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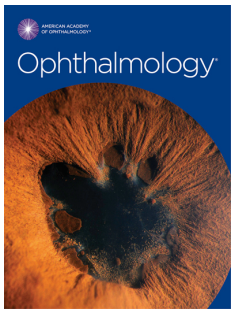

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Anatomical Changes and Predictors of Angle Widening After Laser Peripheral Iridotomy: The Zhongshan Angle Closure Prevention Trial

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Short Title: Predictors of Angle Widening after Laser Peripheral Iridotomy

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ABSTRACT

Purpose: To assess anatomical changes after laser peripheral iridotomy (LPI) and predictors of angle widening based on anterior segment OCT (AS-OCT) and angle opening based on gonioscopy in mainland Chinese primary angle closure suspects (PACS).

Design: Prospective observational study.

Participants: 454 subjects aged 50 to 70 years with PACS.

Methods: Subjects received clinical examinations including gonioscopy and AS-OCT imaging at baseline and 2 weeks after LPI as part of the Zhongshan Angle Closure Prevention (ZAP) Trial. PACS was defined as inability to visualize pigmented trabecular meshwork in two or more quadrants on static gonioscopy. LPI was performed on one eye per subject in a superior (between 11 to 1 o'clock) or temporal or nasal (at or below 10:30 or 1:30 o'clock) location. Biometric parameters in horizontal and vertical AS-OCT scans were measured and averaged. Multivariable linear and logistic regression modeling were performed to determine predictors of angle widening, defined as change in continuous measurements of mean angle opening distance (AOD750), poor angle widening, defined as the lowest quintile of change in mean AOD750, and poor angle opening, defined as residual PACS after LPI based on gonioscopy.

Main Outcome Measures: Anatomical changes and predictors of angle widening and opening after LPI.

Results: 454 subjects were included in the analysis. 219 received superior LPIs and 235 received temporal or nasal LPIs. There were significant changes among most biometric parameters ($p<0.006$) after LPI, including greater AOD750 ($p<0.001$). 120 eyes (26.4%) had residual PACS after LPI. In multivariable regression analysis, several baseline parameters, including superior LPI location ($p=0.004$), smaller AOD750 ($p<0.001$), and greater iris curvature ($p<0.001$), were predictive of greater angle widening. Temporal or nasal LPI locations (OR=2.60, $p<0.0001$) and greater baseline AOD750 (OR=2.58, 0.1 mm increment, $p<0.001$) were most predictive of poor angle widening based on AS-OCT. Smaller mean gonioscopy grade (OR=0.34, 1 grade increment) was most predictive of poor angle opening based on gonioscopy.

Conclusions: Superior LPI location results in significantly greater angle widening based on AS-OCT compared to temporal or nasal locations in a Chinese population with PACS. This supports consideration of superior LPI locations to optimize anatomical changes after LPI.

Introduction

Angle closure, defined as appositional or synechial contact between the trabecular meshwork (TM) and iris, is the primary risk factor for developing primary angle closure glaucoma (PACG), a leading cause of permanent vision loss and blindness worldwide.[1,2] Aqueous humor outflow is impaired by angle closure, which can lead to elevations in intraocular pressure (IOP) and glaucomatous optic neuropathy.[3] There are effective treatments to alleviate angle closure, including laser peripheral iridotomy (LPI) and lens extraction surgery.[4] LPI is commonly performed as primary treatment for angle closure as it is safe, convenient, and produces significant beneficial anatomical changes, including angle widening based on anterior segment OCT (AS-OCT) imaging and resolution of angle closure based on gonioscopy.[5–9]

There is currently no widely-held consensus regarding the optimal location to place an LPI. For some eyecare providers, LPI location is motivated by the presence and location of iris crypts, which are localized areas of iris thinning in the anterior-border layer of the iris.[10] For others, LPI location is motivated by the risk of new-onset dysphotopsias. Traditionally, LPIs were preferentially placed superiorly beneath the upper eyelid to avoid causing dysphotopsias. Recent evidence suggests that temporal and nasal LPI locations may actually result in lower incidence of dysphotopsias, although these findings have not been firmly corroborated.[11–13] One important motivating factor that has not been studied is the relationship between LPI location and anatomical changes after LPI, even though creating angle widening and alleviating angle closure are among the primary objectives for performing LPIs.

While LPI remains the primary form of treatment for angle closure, recent landmark studies such as the Effectiveness in Angle-Closure Glaucoma of Lens Extraction (EAGLE) and Zhongshan Angle Closure Prevention (ZAP) Trials have proposed performing fewer LPIs in specific patient cohorts.[4,14] Therefore, advancing knowledge about predictors of poor anatomical outcomes after LPI could help eyecare providers identify patients who should be considered for alternative forms of management, such as monitoring or lens extraction surgery. In this study, we characterize anatomical changes after LPI in primary angle closure suspects (PACS) from the ZAP Trial. We also develop statistical models to study

the role of baseline parameters, including LPI location and biometric measurements, as predictors of angle widening based on AS-OCT and angle opening based on gonioscopy after LPI.

