# Increase in anterior chamber angle depth after topical pilocarpine measured by spectral domain optical coherence tomography: A possible additional indicator for laser peripheral iridotomy in primary angle-closure suspects in an opportunistic set-up

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Purpose: Indication of laser peripheral iridotomy (LPI) is often conjectural due to dependency on gonioscopy and strict dichotomous classification of occludability. Indentation gonioscopy is the gold standard but is under-utilized for various reasons. The prevalence of primary angle closure disease (PACD) in eastern India is 1.5–1.9%, with a 22% five-year progression rate. Many angle closure patients may go blind without timely diagnosis and iridotomy. General ophthalmologists need alternate, validated methods for diagnoses. Pilocarpine eye drop causes miosis, and flattens the iris, producing angle changes detectable by spectral domain optical coherence tomography (SD-OCT). We hypothesized that the amount of angle change may be a suitable indicator for iridotomy. Methods: Our prospective cross-sectional single-masked observational study evaluated pilocarpine-induced changes in angle parameters detected by SD-OCT. Out of 372 patients enrolled, 273 patients (539 eyes) remained, with a mean age of 48.6 years (SD = 10.36). All eyes were graded by the Van Herick (VH) method, gonioscopy, and anterior segment (AS) SD-OCT and reassessed after pilocarpine drops. Results: The sensitivity and specificity of tomography measurements against gonioscopy grades were 61% and 85%, respectively. The receiver operating characteristic (ROC) curve was 0.85. Pilocarpine-induced angle widening was significant in gonioscopically narrower angles. Low Van Herick grades (217 eyes), narrow gonioscopy grades (238 eyes), and a narrow OCT angle value (165 eyes) were candidates for iridotomy. Conclusion: Our study results showed that pilocarpine-induced angle widening detected by SD-OCT could be a strong objective indicator for LPI.



**Key words:** Gonioscopy, laser peripheral iridotomy, opportunistic set-up, primary angle closure diseases, spectral domain optical coherence tomography, Van Herick method

Gonioscopy is the only one tool to define occludable angles and indication for peripheral iridotomy in primary angle closures and suspects cases. 70% of ophthalmologists are located in cities and suburbs and cater to 23% of the population.<sup>[1]</sup> The prevalence of primary angle closure disease (PACD) is estimated to be 1.5-1.9% in eastern India<sup>[2]</sup> and 22% of primary angle closure suspects (PACS) progress to primary angle closure (PAC)/primary angle closure glaucoma (PACG) in 5-year time.<sup>[3]</sup> Timely identification is the mainstay to prevent irreversible blindness. This opportunistic evaluation should not be missed. Gonioscopy is indispensable for the evaluation of angle structures but unfortunately under-performed<sup>[4,5]</sup> due to time constraints and lack of understanding of gonioscopy among other various reasons.<sup>[6]</sup> A dichotomous classification of drainage angle width as termed "occludable" or "not occludable" is stringent, making evaluation by general ophthalmologists further difficult, and thus excludes many borderline cases.<sup>[7,8]</sup> Gonioscopy is also known for subjectivity and variable agreement.<sup>[9]</sup> Attempts have been made to remove some of the subjectivity from the gonioscopy.

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Received: 25-Mar-2022 Accepted: 29-Aug-2022 Revision: 18-Jun-2022 Published: 30-Nov-2022 Congdon et al.<sup>[10]</sup> designed "Biometric Gonioscopy." But it had controversy.<sup>[11]</sup> Non-gonioscopic methods such as ultrasound biomicroscopy (UBM),[12] Scheimpflug photography, anterior segment optical coherence tomography (AS-OCT), optical biometers, scanning peripheral anterior chamber depth analyzer (SPAC), and eye-cam were evaluated.<sup>[12,13]</sup> These new devices, singly, were not able to substitute conventional slit-lamp-gonioscopy. Maximally they could complement, particularly when gonioscopy was difficult. In an era of telemedicine and virtual ophthalmology, especially in the setting of the so-called coronavirus disease (COVID-19) era, these techniques will be more important.<sup>[14]</sup> There are questions regarding the indication and timing of laser peripheral iridotomy (LPI) in PACS cases. International Society of Geographic and Epidemiologic Ophthalmology (ISGEO) does not provide a clear guideline about the timing of LPI in PACS. The indication they provide is, PACS with uncertain follow-up.

