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Article

Differences in Anterior Chamber Angle Assessments Between Gonioscopy, EyeCam, and Anterior Segment OCT: The Chinese American Eye Study

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Purpose: To quantify interquadrant differences in anterior chamber angle (ACA) configuration assessed on gonioscopy, EyeCam, and anterior segment optical coherence tomography (AS-OCT) in a cohort of Chinese Americans.

Methods: Subjects aged 50 years or older were recruited from the Chinese American Eye Study (CHES), a population-based epidemiologic study in Los Angeles, CA. Each subject underwent a complete ocular exam, including gonioscopy, EyeCam, and AS-OCT, under dark ambient lighting. Gonioscopy and AS-OCT imaging and EyeCam image grading were performed by trained ophthalmologists.

Results: Seven hundred nine eyes from 709 subjects were analyzed. Less anatomic variation among the quadrants was detected on gonioscopy and EyeCam compared with AS-OCT ($P < 0.05$). The mean gonioscopy grade, EyeCam grade, and AS-OCT measurement for each quadrant varied by up to 10.3%, 6.4%, and 46.2% of the superior quadrant value, respectively. There were significant interquadrant differences ($P < 0.05$) among mean AOD750 measurements when grouping by quadrant and gonioscopy or EyeCam grade. Mean AOD750 measurements were smallest for the superior quadrant by between 14.3% and 38.1% and 17.4% and 37.9% on gonioscopy and EyeCam, respectively, compared with other quadrants.

Conclusions: Gonioscopy and EyeCam significantly underrepresent anatomic variations of the ACA compared with AS-OCT. Gonioscopy or EyeCam grades from different quadrants do not appear to be comparable or interchangeable, which supports reconsideration of current definitions and methods used to diagnose and manage primary angle closure disease.

Translational Relevance: AS-OCT imaging raises concerns about current clinical definitions and methods that rely gonioscopy or EyeCam to assess the ACA.

Introduction

Primary angle closure glaucoma (PACG) is a common cause of permanent vision loss worldwide. PACG is the most severe form of primary angle closure disease (PACD), a spectrum of diseases characterized by appositional or synechial closure of the anterior chamber angle (ACA) by the peripheral iris. Partial or complete closure of the ACA can impair aqueous humor outflow through the trabecular meshwork (TM) and contribute to elevated intraocular pressure (IOP), an important risk factor for glaucomatous optic neuropathy. Therefore, accurate assessment of ACA configuration is a crucial step in the diagnosis and management of patients with PACD.

Gonioscopy is the current reference standard for evaluating the configuration of the ACA and is based on an examiner's ability to visualize specific anatomic landmarks. It is accepted based on gonioscopy that there is anatomic variation inherent to the ACA of most eyes, with the superior quadrant being the narrowest, the inferior quadrant the widest, and the temporal and nasal quadrants somewhere between.[1,2] This is indirectly supported by gonioscopic studies on rates of angle closure (no posterior TM visible) and peripheral anterior synechiae (PAS), which are more commonly found in areas of angle narrowing and iridotrabecular contact.[2,3]

Anterior segment optical coherence tomography (AS-OCT) is a noncontact imaging method that acquires cross-sectional images of the AS and its structures by measuring their optical reflections.[4] AS-OCT studies characterizing the anatomic variation of the ACA confirm that the superior quadrant of the angle is narrowest.[5,6] However, the temporal and nasal quadrants tend to be wider than the inferior quadrant on AS-OCT. In addition, there is substantial anatomic variation of the ACA detected on multi-image AS-OCT.[6,7]

Gonioscopy is the current clinical standard for evaluating the ACA. EyeCam (Clarity Medical Systems, Pleasanton, CA) is a camera-based assessment method that has been developed and studied as an alternative to gonioscopy.[8,9] Quantitative studies of anatomic variation detected by gonioscopy and EyeCam are limited, especially ones that analyze data derived from population-based cohorts. Our study uses gonioscopy, EyeCam, and AS-OCT data from the Chinese American Eye Study (CHES) to quantify and compare interquadrant differences in ACA configuration detected by the three assessment methods.

Methods

Subjects were recruited from the CHES, a population-based, cross-sectional study that included 4572 Chinese participants aged 50 years and older residing in the city of Monterey Park, CA. Ethics committee approval was previously obtained from the University of Southern California Medical Center institutional review board. All study procedures adhered to the recommendations of the Declaration of Helsinki.