Methods

The ZAP Trial was approved by the Ethical Review Board of Sun Yat Sen University, the Ethical Committee of Zhongshan Ophthalmic Center, and the Moorfields Eye Hospital and Johns Hopkins University institutional review boards. Ethics committee approval for the current study was also obtained from the University of Southern California Medical Center Institutional Review Board. All study procedures adhered to the recommendations of the Declaration of Helsinki. All study participants provided informed consent at the time of enrollment.

Clinical Assessment

Subjects for the current study were identified from the Zhongshan Angle Closure Prevention (ZAP) Trial, a single-center randomized controlled trial based in Guangzhou, China.[15] Eligible subjects aged 50–70 years with bilateral PACS received complete eye examinations, including gonioscopy and AS-OCT imaging, by trained ophthalmologists at baseline and 2 weeks after LPI. PACS was defined as an eye with two or more quadrants of angle closure, defined as inability to visualize pigmented TM based on gonioscopy, in the absence of peripheral anterior synechiae (PAS), IOP greater than 21 mmHg, and evidence of glaucomatous optic neuropathy or anterior segment ischemia from previous acute IOP increase.

Static gonioscopy was performed under dark ambient lighting standardized at less than 1 lux illumination (EA30 EasyView Light Meter; Extech Instruments, Waltham, MA, USA) with a 1-mm light beam and a Goldmann-type 1-mirror goniolens (Haag-Streit AG, Koniz, Switzerland) prior to pupillary dilation. Gonioscopy was performed by one of two fellowship-trained glaucoma specialists with high intergrader agreement (weighted kappa > 0.80).[15] Care was taken to avoid light falling on the pupil, inadvertent indentation of the globe, and tilting of the lens greater than 10 degrees. The angle was graded

in each quadrant according to the modified Shaffer classification system: grade 0, no structures visible; grade 1, non-pigmented TM visible; grade 2; pigmented TM visible; grade 3, scleral spur visible; grade 4, ciliary body visible.

AS-OCT imaging was performed with the Visante AS-OCT system (Carl Zeiss Meditec, Inc., Dublin, CA, USA) under dark ambient lighting standardized at less than 1 lux illumination prior to pupillary dilation. During imaging, eyelids were gently retracted taking care to avoid inadvertent pressure on the globe. At the start of the ZAP Trial, only scans along the horizontal (temporal-nasal) meridian were performed. Partway through the ZAP Trial, scans along the vertical (superior-inferior) meridian were also performed.

All eligible ZAP subjects received LPI in one eye selected at random using a pre-generated list of random numbers. LPI was performed on the day of the baseline exam by a trained ophthalmologist using an Abraham lens (Ocular Instruments, Bellevue, WA, USA) following a standard clinical protocol. A YAG laser machine (Visulas YAG III, Carl Zeiss Meditec, Dublin, CA, USA) was used to create an iridotomy starting with an initial setting of 1.5 mJ and titrating as needed to create a patent iridotomy of at least 200 μm in diameter. LPIs were preferentially placed beneath the superior eyelid unless there was a prominent iris crypt in a more temporal or nasal location. LPI location was not randomized.

Inclusion criteria for the current study included subjects who received gonioscopy and AS-OCT imaging at baseline and 2 weeks after LPI. Exclusion criteria included eyes missing horizontal or vertical AS-OCT images.

AS-OCT Image Analysis

One or two AS-OCT images per eye oriented along the horizontal and/or vertical meridians were analyzed using custom software (the Zhongshan Angle Assessment Program), which automatically segmented anterior segment structures and produced biometric measurements once the scleral spurs were marked.[16] Image analysis was performed by 5 certified graders who were masked to examination results and intervention assignments. Graders confirmed the segmentation and marked the scleral spurs in each

image. The scleral spur was defined as the inward protrusion of the sclera where a change in curvature of the corneoscleral junction was observed.[17] A set of 20 images from 20 eyes were randomly selected and graded by all 5 graders independently. Good to excellent inter-grader agreement was evidenced by high intraclass correlation coefficients (ICC = 0.74-1.00) among all parameters.

In total, 13 biometric parameters describing the anterior segment were measured.[18] AOD500 and AOD750 were defined as the perpendicular distance from the TM at 500 and 750 µm anterior to the scleral spur to the anterior iris surface, respectively. TISA500 and TISA750 were defined as the areas bounded anteriorly by AOD500 and AOD750, respectively; posteriorly by a line drawn from the scleral spur perpendicular to the plane of the inner scleral wall to the opposing iris; superiorly by the inner corneoscleral wall; and inferiorly by the iris surface. Iris thickness at 750 and 2000 µm from the scleral spur (IT750 and IT2000), iris area (IA), iris curvature (IC), lens vault (LV), anterior chamber depth (ACD), anterior chamber width (ACW), anterior chamber area (ACA), and pupillary diameter (PD) were also measured.[18,19] Eyes with one or more images in which the scleral spur was not detectable or with at least one missing measurement among the biometric parameters analyzed were excluded from further analysis.