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American Academy of Ophthalmology observed that even in absence of documented benefits of iridotomy for PACS, the relative safety of this procedure has allowed its wider use in the hope of preventing acute angle closure crisis (AACC) and PACG.<sup>[15]</sup> There was no mention of the proportion and prospect of those patients for whom gonioscopy could not be done. The fates of these patients would remain uncertain with the present gonioscopy-dependent management protocol. Anterior segment spectral-domain optical coherence tomography (AS SD-OCT) offers definite advantages for the assessment of iris-pupil dynamics along with resultant anterior chamber configuration. They are now readily available, non-contact, patient-friendly, objective, quantifiable, and reproducible. It can record real-time changes in iris-pupil dynamics in dark and light.<sup>[16]</sup> Likewise, SD-OCT can record changes in angle contour "before miosis by pilocarpine in darkness" and after "maximal miosis with pilocarpine in light." Opening of narrow angles with pilocarpine is a known fact. OCT quantifies the narrowness of the angle and its pilocarpine-induced changes. This study aims to identify a value or percentage, which correlates best with indentation gonioscopic measurements/indications for LPI. A substantial increase in angle after pilocarpine drops is expected in narrow angles without peripheral anterior synechia (PAS). Therefore, in PACS cases, this increase may be used as a predictive diagnostic test for angle closure and can offer an additional indication for LPI. This increase can easily be explained to the patients for informed consent for iridotomies and offer an undisputable indication for LPI. When ophthalmologists need some alternative method that would be readily available, quick to perform, patients-friendly, objective, and reproducible, our method of measuring SD-OCT angle before and after pilocarpine drop could be very useful in the problem of selecting of patients for iridotomies, particularly in borderline cases. A substantial increase in angles after pilocarpine can offer a documentable indication for LPI, thus increasing confidence. PAS and sometimes anterior lens movement may affect the amount of opening of angles measured by OCT after pilocarpine, so it cannot solely be relied upon. However, particularly in borderline cases, our method may provide additional support in decision-making for iridotomy. A well-defined cut-off value of the post-pilocarpine increase in SD-OCT angle value as proposed by our study will help select cases for peripheral iridotomy. Probably this study is the first of this kind.

# Methods

We planned to find whether pilocarpine drop-induced changes in anterior chamber angle detected by AS SD-OCT could predict possible indication of LPI. In that line, we conducted a prospective cross-sectional single-masked observational study of patients at our general ophthalmology outpatient clinic after ethics committee approval was obtained. A sample size of 372 patients was calculated to provide 80% power with a confidence level of 95% and a confidence interval of 5%. Between September 2020 and March 2021, all non-acute patients with age above 30 years attending our general outpatient department (OPD) irrespective of their refractive status, were invited to participate in the study. Exclusion criteria were age less than 30 years, and a documented history of cataracts/cataract extraction, corneal pathology, previous LPI, other intra-ocular surgery, and other risk factors for secondary glaucoma. Patients who could not demonstrate understanding of the study or the informed consent form were also excluded. Participants received a thorough examination including limbal anterior chamber depth (LACD) by the VH method, with scores classified as normal (VH >0.5), borderline (VH = 0.5), or suspect (VH <0.5). Standard and indentation gonioscopy to assess closure angles were performed following standard protocols using a Zeiss 4-mirror gonioscope (Carl Zeiss AG, Oberkochen, Germany). Anterior chamber angles were graded according to the Shaffer classification. Shaffer grades III-IV (20°-45°) were considered normal, grade II (>10°-20°) was classified as borderline, and grades O–I ( $\leq 10^{\circ}$ ) were suspect. The amount of change in angle openings resulting from the indentation gonioscopy was also recorded. Data were recorded meticulously and supported by clinical photographs. AS SD-OCT (AngioVue, Optovue, Inc. USA) was performed in a darkened room with far fixation before pilocarpine drop instillation and repeated after maximal miosis obtained with pilocarpine drop. The second measurement was performed in an illuminated room with near fixation to further maximize miosis. SD-OCT angle measurements were recorded after identifying the scleral spur. All statistical analyses were performed using Microsoft Excel (Microsoft Corporation version 2016). Statistical tests were used to assess the differences in the mean of pre-pilo and post-pilo OCT angle values in different grades of angles. The sensitivity and specificity of the SD-OCT angles compared to the gonioscopy results were calculated using Shaffer grades O-I (≤10°) to delineate disease status, as well as with a cut-off value of angle OCT ( $\leq 10^{\circ}$ ) for disease status. We further tested the sensitivity and specificity of narrow angles by SD-OCT ( $\leq 10^{\circ}$ ) and their increase ( $\geq 100\%$ ) in the SD-OCT angle after pilocarpine.