Inclusion criteria for the study included CHES subjects who received gonioscopy, EyeCam, and AS-OCT imaging. Angle closure was defined as an angle quadrant in which pigmented TM could not be visualized. PACD was defined as an eye that had three or more quadrants ($\geq$270°) of angle closure on gonioscopy in the absence of potential causes of secondary angle closure, such as inflammation or neovascularization.[10] Exclusion criteria included history of prior eye surgery (e.g., cataract extraction, corneal transplant, incisional glaucoma surgery, retina surgery), penetrating eye injury, or media opacities that precluded visualization of ACA structures. Subjects with history of laser peripheral iridotomy (LPI) were not excluded, and presence of a prior LPI at the time of exam did not affect how angle closure or PACD were defined. One eye per subject was randomly selected for analysis.

Clinical Assessment

As participants of CHES, each subject received a complete ocular examination, including gonioscopy, AS-OCT imaging, and EyeCam imaging.[11] Clinical examinations were performed by two trained ophthalmologists (DW, CLG).

Gonioscopy was performed with a 1-mm light beam and a Posner-type 4-mirror lens (Model ODPSG; Ocular Instruments, Inc., Bellevue, WA) under dark ambient lighting (0.1 cd/m^2) by two trained ophthalmologists (DW, CLG) masked to other examination findings. Care was taken to avoid light falling on the pupil and inadvertent indentation of the globe. The gonioscopy lens could be tilted to gain a view of the angle over the convexity of the iris. The angle in each quadrant (inferior, superior, nasal, and temporal) was graded using the modified Shaffer classification system based on identification of anatomic landmarks as follows: grade 0, no structures visualized; grade 1, nonpigmented TM visible; grade 2; pigmented TM visible; grade 3, scleral spur visible; and grade 4, ciliary body visible.

EyeCam Imaging and Image Grading

EyeCam imaging was performed by a trained technician with the subject in the supine position under dark ambient lighting. Topical anesthetic drops (Proparacaine hydrochloride 0.5%; Alcon Laboratories, Inc., Fort Worth, TX) and a coupling gel were applied to the eye. Images were obtained from all four quadrants of both eyes. Care was taken to avoid deformation of the eye. If the view of the angle was blocked by a convex iris curvature, the technician was permitted to rotate the probe up to 10° anteriorly along the cornea to better visualize the angle.

EyeCam images were graded by a single glaucoma trained specialist (SCL) masked to other examination findings. Image quality was graded from 1 to 3 as follows: grade 1, a clear image; grade 2, a slightly blurred image with distinguishable ACA structures; and grade 3, a blurry image with indistinguishable ACA structures. Angle grading was based on the identification of anatomic landmarks similar to the modified Shaffer classification system used for gonioscopy.

AS-OCT Imaging and Image Analysis

AS-OCT imaging was performed prior to pupillary dilation under dark ambient lighting by a single trained ophthalmologist (DW) with the Tomey CASIA SS-1000 swept-source Fourier-domain device (Tomey Corporation, Nagoya, Japan). One hundred twenty-eight two-dimensional cross-sectional AS-OCT images were acquired per eye. During the imaging, the eyelids were gently retracted taking care to avoid inadvertent pressure on the globe.

Raw image data were imported into the Tomey SS-OCT Viewer software (version 3.0), which automatically segmented anterior chamber structures and measured AS-OCT parameters once the scleral spurs were marked. Two images were analyzed per eye, one was oriented along the horizontal (temporal-nasal) meridian and the other along the vertical (superior-inferior) meridian.

One observer (AAP) masked to the identities and examination results of the subjects confirmed the structural segmentation and marked the scleral spurs in each image.[12] Eyes that were not imaged under dark ambient lighting conditions or had corrupt images were excluded from the analysis.

Angle opening distance (AOD) at 750 μm from the scleral spur was chosen to describe the configuration of the angle due to its correlation with gonioscopy grades.[13] Intraclass correlation coefficients (ICCs) were calculated to assess intraobserver reproducibility of AOD750 measurements based on images from 20 open angle and 20 PACD eyes graded 3 months apart. All data analysis was performed using MATLAB (MathWorks, Natick, MA).