Statistical Analysis

Mean parameter measurements were calculated by averaging all sectoral measurements from both horizontal and vertical images. Anatomical changes after LPI were calculated by subtracting pre-LPI mean parameter measurements from post-LPI mean parameter measurements. Normality of pre- and post-LPI parameter measurements was assessed using the Kolmogorov-Smirnov test. All distributions were non-normal, and pre- and post-LPI parameter measurements were compared using the Wilcoxon signed-rank test. Change in mean AOD750 after LPI was compared between superior and temporal or nasal LPI locations using the Wilcoxon rank sum test. Frequencies of poor angle widening and poor angle opening after LPI were compared between superior and temporal or nasal LPI locations using the chi-square test.

Age- and sex- adjusted univariable linear regression analysis was performed to assess the relationship between baseline parameters and change in mean AOD750 after LPI in µm. AOD750 was selected as the outcome measure due to its strong association with gonioscopic angle closure and to compare our findings to previous studies.[6,20] Spearman correlation coefficients were calculated to assess for collinearity among biometric parameters. AOD500, TISA500, and TISA750 ($r > 0.76$ with AOD750), ACA (($r = 0.94$ with ACD), and IT2000 ($r > 0.79$ with IT750) were excluded from multivariable stepwise models due to high collinearity with other parameters and to maintain variance inflation factors (VIF) less than 3.0.

Multivariable stepwise models based on optimization of the Akaike Information Criteria (AIC) were developed with the remaining parameters while adjusting for age, sex, and change in PD after LPI. Units for biometric parameters were modified for physiologic significance and interpretability of beta coefficients and odds ratios. Multivariable linear and logistic regression modeling were performed to determine predictors of angle widening, defined as change in continuous measurements of mean AOD750, poor angle widening, defined as the lowest quintile (20%) of change in mean AOD750, and poor angle opening, defined as residual PACS (two or more quadrants of angle closure) based on gonioscopy after LPI. All analyses were performed using the R programming interface (version 4.0.2). Statistical analyses were conducted using a significance level of 0.05.

Results

In total, 918 subjects received LPI and clinical examinations, including gonioscopy and AS-OCT imaging, at baseline and 2 weeks after LPI. 238 subjects (25.9%) were excluded due to missing vertical images, which were not collected until partway through the ZAP Trial. 37 subjects (4.0%) were excluded due to missing horizontal images. 189 subjects (20.6%) were excluded due to at least one missing measurement among the biometric parameters analyzed.

454 eyes of 454 subjects were included in the current study. All AS-OCT images from these eyes had detectable scleral spurs and measurements for all biometric parameters. The mean age of subjects

included in the study was 58.2 ± 4.7 years (range 50-69 years). 73 subjects (16.1%) were male and 381 subjects (83.9%) were female, which was consistent with the overall distribution of the ZAP Trial (17% male, 83% female).[14] All 454 subjects (100.0%) had PACS at baseline prior to LPI. 120 subjects (26.4%) had residual PACS at 2 weeks after LPI. The mean modified Shaffer grade was 0.85 ± 0.58 at baseline and 1.12 ± 0.78 at 2 weeks after LPI. 219 subjects received LPIs in superior locations (between 11:00 to 1:00 o'clock) and 235 subjects received LPIs in temporal or nasal locations (at or below 10:30 or 1:30 o'clock).

There was a significant difference ($p < 0.006$) between baseline and 2-week measurements for all biometric parameters except IT2000 ($p = 0.11$) (Table 1). There were significant increases ($p < 0.006$) in AOD500, AOD750, TISA500, TISA750, IT750, ACD, ACW, ACA, and LV and significant decreases ($p < 0.001$) in IA, IC, and PD at 2 weeks after LPI.

There was a significant difference ($p = 0.03$) in the median change in mean AOD750 after LPI between eyes receiving LPI in superior (84.3 ± 51.8 µm) and temporal or nasal (73.4 ± 52.6 µm) locations. There was a significant difference ($p = 0.002$) in the frequency of eyes with poor angle widening between superior (31 out of 219; 14.2%) and temporal or nasal (61 out of 235; 26.0%) LPI locations. There was no significant difference ($p = 0.69$) in the frequency of eyes with poor angle opening between superior (56 out of 219; 25.6%) and temporal or nasal (64 out of 235; 27.2%) LPI locations.

On univariable linear regression analysis, there was a significant association ($p < 0.05$) between 7 baseline parameters and change in AOD750 after LPI after adjusting for age and sex (Table 2). Temporal or nasal LPI locations were associated with smaller change in AOD750 ($\beta = -11.09$, $p = 0.025$). Greater AOD750, IC, ACD, ACA, and LV and smaller IT750 and PD were also associated with smaller change in AOD750 ($p <= 0.001$). Greater change in PD and smaller change in AOD750 after LPI were significantly associated ($\beta = -1.72$, $p = 0.004$). There was no association ($p > 0.29$) between age or sex and change in AOD750 after adjusting for sex and age, respectively.

On multivariable linear regression analysis assessing predictors of angle widening after LPI (overall model adjusted $R^2 = 0.24$), there was a significant association ($p < 0.01$) between 6 baseline

parameters and change in AOD750 after LPI after adjusting for age, sex, and change in PD (Table 2). Temporal or nasal LPI locations were associated with smaller change in AOD750 (β = -12.81, p = 0.004). Greater AOD750, IA, and PD and smaller IC and ACD were also significantly associated ($p < 0.01$) with smaller change in AOD750.