# Results

After exclusion, 273 patients (539 eyes) remained. Of these, 79 (28.9%) were male and 194 (71.1%) female, with an overall mean age of 48.6 years (standard deviation [SD] = 10.36). All eyes were graded according to the Van Herick (VH) method, gonioscopically, and by AS SD-OCT. Some patients were apprehensive about gonioscopy. A comparison of the normal distribution curves of gonioscopy and OCT-measured angles showed equal height and spread, but different means (16.39 and 13.84, respectively) with z (cal) 3.843 at a *P* value of 0.0001. Strong correlations were observed between any two grading systems. Pearson's correlations were 0.861, 0.72, and 0.70 between VH and gonioscopy grades, gonioscopy grades and SD-OCT angle, and VH and SD-OCT [Table 1].

The sensitivity and specificity of OCT measurements against the gonioscopy grades ( $\leq 10^{\circ}$ ) were 61%, with 85%, respectively [Table 2]. Sensitivity improved to 85%, but specificity was reduced to 68% when the cut-off value was set at 16.5° (mean [9.11°] + one SD [6.39°]). The receiver operating characteristic (ROC) curve for gonioscopy and angle OCT measurements showed a positive outcome with an area under the curve (AUC) of 0.85 [Fig. 3].

After the instillation of the pilocarpine drops, an increase in angle OCT values was significant (*p*-value <.000001) in eyes with gonioscopically determined narrower initial angles [Table 3]. An increase of angle opening of the open-angle group (more than 30°) vs closed angle group  $(0^{\circ}-10^{\circ})$  two-sample t-test (Welch) showed H<sub>0</sub> is rejected (*P*-value 2.87129e-9, effect size 1.50). The widest gap in trend lines (pre-pilo vs post-pilo) was observed at the narrowest angles, becoming insignificant at wide-open angles [Fig. 4].

The number of eyes found to be eligible for LPI varied with the method (VH, Gonio, SD-OCT) of assigning the disease state. A total of 238 (44.2%) LPI-eligible eyes were diagnosed by Shaffer grades of O-I for gonioscopy-determined angles. When AS SD-OCT angles  $\leq 10^{\circ}$  were considered as the cut-off value, 165 (30.6%) eyes were identified, while

# Table 1: Pearson's correlation of different methods of anterior chamber angle assessment

Comparison between	Pearson's R	Р
VH and Gonio	0.86	< 0.00001
Gonio and angle OCT	0.72	< 0.00001
VH and angle OCT	0.70	< 0.00001

Analysis of correlation of grading by different methods (VH, Gonio, and anterior segment SD-OCT) by Pearson method (determining "R") between any two methods

the Van Herick method (LACD: 0–25% of corneal thickness) identified 217 (40.2%). The strictest criterion for identifying LPI candidate eyes is based on a "diseased" diagnosis by all three measurements (Gonioscopy, angle of anterior chamber, and  $\geq$ 100% increase in SD-OCT angle value after pilocarpine) identifying 122 (22.6%) eyes.

# Discussion

The main objective of our study was to determine whether pilocarpine-induced changes in anterior chamber angle

#### Table 2: Sensitivity/specificity of SD-OCT grading vs other grading methods

	$VH \leq 0.25$	<b>Gonio Gr 0-I (</b> ≤10° <b>)</b>	Gonio ≤(mean 9.0°)	Gonio≤16.5° (mean+1 SD)
Sensitivity	0.609489	0.6066946	0.569038	0.853556
Specificity	0.819495	0.8508287	0.878453	0.679558
Accuracy	0.715064	0.7119048	0.702381	0.778571
PPV	0.769585	0.8430233	0.860759	0.778626
NPV	0.679641	0.6209677	0.60687	0.778481

Sensitivity, Specificity, Accuracy, PPV, and NPV of angle SD-OCT against VH,  $Gonio \le 10^\circ$ ,  $Gonio \le 9^\circ$  (mean in our study),  $Gonio 16.5^\circ$  (mean + one SD of our study)

#### Table 3: SD-OCT angle changes after pilocarpine, two-sample t-test (Shapiro-Wilk)

Angle Grade No.	Mean			H,	Р	T-cal	Effect Size	
	Pre-Pilo	Post-Pilo	Increase	% Increase				
All (539)	13.84	20.19	6.36	137.4	Rejected	0.0000	23.666	1.02
0-10° (213)	5.08	14.72	9.62	303	Rejected	0.0000	24.876	1.7
10-<20° (199)	14.4	19.82	5.47	41.8	Rejected	0.0000	16.034	1.14
20°-<30° (88)	24.2	27.12	2.96	12.57	Rejected	0.0000	4.7312	0.5
Above 30° (39)	35.76	36.53	0.78	3.24	Accepted	0.5029	06764	0.11