Statistical Analyses

Means and standard deviations of gonioscopy grades, EyeCam grades, and AOD750 measurements were calculated for each quadrant. Interquadrant comparisons were performed using ANOVA and Tukey honest significance difference tests for multiple comparisons. All analyses were conducted at the significance level of 0.05. Mean grades or measurements were normalized based on the mean numeric value of the superior quadrant for each assessment method.

Means and standard deviations of AOD750 measurements were calculated for each quadrant across all eyes with a particular gonioscopy or EyeCam grade (0, 1, 2, 3, or 4). The Angle Visibility Index (AVI) value for a given quadrant was computed by dividing the mean AOD750 measurement of the superior quadrant by the mean AOD750 measurement of that quadrant. The superior quadrant was chosen due to it consistently having the lowest mean AOD750 measurement. The AVI value of the superior quadrant was always equal to 1. This definition was devised to illustrate the point that similar AS-OCT measurements could correspond to two different gonioscopy or EyeCam grades depending on the quadrants. Higher AVI values corresponded to quadrants receiving higher grades (increased angle visibility) and lower AVI values corresponded to quadrants receiving lower grades (decreased angle visibility).

Results

Seven hundred nine eyes from 709 subjects (272 consecutive with PACD and 437 consecutive with open angles) were recruited from CHES after excluding eyes with history of intraocular surgery (13), incomplete or corrupt AS-OCT imaging data (55), or poor quality of one or more EyeCam images (45).

The mean age of the subjects was 60.8 $\pm$ 7.7 years (range, 50–91). Of the subjects, 230 (32.4%) were male and 479 (67.6%) were female. The mean gonioscopy grade was 2.1 $\pm$ 1.3 (range, 0–4.0), the mean EyeCam grade was 2.4 $\pm$ 1.2 (range, 0–4.0), and the mean AOD750 was 0.30 $\pm$ 0.17 mm (range, 0.01–1.29).

The intraobserver ICC value reflected excellent reproducibility of AOD750 measurements (ICC = 0.96).

Anatomic Variation Detected on Gonioscopy, EyeCam, and AS-OCT

Mean gonioscopy grade by quadrant in ascending order was superior, inferior, nasal, and temporal (Fig. 1). There was a significant difference in mean gonioscopy grades among the quadrants (ANOVA, $P < 0.01$). However, this difference was only significant for the superior-temporal pair-wise comparison (Tukey pairwise, $P < 0.05$).

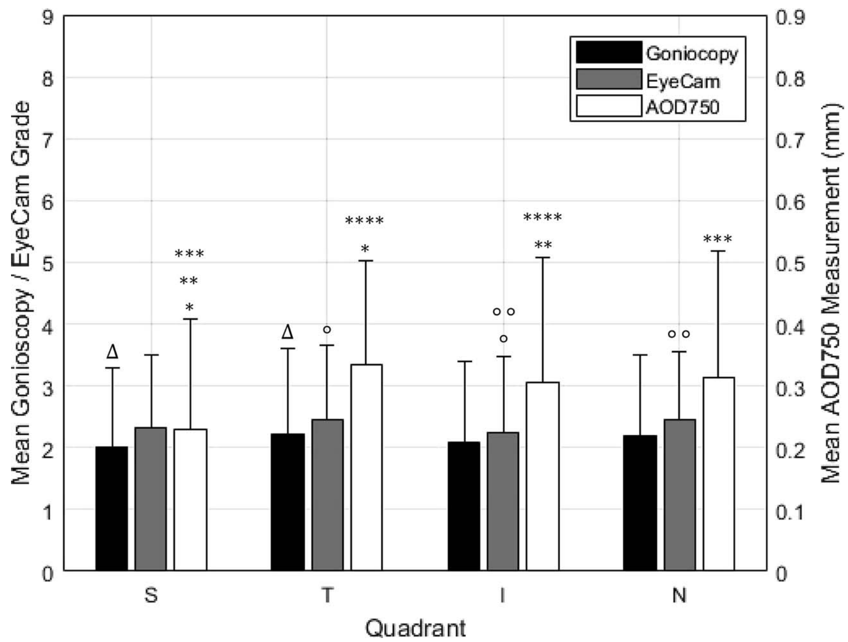

Figure 1. Amounts of anatomic variation detected on gonioscopy, EyeCam, and AS-OCT. Mean gonioscopy grade, EyeCam grade, or AOD750 measurement with standard deviation (*error bars*) plotted by quadrant. Matching numbers of *triangles*, *circles*, or *asterisks*, indicate significant interquadrant differences in mean quadrant grades or measurements on pair-wise comparison (Tukey HSD, $P < 0.05$).