On multivariable logistic regression analysis assessing predictors of poor angle widening after LPI (overall model pseudo $R^2 = 0.18$), 5 baseline parameters significantly predicted poor angle widening after adjusting for age, sex, and change in PD (Table 3). Temporal or nasal LPI locations were associated with higher odds of poor angle widening (OR = 2.60, $p < 0.001$). Greater AOD750 (OR = 2.58, 0.1 mm increment), IA (OR = 1.35, 0.1 mm^2 increment), and PD (OR = 1.13, 0.1 mm increment) were also associated with higher odds of poor angle widening ($p < 0.001$). Greater IC was significantly associated with lower odds (OR = 0.40, 0.1 mm increment, $p < 0.001$) of poor angle widening.

On multivariable logistic regression analysis (overall model pseudo $R^2 = 0.08$), 3 baseline parameters significantly predicted poor angle opening, after adjusting for age, sex, and change in PD (Table 4). Greater IA (OR = 1.209, 0.1 mm^2 increment) was associated with higher odds of poor angle opening ($p < 0.006$). Greater IC (OR = 0.54, 0.1 mm increment, $p < 0.001$) and mean gonioscopy grade (OR = 0.34, 1 modified Shaffer grade, p = 0.001) were associated with lower odds of poor angle opening.

There were significant differences between baseline measurements of ACD (2.25 mm for superior LPI location, 2.21 mm for temporal or nasal LPI locations; p = 0.024) and ACA (16.14 mm^2 for superior location, 15.75 mm^2 for temporal or nasal locations; p = 0.039) by LPI location (Table 5). There were no significant differences ($p > 0.065$) among other baseline parameters, including age and sex.

Discussion

We found significant anatomical changes after LPI, including increased angle width based on AS-OCT and decreased prevalence of PACS based on gonioscopy after LPI in a cohort of mainland Chinese with PACS. Univariable and multivariable models revealed that angle widening is significantly associated with not only baseline biometric parameters, such as AOD750 and iris curvature, but also LPI location.

Temporal or nasal LPI locations were also strongly predictive of poor angle widening based on AS-OCT, although they were not predictive of angle opening based on gonioscopy. These results provide the first evidence of an anatomical benefit to performing LPIs in superior iris locations, which may support reconsideration of current practice patterns and provide insights into increasing the efficacy of LPI treatment in angle closure eyes.

LPI prevents acute angle closure attacks and at times lowers IOP, especially when IOP is elevated.[4,14] We hypothesize that it is angle widening after LPI that reduces the likelihood of developing PAS and elevations in IOP over time. Currently, location of iris crypts and concern for new-onset dysphotopsias after LPI are the two primary motivating factors for selecting a location for LPI. Our results suggest that superior LPI locations centered between 11 to 1:00 o'clock provide greater angle widening than temporal or nasal locations. In our multivariable linear regression model, superior LPI location resulted in 12.8 µm greater increase in mean AOD750 on average compared to temporal or nasal LPI locations, which amounts to 16.3% of the 77.7 µm of angle widening observed on average after LPI in any location. In addition, based on our multivariable logistic regression model, the odds of poor angle widening after LPI increases by 2.6 times with temporal or nasal LPI locations compared to superior LPI location. We believe these results support consideration of superior LPI locations to optimize anatomical changes after LPI.

The explanation for the benefit of superior LPI locations is less apparent than the anatomical benefits. One possible explanation is that the average angle is narrowest superiorly, which makes the superior sector more likely to respond to LPI.[21,22] However, little is known about the localized or sectoral effects of LPI treatment and whether angle widening occurs predominantly in the sector in which the LPI is performed. An alternative explanation is that a superior LPI is more effective at reestablishing aqueous flow and reducing the pressure gradient between the anterior and posterior chambers, although why this would be the case is difficult to postulate. Finally, an LPI that is clearly visible in an AS-OCT image may introduce localized anatomical changes (e.g. iris strands, stromal deformations, PAS) and biases when measuring biometric parameters. However, there was a visible LPI in only one horizontal (temporal-

nasal) image of one subject, which, when removed from the analyses, did not affect our findings. Therefore, further work is required to elucidate the mechanisms by which superior LPI locations produce more effective angle widening after LPI.

Anatomical changes after LPI are well-characterized and our results based on data from the ZAP Trial are in agreement with previously reported findings. [5–9] On average, all parameters describing angle width increased after LPI. In addition, IC decreased, indicating flattening of the convex iris and reduction of pupillary block. Conversely, LV increased, which may be related to equilibration of pressures in the anterior and posterior chambers.[6,23] Interestingly, PD decreased after LPI despite carefully controlled lighting conditions during AS-OCT imaging. This finding may be related to flattening of the iris or reduction of appositional forces between the iris and lens at their point of contact after LPI.[24] While there were also significant changes in IT750, IT2000, IA, and ACD after LPI, these changes are likely statistically but not physiologically significant given their small magnitude and the relatively large study sample size.

