Ocular coherence tomography-measured changes over time in anterior chamber angle and diurnal intraocular pressure after laser iridotomy: IMPACT study

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Running title: OCT measured changes in anterior chamber dimensions following laser iridotomy in angle closure

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The corresponding author (R Bourne) confirms that he had full access to all the data in the study and has final responsibility for the decision to submit for publication.
**Importance:** The change in the anatomical dimensions over time and the effect on diurnal intraocular pressure following laser peripheral iridotomy is poorly understood.

**Background:** To evaluate change over time in anterior chamber angle anatomy following laser peripheral iridotomy (LPI) in patients with primary angle closure compared to control eyes. Additionally, the effect of LPI on diurnal intraocular pressure (DIOP) fluctuation was investigated.

**Design:** Longitudinal, prospective, double-randomised research study.

**Participants:** Adults with suspected angle closure or angle closure diagnosis referred to hospital services in the United Kingdom.

**Methods:** Thirty-nine patients newly diagnosed with bilateral primary angle closure/suspects (PAC/PACS) received LPI to one eye and changes in angle morphology were measured over 8 sections with swept source AS-OCT. The other eye acted as control with intraocular pressure (IOP) measured hourly.

**Main outcome measures:** Angle opening distance (AOD), trabecular–iris angle (TIA), angle recess area (ARA), and trabecular–iris space area (TISA) at 500 µm and 750 µm from scleral spur

**Results:** There was an increase in all angle parameters following LPI, which was maintained for 6 months (e.g. inferotemporal segment AOD500 0.041mm (p=0.008) at 1 week and 0.039mm (p=0.003) at 6 months) following LPI.
Greatest effect at 6 months post-LPI was observed opposite the iridotomy site in the inferior/inferotemporal sections (AOD500 0.039mm, p=0.003 and AOD750 0.075mm, p=0.002). There were no statistically significant differences for the overall DIOP fluctuation values in the treated group at 6 months post-LPI compared to baseline.

**Conclusions and Relevance:** LPI widened all angle sections with maximum effect observed in the site opposite the iridotomy. Angle changes were maintained up to 6 months after LPI treatment without any statistically significant change in DIOP fluctuation.
Introduction:

Primary angle closure glaucoma (PACG) is a leading cause of blindness estimated to affect up to 20 million people worldwide. Laser peripheral iridotomy (LPI) is an established prophylactic treatment for primary angle closure (PAC) and primary angle closure suspects (PACS) and its effectiveness in opening the peripheral angle has been demonstrated on gonioscopic examination. However, the change in the anatomical dimensions over time following laser peripheral iridotomy is less well understood. Previous studies have used gonioscopy, ultrasound biomicroscopy (UBM), time domain anterior segment optical coherence tomography (TD-ASOCT) and more recently swept source anterior segment optical coherence tomography (SS-ASOCT). Gonioscopy can readily visualise the angle and qualitatively assess associated changes, but it is a challenging operator-dependent examination. Quantifying the peripheral angle parameters changes following LPI has until recently been a difficult process as high resolution UBM is difficult to standardise due to the challenges of obtaining reproducible angle measurements before and after iridotomy. Furthermore, most of the studies using UBM for anterior segment imaging post-LPI have measured the effect only on the treated eye. Anterior segment optical coherence tomography allows for consistent and reproducible measurement of angle parameters over time. Recent studies have utilised the advantages of SS-OCT to assess particular angle parameters. Most of these had short follow up times, such as up to 3 months post-LPI and have involved East Asian populations. Previously we have reported that in patients with PACS and PAC intraocular
(IOP) pressure declined as the day progressed (p < 0.001) and diurnal IOP (DIOP) fluctuation, (maximum minus minimum intraocular pressure measured during office hours) varied from 1.50 to 14.50 mmHg while DIOP fluctuation was unrelated to the presence of peripheral anterior synechiae (PAS). Currently it is unknown whether laser peripheral iridotomy (LPI) would have an effect on this fluctuation. Baskaran et al. studied DIOP fluctuation in treated PAC and PACS eyes in comparison with PACG and normal non-glaucomatous eyes and found the fluctuation was lower in the latter. However, the effect of the LPI on DIOP fluctuation in their patient sample was not evaluated as all the patients with occludable angles had already been treated. Considering the importance of IOP in the clinical management of patients with occludable angles, it is important to understand if LPI has an effect on DIOP fluctuation.