Mean EyeCam grade by quadrant in ascending order was inferior, superior, nasal, and temporal (Fig. 1). There was a significant difference in mean EyeCam grades among the quadrants (ANOVA, $P < 0.01$). However, this difference was only significant for the inferior-temporal and inferior-nasal pair-wise comparisons (Tukey pairwise, $P < 0.01$).

Mean AOD750 measurement by quadrant in ascending order was superior, inferior, nasal, and temporal (Fig. 1). There was a significant difference in mean AOD750 measurements among the quadrants (ANOVA, $P < 0.01$). This difference was significant (Tukey pairwise, $P < 0.01$) for all pair-wise comparisons except the nasal-temporal and inferior-nasal comparisons (Tukey pairwise; $P < 0.01$).

There was less anatomic variation detected on gonioscopy and EyeCam compared with AS-OCT (Fig. 2). Mean gonioscopy grades differed by 3.5% (inferior), 8.9% (nasal), and 10.3% (temporal) of the superior mean gonioscopy grade. Mean EyeCam grades differed by –3.2% (inferior), 5.9% (nasal), and 6.4% (temporal) of the superior mean EyeCam grade. Mean AOD750 measurements differed by 33.0% (inferior), 36.9% (nasal), and 46.2% (temporal) of the superior mean AOD750 measurement on AS-OCT imaging.

Relationships Between Gonioscopy or EyeCam Grades and AS-OCT Measurements

There was a significant difference in mean AOD750 measurements among the quadrants for all gonioscopy grades (ANOVA, $P < 0.01$). The mean AOD750 measurement by quadrant was smallest for the superior quadrant and differed significantly from AOD750 measurements of the other three quadrants for all gonioscopy grades (Tukey pairwise, $P < 0.05$) except grade 2 (Fig. 3). The interquadrant relationships among mean AOD750 measurements of the other quadrants varied, with the temporal quadrant generally having the largest value. The significance of interquadrant differences in mean AOD750 measurements varied by gonioscopy grade.

The superior quadrant's AVI reference value of 1 was greater than that of the other three quadrants for all gonioscopy grades (Fig. 4). The interquadrant AVI relationship varied among the other quadrants, with values ranging between 61.9% and 85.7% of the superior AOD750 measurement, depending on the gonioscopy grade. The smallest AVI value most commonly occurred in the temporal or nasal quadrant.

There was a significant difference in mean AOD750 measurements among quadrants for all EyeCam grades (ANOVA, $P < 0.01$). The quad-

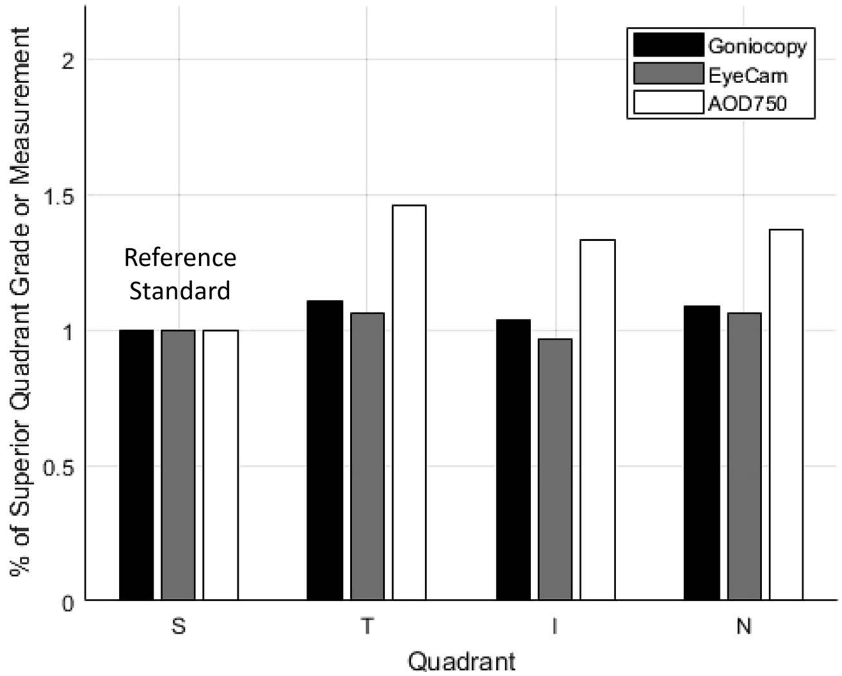

Figure 2. Relative amounts of anatomic variation detected on gonioscopy, EyeCam, and AS-OCT. Mean gonioscopy grade, EyeCam grade, or AOD750 normalized as percentage of superior quadrant grade or measurement (reference standard) and plotted by quadrant.