The results of our multivariable model of baseline predictors of angle widening, defined by continuous measurements of AOD750, are also consistent with previous studies.[6,25] Greater mean angle width at baseline is associated with smaller angle widening after LPI. This is logical, since LPI primarily treats pupillary block, which likely plays a smaller role in PACS eyes with wider angles. Greater IA and PD are also associated with smaller angle widening after LPI, presumably due to residual iris tissue crowding the angle even after LPI. Greater IC is strongly associated with greater angle widening, which reflects the role of IC as a marker of pupillary block.[26] Greater ACD is also associated with greater angle widening, presumably because it suggests against a lens-related phacomorphic etiology underlying the angle closure. Finally, we included change in PD in all models to control for differences in PD between examinations at baseline and 2 weeks after LPI. The significant association between change in PD and AOD750 is a reminder that pupil size is a key determinant of angle width and should be controlled or adjusted for when performing quantitative analyses of angle width across multiple imaging sessions, even when lighting conditions are carefully controlled.[27,28]

Gonioscopy remains the clinical standard for detecting angle closure and forms the basis for current definitions of primary angle closure disease (PACD).[29] In our study, the majority of LPI-treated eyes (26.4%) had open angles based on gonioscopy after LPI, consistent with previous studies.[6] In addition, smaller baseline mean modified Shaffer grade was predictive of poor angle opening after LPI, which is consistent with previous findings.[6] However, this result stands in contrast to smaller baseline mean AOD750 predicting greater angle widening. In addition, neither LPI location nor baseline mean AOD750 were predictive of angle opening based on gonioscopy. These differences among predictors of angle widening based on AS-OCT and angle opening based on gonioscopy serve as an important reminder of fundamental differences between AS-OCT and gonioscopic angle assessments, especially in angle closure eyes.[30,31]

We assessed anatomical effects of LPI using horizontal and vertical AS-OCT scans, which is an important strength of our study. There is significant sectoral variation among biometric measurements, and analyzing a single horizontal image could miss or misrepresent localized effects of LPI on mean angle width.[22] However, the increased anatomical accuracy conferred by analyzing more images may also come at a cost, since each parameter measurements reflects the contributions of a greater number of localized anatomical features. This may explain why the R-squared metric of our multivariable model of angle widening (R^2 = 0.24) was less than that of a previously reported model (R^2 = 0.34), despite analyzing similar biometric parameters.

Our study has some limitations. First, LPI location was not randomized; LPIs were preferentially placed beneath the superior eyelid unless there was a convenient iris crypt elsewhere. Therefore, iris crypt status may be a confounder in the relationship between LPI location and angle widening after LPI. That said, there is no evidence to suggest that performing an LPI at the site of an iris crypt should mitigate its angle-widening effect. In addition, there were few differences among baseline parameter measurements when grouped by LPI location, and the greater mean ACD and ACA measurements observed in the superior LPI group would be expected to decrease rather than increase the apparent angle-widening effect based on our multivariable linear regression model. Second, all subjects had PACS. Therefore, our results

may not generalize to patients with primary angle closure (PAC) and PACG. However, no differences were observed in the effect of LPI in PACS and PAC/PACG eyes in a previous study, which suggests that there may not be differences in anatomical changes after LPI based on disease status.[6] Third, all subjects in the ZAP Trial were Chinese, which again may limit the generalizability of our results. However, there are many similarities between our findings, including key predictors of angle widening after LPI, and findings in data from South Indian eyes.[6] Finally, the R-squared metrics of our multivariable models were poor. Therefore, further work is required to identify more predictive parameters before statistical models can be used to predict precisely how a patient will or will not benefit from LPI.

In conclusion, we characterized and modeled LPI-related anatomical changes in Chinese subjects with PACS. Our key finding is that a superiorly placed LPI results in greater angle widening on average and lower odds of poor angle widening compared a temporally or nasally placed LPI. Based on these results, eyecare providers may consider a superior LPI location to optimize anatomical changes after LPI. However, the long-term clinical implications of this additional angle widening and the mechanism that underlies this effect remain unclear. This approach may also predispose patients to a higher risk of dysphotopsias.[11–13] We hope this study inspires additional research to improve the effectiveness of LPI for widening the angle and reducing the risk of PACG in angle closure eyes.

