significantly lower ACA than those of the first cluster. Hence, the main mechanism of angle closure in the second cluster may be based on the lens or crowding of intraocular structures in eyes with smaller

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dimensions. Forward movement of the lens due to zonular weakness and increased lens thickness, due to aging, may induce increment of LV. Such a change will eventually lead to closure of the anterior chamber angle and will not be resolved by peripheral iridotomy. Obviously, such increment of LV induced by forward movement of lens or increase of lens thickness may aggravate angle closure more dramatically in eyes with smaller dimensions.

When we compared PAC and PACG in terms of cluster numbers and AS parameter characteristics, the two groups did not show significant difference.

Our study has several limitations. AS OCT does not include all features; for example, structures behind the iris are not included. It also cannot measure dynamic factors. AS OCT imaging was performed before LPI in our current analysis. Thus, we could not exclude the effect of PB on our participants as a pathogenic mechanism of angle closure. PB may be the sole mechanism or combined mechanism with other factors of angle closure. Our original intention was to explore the possibility of classifying angle closure according to anatomical features determined by AS OCT. By this classification, if we have some level of cutoff value for each parameter, it would be helpful for using this instrument in the diagnosis of the direct pathogenic mechanisms of angle closure. Our current study is somewhat preliminary. Thus, the next step would be the setting of appropriate cutoff values to categorize angle closure eyes using AS OCT parameters and to validate such a classification. If we can classify angle closure patients according AS OCT parameters, it would be more helpful for understanding different pathogenic mechanisms of angle closure and for better adjusting treatment of angle closure based on different pathogenic mechanisms. Because there are no established criteria for the subclassification of angle closure, more research is needed.

In conclusion, our hierarchical cluster analysis indicated the existence of two clusters in our angle closure population and these two clusters had quite different features. Our results may suggest the possibility of subclassifying angle closure according to AS OCT parameters.

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