rant-specific mean AOD750 measurement was smallest for the superior quadrant, which differed significantly from AOD750 measurements of the other three quadrants for all EyeCam grades (Tukey pairwise, $P < 0.05$) except grade 2 (Supplementary Fig. S1). The interquadrant relationships of mean AOD750 measurements varied for the other quadrants, with the temporal quadrant generally having

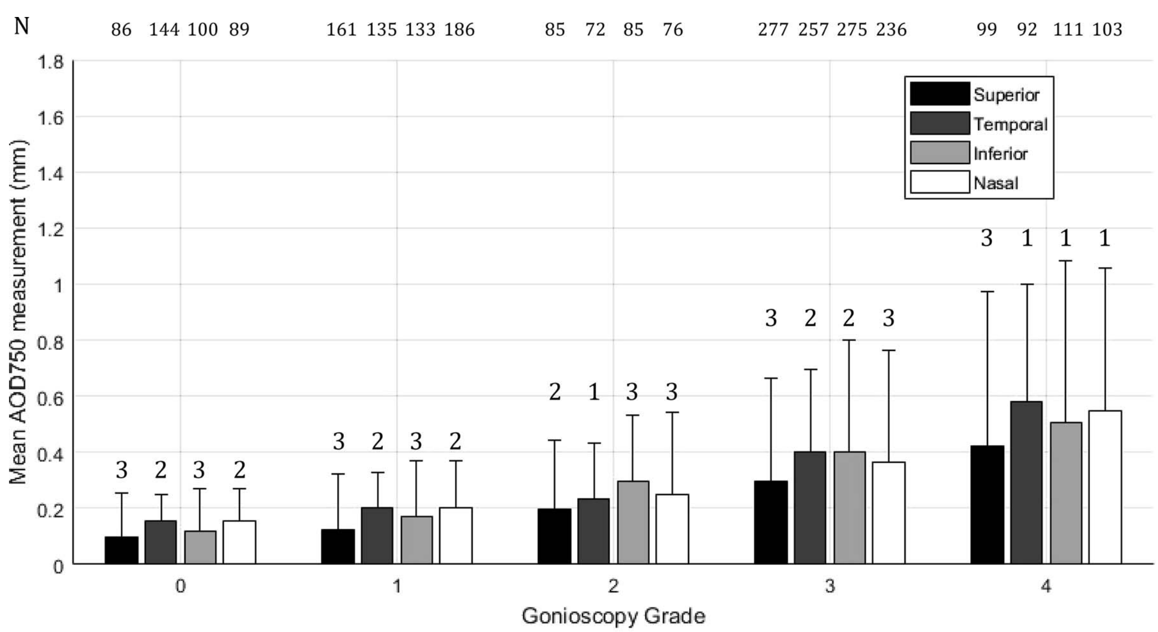

Figure 3. Interquadrant differences in ACA configuration measured on AS-OCT for gonioscopy. Mean AOD750 measurement with standard deviation (*error bars*) plotted by quadrant and gonioscopy grade (0–4). Numbers above *error bars* indicate number of significant interquadrant differences among mean AOD750 measurements on pair-wise comparison (Tukey HSD, $P < 0.05$). Numbers at *top* indicate number of subjects represented by each bar.