**Methods:**

This was a longitudinal, prospective, double-randomised research study. A sample size of 40 patients was chosen based on the minimal detectable difference for intraocular pressure with sample power of 80% and an alpha error of 0.05 in order to achieve statistically significant difference in pressure change of 5%. This sample size exceeded most of the current studies in the published literature. Forty Caucasian consecutive patients newly referred to a hospital glaucoma service with a gonioscopic diagnosis (less than 180 degrees posterior pigmented trabecular meshwork visible on applanation gonioscopy) of bilateral PAC, PACS, or a combination of both conditions and
no other ocular comorbidity were recruited for the Investigating Management of Angle Closure and Treatment (IMPACT) study. The initial clinical examination and gonioscopy were performed by a single consultant ophthalmic surgeon with a specialist interest in angle-closure glaucoma (RB). LPI procedures were performed using the surgeon’s (RB) standard technique with superior placement of the iridotomy in a randomly allocated eye of each patient. The mean total power used to perform the iridotomy was 16.11mJ (SD 10.8 mJ) and the mean number of shots was 13 (SD 8.6). A patent iridotomy post-LPI was present in all the treated eyes post-LPI and throughout the study. Patency was tested at the slit-lamp using a retroillumination technique.

Measurements from 39 participants (78 eyes) were analysed until the second randomisation (where eyes with gonioscopically closed anterior chamber angles were randomised to argon laser peripheral iridoplasty or no further treatment), which took place 3 months post LPI. From this time point onwards only the data obtained for those patients who received LPI alone as a laser treatment was used for analysis (29 treated and their fellow 29 untreated eyes). A gonioscopically occludable anterior chamber angle was defined as an angle in which 180 degrees or more of the posterior trabecular meshwork was obscured on applanation gonioscopy. An overview of the patient pathway is given in Figure 1.

**Figure 1. Schematic of IMPACT Study Pathway.** Primary angle closure (PAC), Primary angle closure suspects (PACS), Laser Peripheral Iridotomy (LPI), Argon Laser Peripheral Iridoplasty (ALPI). Patients who
received ALPI treatment (red outline) were excluded from further analysis regarding effect of LPI from time of treatment.

Three-dimensional SS-OCT (Casia device; Tomey, Nagoya, Japan) images were obtained on the same day as the IOP measurements. The scans were taken in darkness (between 0.3 and 0.5 lux) and the images taken were subsequently analyzed using the commercially available software with this instrument. Image acquisition was always by the same examiner and an ophthalmologist subspecialising in glaucoma performed all the gonioscopic examinations (RB).

The analysis of SS-OCT images involved calculation of the following parameters in each eye: the angle opening distance (AOD), the trabecular–iris angle (TIA), the angle recess area (ARA) and the trabecular–iris space area (TISA). Eight sectors (Superior, Superonasal, Nasal, Inferonasal, Inferior, Inferotemporal, Temporal and Superotemporal) for each eye with their corresponding 8 parameters (AOD, ARA, TISA and TIA at 500 and 750 \( \mu \text{m} \)) were assessed with the CASIA analysis software (Figure 2).

The analysis was conducted based on trace lines on the cornea anterior and posterior surfaces and the iris anterior surface as calculated by the software. The scleral spur position was identified by the software and was checked by an observer before starting analysis. In cases where the position had to be manually corrected, the position of the scleral spur was confirmed by a second observer. The inter-observer coefficients of variations (CV) were calculated according to the formula -

\[ CV = \frac{SD(X_{1\text{st}}, X_{2\text{nd}})}{mean(X_{1\text{st}}, X_{2\text{nd}})} \]

where SD means standard deviation and \((X_{1\text{st}}, X_{2\text{nd}})\) are measurement
obtained in twice repeated evaluation on the same image.

Figure 2. Schematic representation of the eight iridotrabecular angle sections under study. Iridotrabecular angle parameters as measured with the Casia AS-OCT analysis software. AOD (angle opening distance), ARA (angle recess area), TISA (trabecular–iris space area), and TIA (trabecular–iris angle) at 500 and 750 µm are highlighted in bright green.