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References

1. Quigley H, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90(3):262-267.
2. 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(11):2081-2090.
3. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: A review. *JAMA - J Am Med Assoc*. 2014;311(18):1901-1911.
4. Azuara-Blanco A, Burr J, Ramsay C, et al. Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): a randomised controlled trial. *Lancet*. 2016;388(10052):1389-1397.
5. Radhakrishnan S, Chen PP, Junk AK, Nouri-Mahdavi K, Chen TC. Laser Peripheral Iridotomy in Primary Angle Closure. *Ophthalmology*. 2018;125(7):1110-1120.
6. Zebardast N, Kavitha S, Krishnamurthy P, et al. Changes in Anterior Segment Morphology and Predictors of Angle Widening after Laser Iridotomy in South Indian Eyes. *Ophthalmology*. 2016;123(12):2519-2526.
7. How AC, Baskaran M, Kumar RS, et al. Changes in anterior segment morphology after laser peripheral iridotomy: An anterior segment optical coherence tomography study. *Ophthalmology*. 2012;119(7):1383-1387.
8. Lee RY, Kasuga T, Cui QN, Huang G, He M, Lin SC. Association between baseline angle width and induced angle opening following prophylactic laser peripheral iridotomy. *Invest Ophthalmol Vis Sci*. 2013;54(5):3763-3770.
9. Huang G, Gonzalez E, Lee R, et al. Anatomic predictors for anterior chamber angle opening after laser peripheral iridotomy in narrow angle eyes. *Curr Eye Res*. 2012;37(7):575-582.
10. Sidhartha E, Gupta P, Liao J, et al. Assessment of iris surface features and their relationship with

iris thickness in Asian eyes. *Ophthalmology*. 2014;121(5):1007-1012.

11. Vera V, Naqi A, Belovay GW, Varma DK, Ahmed IIK. Dysphotopsia after temporal versus superior laser peripheral iridotomy: A prospective randomized paired eye trial. *Am J Ophthalmol*. 2014;157(5).

12. Srinivasan K, Zebardast N, Krishnamurthy P, et al. Comparison of New Visual Disturbances after Superior versus Nasal/Temporal Laser Peripheral Iridotomy: A Prospective Randomized Trial. *Ophthalmology*. 2018;125(3):345-351.

13. Congdon N, Yan X, Friedman DS, et al. Visual symptoms and retinal straylight after laser peripheral iridotomy: The zhongshan angle-closure prevention trial. *Ophthalmology*. 2012;119(7):1375-1382.

14. He M, Jiang Y, Huang S, et al. Laser peripheral iridotomy for the prevention of angle closure: a single-centre, randomised controlled trial. *Lancet*. 2019;393(10181):1609-1618.

15. Jiang Y, Friedman DS, He M, Huang S, Kong X, Foster PJ. Design and methodology of a randomized controlled trial of laser iridotomy for the prevention of angle closure in Southern China: The zhongshan angle closure prevention trial. *Ophthalmic Epidemiol*. 2010;17(5):321-332.

16. Console JW, Sakata LM, Aung T, Friedman DS, He M. Quantitative analysis of anterior segment optical coherence tomography images: The zhongshan angle assessment program. *Br J Ophthalmol*. 2008;92(12):1612-1616.

17. Ho SW, Baskaran M, Zheng C, et al. Swept source optical coherence tomography measurement of the iris-trabecular contact (ITC) index: A new parameter for angle closure. *Graefe's Arch Clin Exp Ophthalmol*. 2013;251(4):1205-1211.

18. Leung CKS, Weinreb RN. Anterior chamber angle imaging with optical coherence tomography. *Eye*. 2011;25(3):261-267.

19. Mansouri M, Ramezani F, Moghimi S, et al. Anterior segment optical coherence tomography parameters in phacomorphic angle closure and mature cataracts. *Investig Ophthalmol Vis Sci*. 2014;55(11):7403-7409.

20. Narayanaswamy A, Sakata LM, He MG, et al. Diagnostic performance of anterior chamber angle measurements for detecting eyes with narrow angles: An anterior segment OCT study. *Arch Ophthalmol*. 2010;128(10):1321-1327.

21. Tun TA, Baskaran M, Perera SA, et al. Sectoral variations of iridocorneal angle width and iris volume in Chinese Singaporeans: A swept-source optical coherence tomography study. *Graefe's Arch Clin Exp Ophthalmol*. 2014;252(7):1127-1132.

22. Xu BY, Israelsen P, Pan BX, Wang D, Jiang X, Varma R. Benefit of measuring anterior segment structures using an increased number of optical coherence tomography images: The Chinese American Eye Study. *Investig Ophthalmol Vis Sci*. 2016;57(14):6313-6319.

23. Lee RY, Kasuga T, Cui QN, Huang G, He M, Lin SC. Comparison of anterior segment morphology following prophylactic laser peripheral iridotomy in Caucasian and Chinese eyes. *Clin Exp Ophthalmol*. 2014;42(5):417-426.

24. Zheng C, Guzman CP, Cheung CY, et al. Analysis of anterior segment dynamics using anterior segment optical coherence tomography before and after laser peripheral iridotomy. *Arch Ophthalmol*. 2013;131(1):44-49.

25. Huang G, Gonzalez E, Lee R, Chen YC, He M, Lin SC. Association of biometric factors with anterior chamber angle widening and intraocular pressure reduction after uneventful phacoemulsification for cataract. *J Cataract Refract Surg*. 2012;38(1):108-116.

26. Moghimi S, Chen R, Hamzeh N, Khatibi N, Lin SC. Qualitative evaluation of anterior segment in angle closure disease using anterior segment optical coherence tomography. *J Curr Ophthalmol*. 2016;28(4):170-175.

27. Leung CKS, Cheung CYL, Li H, et al. Dynamic analysis of dark-light changes of the anterior chamber angle with anterior segment OCT. *Investig Ophthalmol Vis Sci*. 2007;48(9):4116-4122.