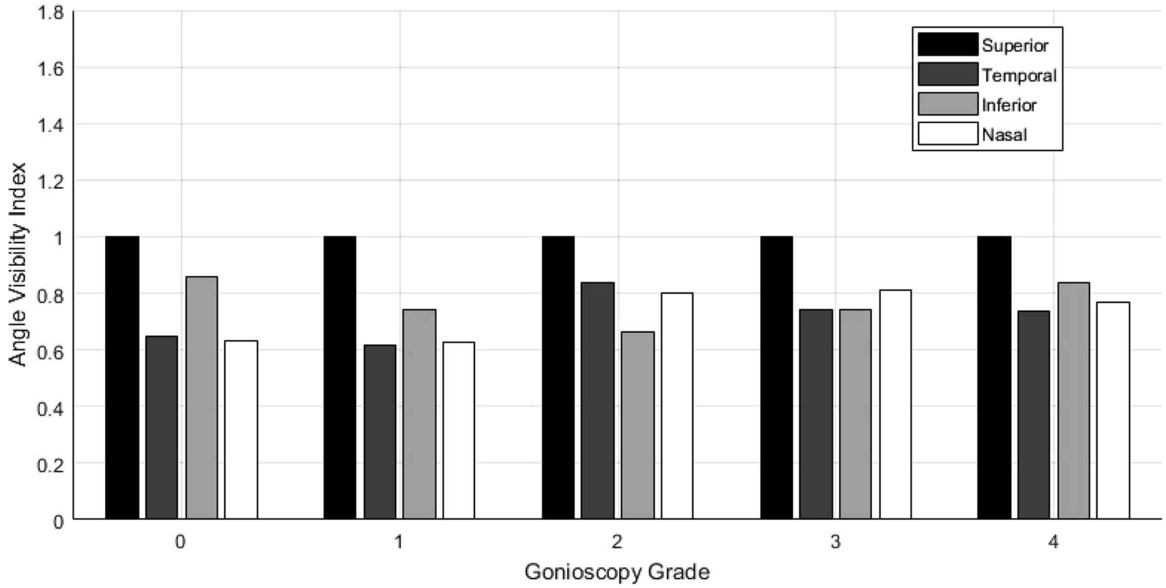

Figure 4. Interquadrant differences in AVI for gonioscopy. AVI values plotted by quadrant for each gonioscopy grade (0–4). AVI = superior quadrant AOD750 / quadrant-specific AOD750.

the largest value. The significance of interquadrant differences in mean AOD750 measurements varied by EyeCam grade.

AVI values for the superior quadrant were the largest among the four quadrants for all EyeCam grades (Supplementary Fig. S2). The interquadrant relationships of AVI values for the other quadrants varied, ranging between 62.1% and 82.6% of the superior AOD750 measurement, depending on the gonioscopy grade. The smallest AVI value most commonly occurred in the temporal or nasal quadrant.

Discussion

In this cross-sectional study, we examined anatomical variations of the ACA assessed by gonioscopy, EyeCam, and AS-OCT using data derived from a population-based cohort of Chinese Americans. We show that gonioscopy and EyeCam underrepresent the amount of anatomic variation compared with AS-OCT. We also demonstrate that this underrepresentation may be due to decreased visibility of ACA structures in the inferior, nasal, and temporal quadrants relative to the superior quadrant. To our knowledge, this is the first study to quantify and compare interquadrant differences between gonioscopic, EyeCam, and AS-OCT assessments. This is also the first study to demonstrate that gonioscopy and EyeCam grades are not comparable or interchangeable between quadrants. We believe these findings raise important concerns regarding current clinical practices that rely on gonioscopy or EyeCam to diagnose and manage patients with PACD.

Anatomic variations of the ACA have been described based on gonioscopic examinations and AS-OCT imaging.[1,2,5,6] However, there is a significant reduction of anatomic variation detected on gonioscopy compared with AS-OCT when quantified in the same cohort. One possible explanation for this finding is that the configuration of ACA structures, such as the iris, are more advantageous for visualizing the superior quadrant, especially in eyes with pupillary block.[14,15] In order to test this hypothesis, we analyzed data obtained on EyeCam, which demonstrated a similar reduction in anatomic variation. This suggests that gonioscopy and EyeCam are hindered by a process common to methods based on direct visualization of ACA structures. Another possible explanation for the reduced anatomic variation is that gonioscopy requires contact with the corneal surface, which can distort the cornea and affect ACA configuration. Therefore, poor gonioscopy technique could have contributed to decreased anatomic variation. We believe this to be unlikely given that similar results were obtained on EyeCam, which is performed in a completely different fashion with a soft, malleable probe tip rather than a hard glass goniolens.