Following recruitment to the study, participants attended for IOP measurement every hour from 9 AM to 4 PM (a time window of 15 minutes around each clock hour was permitted). Intraocular pressure measurements involved Goldmann tonometry (Goldman tonometer AT900; Haag-Streit International, Koeniz, Switzerland) using disposable prisms to reduce the risk of cross-contamination. The same tonometer was used for every IOP measurement for every participant and regular calibration checks were undertaken with no calibration errors detected during the study. Two IOP measurements were taken per eye, with a maximum of 1 mm Hg difference permitted between these measurements. In cases where the difference was exceeded 1 mm Hg, additional measurement(s) were taken. Hourly DIOP measurements were performed at the initial and final visits only with single time point measurements at the intermediate assessments.

Diurnal IOP fluctuation data of 29 participants who only received LPI and no further interventions during the study were analysed. Of the 29 treated eyes, 19 (65%) eyes had gonioscopically open angles and 10 (35%) remained with occludable angles 3 months after LPI.
Statistical analyses were performed using SPSS software (IBM Corporation, Armonk, New York) and Microsoft Office Excel software (Microsoft Corporation, Redmont, Washington) with p<0.05 values considered statistically significant. Angle width–related measures at different visits before and after LPI were compared using 1-way repeated-measures analysis of variance, with inter-visit difference analyzed using Tukey’s method.

Ethical approval by Cambridgeshire Research Ethics Committee (REC) for the IMPACT study was obtained on August 3, 2010 (REC Reference 10/H0301/14). The study was entered on the National Institute for Health Research Clinical Research Network (NIHR CRN) Portfolio on September 9, 2010 (NIHR CRN Study ID: 8955). The research adhered to the tenets of the Declaration of Helsinki.

**Results:**

Of the 39 participants recruited, 26 were women and 13 men. The average age in the group was 59.6 years at the time of recruitment (range, 25–77 years).

We observed a widening effect in all parameters and sections following LPI treatment and a paired samples t-test showed a statistically significant widening effect maintained over time (measurements obtained for AOD are presented in Table 1; for additional angle parameters ARA, TISA and TIA see Supplementary Tables S2, S3 and S4 respectively [Supplementary material]). There was no significant widening effect observed in the untreated eye at 1 week and 6 months when compared to baseline.
Table 1. Parameters (AOD) from swept-source OCT-measured anterior chamber angle sections before and after laser peripheral iridotomy.

In the treated eye, the most marked widening effect was found for the Inferior-Temporal angle. The increase in angle parameters was maintained for 6 months post-LPI as illustrated by the dimensional changes in the AOD500 and AOD750 for the section opposite the iridotomy (Figure 3).

Figure 3. Changes in Angle Opening Distance at 500 µm and 750 µm from scleral spur in the inferotemporal section of the anterior chamber angle (39 eyes) opposite the iridotomy site in treated eyes and in the inferotemporal section of untreated eyes, measured with swept-source OCT in dark conditions.

The treated eyes experienced the most marked widening 1 week post-LPI (AOD500 0.041mm, p=0.008 and AOD750 0.065mm, p=0.001), which was maintained at 6 weeks (AOD500 0.036mm, p=0.006 and AOD750 0.061mm, p=0.002), 3 months (AOD500 0.044mm, p=0.001 and AOD750 0.071mm, p=0.005) and 6 months post-LPI (AOD500 0.038mm, p=0.003 and AOD750 0.075mm, p=0.002) (Figure 4). In the case of the untreated eyes the dimensional changes through time were not statistically significant and remained relatively constant. Similar statistically significant widening of all parameters was also observed in other sections of the treated eyes (Supplementary Materials).
Figure 4. Changes in Angle Opening Distance at 500 µm and 750 µm from scleral spur in the superior section of the anterior chamber angle (39 eyes) at the iridotomy site in treated eyes and in the superior section of untreated eyes, measured with swept-source OCT in dark conditions.

Due to the small change in AOD500, the treated eyes in the superior section, however, showed an increase in angle dimensions 1 week post-LPI with statistically significant increase only for AOD750 (AOD500 0.009mm, p=0.057 and AOD750 0.023mm, p=0.002). The AOD750 angle measurements were maintained at 6 weeks (AOD500 0.008mm, p=0.059 and AOD750 0.018mm, p=0.002), 3 months (AOD500 0.013mm, p=0.034 and AOD750 0.024mm, p=0.002) and 6 months post LPI (AOD500 0.012mm, p=0.029 and AOD750 0.021mm, p=0.006).