Analysis of SD-OCT angle changes after pilocarpine, by two-sample t-test (Shapiro-Wilk). Alternate hypothesis tests for all eyes and according to different grades of gonioscopy



Figure 1: Normal (a) Van Herick limbal AC depth (0.5). (b) Pre indentation gonioscopy Shaffers grade III. (c) Post indentation gonioscopy Shaffers grade IV. (d) Pre pilocarpine in dark angle SD OCT 26.630. (e) Post pilocarpine in light angle SD OCT 30.790. Please note: Angle did not improve though iris is flattened



Figure 2: Suspect (a) Van Herick limbal AC depth (<0.25). (b) Pre indentation gonioscopy Shaffers grade 0. (c) Post indentation gonioscopy Shaffers grade IV. (d) Pre pilocarpine in dark angle SD OCT 6.980. (e) Post pilocarpine in light angle SD OCT 17.010. Please note: Angle improved and iris is flattened



**Figure 3:** Receiver operating characteristic (ROC) curve for gonioscopy and angle OCT with an area under the curve (AUC) of 0.85

parameters measured by AS SD-OCT, could provide additional indications for LPI additional to gonioscopy. Our results demonstrate that SD-OCT can objectively measure the changes and reliably identify LPI candidates. Though gonioscopy is the gold standard, however, it is underused by general ophthalmologists. To address these deficiencies, ophthalmologists continuously endeavor to find and evaluate different methods to complement gonioscopy in the detection and management of glaucoma that would allow greater inter-observer reliability and more clearly define screening cut-offs for angle closure. The pharmacologically induced mydriatic provocative test was evaluated in angle closure cases. Our method of flattening the lens-iris diaphragm and opening of angle by pilocarpine may be considered as reverse of the provocative test. This observation aimed to find out how



Figure 4: Scatter plots trendlines of OCT angle values (Pre-Pilo vs Post-Pilo)

accurate non-invasive screening tests could be in identifying those at risk of developing PACG. Non-contact AS SD-OCT might be more important in COVID-19 time and useful in telemedicine.<sup>[14]</sup> However, no study did discuss how the techniques could aid in decision-making for borderline cases. We were unable to find any statistical reports that mentioned patients who refused gonioscopy or for whom it could not be performed. Radhakrishnan S<sup>[17]</sup> mentioned the importance of OCT assessment where patients could not tolerate the Gonio contact lens. The candidacy of such patients to receive treatment is uncertain. In our study, 24% of the participants refused gonioscopy in clinic examinations. Though we did not probe for reasons in detail but one very common reason, we found, the apprehension of the bulky Gonio contact lens. The number of female patients (194, 71.1%) in our study was higher than that of male patients (79, 28.9%). This observation is consistent with reports from other studies.<sup>[18-20]</sup> Grades based on VH and gonioscopy were in strong correlation (r = 0.86, P = 0.00001), in line with several published reports,<sup>[21,22]</sup> although Bhartiya and Shaarawy,<sup>[23]</sup> Thompson et al.,<sup>[24]</sup> and Johnson et al.<sup>[25]</sup> reported lower levels of agreement. Interestingly, the last three studies<sup>[23-25]</sup> were all of the African and African-origin populations. Regarding agreement between gonioscopy and AS SD-OCT, different studies found variable agreements. Nolan<sup>[26]</sup> found AS-OCT to be highly sensitive and Radhakrishanan reported high sensitivity in compiled data across several studies.<sup>[17]</sup> Tay et al.,<sup>[27]</sup> however, found low agreement (kappa = 0.31) between gonioscopy and AS-OCT. We found strong correlation between them (r = 0.7323; P < 0.00001). Pilocarpine-induced anterior chamber angle changes were studied as early as 1992 (Mehrotra),<sup>[28]</sup> 1995 (Hung),<sup>[29]</sup> and 1999 (Kobayashi et al. 1999).<sup>[30]</sup> A study by Kobayashi et al. pointed out the usefulness of pilocarpine-induced increase of anterior chamber angle detected by UBM.[30] But studies by Merhotra<sup>[28]</sup> and Hung<sup>[29]</sup> reported that pilocarpine decreased the angle depth. However, they were on normal subjects. Our study found that 13.0% (70/539) of eyes showed a decrease in angle width. Of these 70 eyes, only 9 (12.9%) had angles below 10°.