Our findings highlight an important point in the clinical evaluation of patients with suspected PACD:

the relationship between gonioscopic grades and quantitative measurements of ACA configuration varies among quadrants. When we analyzed mean AOD750 measurements based on gonioscopic grade, we found that for the same gonioscopy grade, mean AOD750 measurements tended to be lower for the superior and inferior quadrants compared with the temporal and nasal quadrants. As a result, the mean AOD750 measurement corresponding to a gonioscopy grade of 2 in the superior quadrant was equivalent to the mean AOD750 measurement corresponding to a gonioscopy grade of 1 in the inferior quadrant or 0 in the temporal and nasal quadrants. This result suggests that ACA structures are more easily visualized in the superior and inferior quadrants compared with the temporal and nasal quadrants, which helps to explain the observed reduction in anatomic variation on gonioscopy. However, it does not identify the source of the presumptive interquadrant differences in the visibility of ACA structures.

The reduced anatomic variation and interquadrant differences in assessing the ACA raise concerns about applying gonioscopy to the evaluation and management of patients with PACD. Currently, the diagnosis of PACD relies on an examiner's ability to visualize the pigmented TM in two or more quadrants. In current definitions of PACD, all quadrants are equally weighted. AVI analyses suggest that it is more difficult to visualize and assess the configuration of the ACA in the temporal and nasal quadrants. Therefore, gonioscopic angle closure (grade 0 or 1) observed in these quadrants may be less clinically significant than similar grades in the superior quadrant. In addition, it may be more difficult to detect early synechial changes in the temporal and nasal quadrants, which could delay detection of PACD progression. These observations may also explain why the frequency of PAS on gonioscopy appears to be higher in the superior quadrant compared with other quadrants.[2,16]

The patterns of anatomic variation detected on gonioscopy are consistent with those of AS-OCT, even though they are reduced. While not statistically significant, the mean gonioscopy grade of the inferior quadrant was smaller than those of the nasal and temporal quadrants, contrary to previous opinion.[1,17] These patterns are consistent with prior studies of angle closure based on AS-OCT and ultrasound biomicroscopy (UBM).[14,15] This finding supports the notion that angle closure is most likely to occur in the narrowest portions of the angle, further emphasizing the importance of accurate ACA assessments in these quadrants. While anatomic variation was also reduced on EyeCam compared with AS-OCT, the inferior rather than the superior quadrant was the narrowest. This is consistent with and likely related to postural effects on intraocular structures and ACA configuration.[18]

Our study has several strengths. The sample size was relatively large, and data were derived from a population-based study. This helped to establish a broad distribution of ACA configurations on gonioscopy, EyeCam, and AS-OCT. In addition, this was the first population-based study to examine and compare interquadrant differences in ACA assessment methods. Lighting conditions and examination techniques were also carefully standardized across all three assessment methods. This was crucial given that small lighting condition changes can strongly affect pupil size, an important determinant of ACA configuration and AS-OCT measurements.[19]

Our study also has several limitations. In CHES, gonioscopy was performed primarily by one examiner (DW). Therefore, the reduction of anatomic variation could be attributed to examiner technique. However, as previously discussed, EyeCam data obtained in a completely different fashion support our conclusions on gonioscopy. In addition, there is no gold standard to assess the accuracy of AS-OCT measurements. However, previous studies have shown that AS-OCT measurements are fairly consistent across devices, which indirectly confirms their validity.[20] Third, testing was performed at all times of day. While it is possible diurnal variation affects properties of ACA structures, these do not appear to affect ACA configuration.[21,22] Finally, one observer graded all of the AS-OCT images. Nevertheless, our grader demonstrated excellent intraobserver measurement reproducibility and prior studies have demonstrated good interobserver reproducibility of measurements obtained on modern AS-OCT devices.[6,23,24]

In summary, we demonstrated reduced anatomic variation of the ACA detected by gonioscopy or EyeCam compared with AS-OCT. We also demonstrated that gonioscopy and EyeCam grades are not comparable or interchangeable between quadrants, likely due to differences in the visibility of ACA structures. These findings serve as an important reminder to the many clinicians who perform gonioscopy that direct visual assessments of the ACA may not accurately reflect its width and could be affected by other factors, such as the configuration of the iris. In addition, these findings provide an explanation for some of the challenges that clinicians encounter when performing gonioscopy, especially when attempting to visualize the nasal and temporal quadrants. We hope this study prompts further study of current classification systems and clinical methods for managing patients with PACD.

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