28. Xu BY, Lifton J, Burkemper B, et al. Ocular Biometric Determinants of Anterior Chamber Angle Width in Chinese Americans: The Chinese American Eye Study. *Am J Ophthalmol*. 2020;220.

29. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in

prevalence surveys. *Br J Ophthalmol*. 2002;86(2):238-242.

30. Porporato N, Baskaran M, Tun TA, et al. Understanding diagnostic disagreement in angle closure assessment between anterior segment optical coherence tomography and gonioscopy. *Br J Ophthalmol*. 2019;104(6).

31. Xu BY, Pardeshi AA, Burkemper B, et al. Differences in Anterior Chamber Angle Assessments Between Gonioscopy, EyeCam, and Anterior Segment OCT: The Chinese American Eye Study. *Transl Vis Sci Technol*. 2019;8(2):5.

Table Captions

Table 1. Mean parameter measurements at baseline and 2 weeks after LPI and change in mean parameter measurements after LPI.

Table 2. Univariable and multivariable linear regression analysis of the relationship between baseline parameters and change in mean AOD750 after LPI adjusted for age and sex.

Table 3. Multivariable logistic regression model with significant baseline predictors of poor angle widening (lowest quintile of change in AOD750) after LPI adjusted for age and sex.

Table 4. Multivariable logistic regression model with significant baseline predictors of poor angle opening (residual PACS) after LPI adjusted for age and sex.

Table 5. Mean parameter measurements at baseline by LPI location.

Table 1: Mean parameter measurements at baseline and 2 weeks after LPI and change in mean parameter measurements after LPI.

	Baseline Before LPI		**2 Weeks After LPI**			**Change After LPI**	
Parameter	Mean	STD	Mean	STD	**P-value ***	Mean	STD
AOD500, mm	0.082	0.044	0.136	0.055	**<0.001**	0.054	0.042
AOD750, mm	0.127	0.058	0.206	0.071	**<0.001**	0.079	0.052
TISA500, mm^2	0.041	0.020	0.059	0.024	**<0.001**	0.018	0.016
TISA750, mm^2	0.074	0.030	0.110	0.036	**<0.001**	0.036	0.025
IT750, mm	0.496	0.061	0.499	0.060	**0.006**	0.004	0.034
IT2000, mm	0.640	0.059	0.637	0.059	0.114	-0.003	0.039
IA, mm^2	1.625	0.196	1.607	0.200	**<0.001**	-0.017	0.104
IC, mm^2	0.355	0.078	0.199	0.084	**<0.001**	-0.157	0.098
ACD, mm	2.227	0.197	2.236	0.197	**<0.001**	0.009	0.022
ACW, mm	11.640	0.365	11.681	0.363	**<0.001**	0.040	0.140
ACA, mm^2	15.938	1.992	16.723	1.891	**<0.001**	0.786	0.441
LV, mm	0.760	0.177	0.782	0.180	**<0.001**	0.022	0.068
PD, mm	4.528	0.753	4.404	0.835	**<0.001**	-0.121	0.691

Abbreviations: AOD500/750: Angle opening distance 500/750 um from the scleral spur. TISA500/750: Trabecular-iris space area 500/750 um from the scleral spur. IT750/2000: Iris Thickness 750/2000 um from the scleral spur. IA: Iris Area. IC: Iris Curvature. ACD: Anterior Chamber Depth. ACW: Anterior Chamber Width. ACA: Anterior Chamber Area. LV: Lens Vault. PD: Pupillary Diameter.

* P-values calculated using Wilcoxon signed-rank test.

Boldface indicated significant at $P < 0.05$.

Table 2: Univariable and multivariable linear regression analysis of the relationship between baseline parameters and change in mean AOD750 after LPI adjusted for age and sex.

		Univariable *		**Multivariable *** [b]	
Parameter	**Interval**	**Change in AOD750 (um)**	**P-value**	**Change in AOD750 (um)**	**P-value**
Age	Years	0.573	0.288 [a]		
Sex	Female	-0.447	0.948 [a]		
Mean gonioscopy grade	1 mShaffer grade	7.1677	0.306		
LPI location	Temporal/Nasal	**-11.087**	**0.025**	**-12.809**	**0.004**
AOD500	0.1 mm	-4.552	0.423		
AOD750	0.1 mm	**-16.978**	**<0.001**	**-20.806**	**<0.001**
TISA500	0.1 mm^2	-2.682	0.832		
TISA750	0.1 mm^2	-8.142	0.328		
IT750	0.1 mm	**-13.150**	**0.001**		
IT2000	0.1 mm	-6.223	0.142		
IA	0.1 mm^2	0.669	0.597	**-6.546**	**<0.001**
IC	0.1 mm	**19.360**	**<0.001**	**18.178**	**<0.001**
ACD	0.1 mm	**-3.238**	**0.010**	**3.849**	**0.010**
ACW	1 mm	-9.221	0.173		
ACA	1 mm^2	**-4.364**	**<0.001**		
LV	0.1 mm	**4.622**	**0.001**		
PD	0.1 mm	**-1.199**	**<0.001**	**-2.332**	**<0.001**
ΔPD	0.1 mm	**-1.242**	**0.001**	**-1.720**	**<0.001**

Abbreviations: AOD500/750: Angle opening distance 500/750 um from the scleral spur. TISA500/750: Trabecular-iris space area 500/750 um from the scleral spur. IT750/2000: Iris Thickness 750/2000 um from the scleral spur. IA: Iris Area. IC: Iris Curvature. ACD: Anterior Chamber Depth. ACW: Anterior Chamber Width. ACA: Anterior Chamber Area. LV: Lens Vault. PD: Pupillary Diameter. ΔPD: Change in PD after LPI.