Dynamic changes of the anterior chamber angle in dark-light with AS-OCT were studied.<sup>[16,31,32]</sup> They all found an increase in angle opening distance (AOD), and trabecular-iris space area (TISA) in anterior chamber parameters from dark to light room examination. Those changes were more pronounced at narrower angles than in normal people. SD-OCT angle measurement in the dark with far fixation is a feasible alternative to gonioscopic grading. We calculated the sensitivity and specificity of SD-OCT angle measurements against gonioscopy, with Shaffer grade O-I as "having disease" and grades II-IV as "not having disease." At a cut-off value of ≤10°, AS SD-OCT 85% specificity might result in missing some borderline cases  $(10^{\circ}-20^{\circ})$ . Our study showed that while using the angle parameter as an indication for LPI, the chance of over-doing of LPI is very low (specificity 85%). However, at a cut-off value of 16.5° (mean + SD) with sensitivity improving to 85%, might result in over-diagnosing of angle closure. Results for sensitivity, specificity, ROC, and AUC showed SD-OCT angles to be a feasible independent screen of LPI candidacy. We evaluated two additional potential classifiers based on changes in SD-OCT angles after pilocarpine drops. Based on a pre-pilo gonioscopy angle of less than 10°, 238 (44%) eyes were eligible for LPI, while 142 (26%) eyes were eligible based on an angle increase of more than 100%. Angle increase of more than 100% after pilocarpine drop was highly specific (specificity 82% and sensitivity 49%). Our study found that increase in angle width after pilocarpine treatment was more pronounced in gonioscopically narrower angles [Figs. 1,2 and 4]. Subgroup analysis at different grades also found significant differences except for gonioscopy grades above 30°. Eleven out of 22 eyes with gonioscopy Shaffer grade O that did not open on indentation, showed very high intra-ocular pressures (IOPs) ranging from 40 to 72 mm Hg. These eyes likely represented previously undiagnosed PAC or PACG. Further studies are required to explore these results. Among eyes with Shaffer grades III and IV, 35% and 23%, respectively, had IOP ≥21 mm Hg (as high as 43 mm Hg). These open-angle groups likely represent previously undetected primary open-angle glaucoma (POAG) or ocular hypertension (OHT) and need further evaluation.

Strengths of our study include the robust sample size and a participant base from northeastern regions of India that are under-privileged and under-represented in health studies. We are unaware of previous studies evaluating AS SD-OCT as a screening tool for LPI. As the study was conducted in a single hospital in eastern India, there was little variation in participant demographics and findings may differ in other parts of India and the world. We also used a relatively low age (30 years) in the exclusion criteria, as many of the participants did not know their actual ages and the interviewer recorded an approximation.

This was a single-masked, prospective comparative study. With limited study personnel, we were not able to evaluate the inter-rater agreement between the different assessments (VH, gonioscopy, and SD-OCT angles). However, gonioscopy graders did not know the findings from SD-OCT and vice versa. The screening protocol based on quadrant quality and visibility of the posterior trabecular meshwork (≤180°) is less stringent than other screening protocols. However, other authors<sup>[25,26]</sup> have suggested that it provides more flexibility to general ophthalmologists diagnosing potential glaucoma patients. This is similar to the initial screening by the VH method when the cut-off is set at 0.5. Our approach may thus create a chance of over-diagnosis, which is preferred over missing genuine cases in a region with high need. OCT-based angle assessment is not yet standardized and identifying scleral spur is sometimes difficult or inaccurate. In spite of these limitations, scleral spur or Schlem canal identification-based OCT evaluation of angle configuration is getting momentum. Hopefully, in near future, we will get an accepted algorithm.

### Conclusion

In conclusion, our study of pilocarpine-induced SD-OCT angle changes offers additional support for peripheral iridotomy in borderline cases of angle closure disease as detected by the VH method and gonioscopic evaluation. When we get an accepted algorithm after a multicenter randomized control trial, this method could be used when gonioscopy could not be done for any reason. For counseling purposes, documented increase in angles after pilocarpine drops creates a better understanding of the disease. These illustrated OCT results also create confidence about gonioscopy in those patients who refused gonioscopy initially. Results of our study can also be used to inform future multicenter randomized controlled trials on the use of SD-OCT angle values to find an exact cut-off value. We plan to accumulate data of those who will undergo LPI according to gonioscopic indication and in those cases by SD-OCT angle changes where gonioscopy cannot be done. We also plan to continue this work as a cohort study, comparing progression from pre-glaucomatous to PAC/PACG between patients with and without iridotomy. In regions such as ours where there are many barriers to ongoing monitoring for ocular diseases, additional validated indications for iridotomy will likely prevent many unnecessary cases of irreversible vision loss. A well-designed multicenter study might offer a cut-off value in angle changes after pilocarpine drop to select cases for peripheral iridotomy.

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#### **Conflicts of interest**

There are no conflicts of interest.

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