* P-values calculated using age- and sex-adjusted linear regressions.

[a] Univariable models of sex and age adjusted for age and sex, respectively.

[b] Variance inflation factor (VIF) < 1.75 for all parameters.

Boldface indicated significant at $P < 0.05$.

Table 3. Multivariable logistic regression model with significant baseline predictors of poor angle widening (lowest quintile of change in AOD750) after LPI adjusted for age and sex.

		Multivariable *		
Parameter	**Interval**	**OR**	**95% CI**	**P-value**
LPI location	Temporal/Nasal	2.597	1.541 - 4.470	<0.001
AOD750	0.1 mm	2.583	1.507 - 4.538	<0.001
IA	0.1 mm^2	1.351	1.127 - 1.628	<0.001
IC	0.1 mm	0.395	0.262 - 0.579	<0.001
PD	0.1 mm	1.125	1.070 - 1.188	<0.001
ΔPD	0.1 mm	1.060	1.014 - 1.112	0.013

Abbreviations: AOD500/750: Angle opening distance 500/750 um from the scleral spur. TISA500/750: Trabecular-iris space area 500/750 um from the scleral spur. IT750/2000: Iris Thickness 750/2000 um from the scleral spur. IA: Iris Area. IC: Iris Curvature. ACD: Anterior Chamber Depth. ACW: Anterior Chamber Width. ACA: Anterior Chamber Area. LV: Lens Vault. PD: Pupillary Diameter. ΔPD: Change in PD after LPI.

* P-values calculated using age- and sex-adjusted linear regressions. Variance inflation factor (VIF) < 1.94 for all parameters.

Table 4. Multivariable logistic regression model with significant baseline predictors of poor angle opening (residual PACS) after LPI adjusted for age and sex.

		Multivariable *		
Parameter	**Interval**	**OR**	**95% CI**	**P-value**
IA	0.1 mm^2	1.209	1.056 - 1.388	0.006
IC	0.1 mm	0.539	0.389 - 0.732	<0.001
Mean gonioscopy grade	1 mShaffer grade wider	0.335	0.175 - 0.632	0.001

Abbreviations: IA: Iris Area. IC: Iris Curvature.

* P-values calculated using age- and sex-adjusted linear regressions. Variance inflation factor (VIF) < 1.49 for all parameters.

Table 5: Mean parameter measurements at baseline stratified by LPI location.

	Superior (N = 219)		**Temporal/Nasal (N = 235)**		**P-value ***
Parameter	Mean	STD	Mean	STD	
Age, years	57.991	4.789	58.319	4.586	0.476
Sex (M/F)	33	186	40	195	0.571 [a]
AOD500, mm	0.084	0.044	0.080	0.044	0.387
AOD750, mm	0.129	0.055	0.125	0.060	0.282
TISA500, mm^2	0.041	0.020	0.042	0.019	0.765
TISA750, mm^2	0.075	0.030	0.074	0.030	0.865
IT750, mm	0.481	0.063	0.487	0.071	0.723
IT2000, mm	0.495	0.064	0.498	0.058	0.983
IA, mm^2	0.638	0.056	0.641	0.062	0.514
IC, mm^2	1.618	0.197	1.631	0.195	0.973
ACD, mm	2.247	0.191	2.208	0.202	**0.024**
ACW, mm	11.659	0.344	11.622	0.384	0.199
ACA, mm^2	16.139	1.960	15.751	2.008	**0.039**
LV, mm	0.754	0.165	0.765	0.187	0.793
PD, mm	4.601	0.735	4.460	0.765	0.065

Abbreviations: AOD500/750: Angle opening distance 500/750 um from the scleral spur. TISA500/750: Trabecular-iris space area 500/750 um from the scleral spur. IT750/2000: Iris Thickness 750/2000 um from the scleral spur. IA: Iris Area. IC: Iris Curvature. ACD: Anterior Chamber Depth. ACW: Anterior Chamber Width. ACA: Anterior Chamber Area. LV: Lens Vault. PD: Pupillary Diameter.

* P-values calculated using age- and sex-adjusted linear regressions.

[a] P-value calculated using chi-square test.

Boldface indicated significant at $P < 0.05$.

Précis

Laser peripheral iridotomy in Chinese primary angle closure suspects produces angle widening on anterior segment OCT and opening on gonioscopy. Superior laser locations result in greater angle widening compared to temporal or nasal locations.