Using the paired samples t-test DIOP fluctuation at baseline was not significantly different to DIOP fluctuation at the 6 month visit in treated and untreated eyes. To further investigate DIOP fluctuation at both visits, additional t-tests were carried out for the maxima and the minima of IOP. There was no statistically significant difference in maximal or minimal IOP levels in treated eyes comparing baseline values (19.7 mmHg and 15.87mmHg) with those at 6 months post LPI (18.95 mmHg and 15.84mmHg). However, untreated eyes showed a trend towards increased, though not statistically significant higher maximal IOP from 19.04 mmHg to 19.87 mmHg (0.83mmHg, p=0.057) and a statistically significant increase in minimal IOP
from 15.78 mmHg to 16.37 mmHg (0.59 mmHg, p=0.021), when compared to laser treated eyes at 6 months (Figure 5).

**Figure 5. Intraocular pressure (IOP) measurements in treated (laser peripheral iridotomy) and untreated eyes over 6 months, displayed as diurnal IOP (maximum-minimum IOP) and maximal and minimal IOP separately, y error bars indicate standard error**

DIOP fluctuation at 6 months after LPI was compared between treated eyes that remained with gonioscopically occludable anterior chamber angles and those treated eyes in which the angle had opened on gonioscopy. There were no statistically significant differences for the DIOP fluctuation values at 6 months compared to baseline.

**Discussion:**

All angle parameters under study showed an increase in size following LPI as measured by SS-OCT. There is considerable evidence supporting the widening effect of LPI on the irido-trabecular angle in PAC/PACS eyes where the angle has previously been found to be gonioscopically narrow.\(^9,13\) When such an effect has been quantified with anterior segment imaging technologies, it has commonly been measured solely in the vertical and horizontal meridians and often at one time point after the LPI.\(^8-10,14-16\) Upon reviewing all parameters we found the most significant increase in the inferior/inferotemporal angle opposite the iridotomy, which in our study was
placed superiorly. This is consistent with the results from Kansara et al., where they observed the maximum increase in angle dimensions in the nasal angle opposite the side of a temporally placed iridotomy. It is possible that the maximal increase in angle dimensions opposite iridotomy may be due to a change in the flow of aqueous in the anterior chamber. The changes in the inferior/inferotemporal angle we observed are unlikely to be solely due to gravity given the findings of Kansara et al. One possibility is that the mechanical properties of the iris have changed following laser treatment and the change observed at the site of the PI differs from the rest of the angle. Another possibility is that the maximal increase in angle dimensions opposite iridotomy may be due to a change in the flow of aqueous in the anterior chamber. We are unable to comment on the effect of placing the iridotomy in a different position on account of the standardised approach we used in applying a superiorly placed iridotomy. Considering fluid dynamics, the flow through an iridotomy would be expected to be laminar, observing Poiseuille law as this has been postulated to apply to an iridotomy of more than 3 μm diameter. We postulate that laminar flow through an iridotomy may induce a pressure gradient or volume expansion that explains the observed widening in the opposing angle sector. The clinical relevance of these findings is unclear. Although our observations are consistent with those from other studies, it is difficult to compare the exact values of angle parameters between studies due to variability in anterior chamber angle characteristics in different diagnostic subtypes, differing timeframes for analysis and differing modes of OCT technology between studies. Additionally, if the angle parameters are measured in only one or two meridians then one may question how
representative changes observed in these sections are of the entire
circumference of the angle. Furthermore, all of the aforementioned studies
have studied the effect of the LPI in the treated eye alone. Studies where the
fellow untreated eye was used as a control have reported difference of a
lower magnitude. These studies have often only assessed two meridians,
which may not be representative of the whole angle. The greatest increase in
angle parameters was observed during the first week after iridotomy and the
increase in angle parameters was maintained at 6 months. These results are
similar to those observed in a non-Caucasian population by Jiang et al.,
where no statistically significant change in angle parameters was observed
between 2 weeks and 6 months post-LPI.

We have previously discussed the relationship between diurnal intraocular
pressure and anterior chamber dimensions in angle closure using swept-
source OCT. In PACS and PAC patients, however, the small effect on DIOP
fluctuation may be explained by the smaller change in angle dimensions
following LPI than the wider range of angle dimensions observed in the
untreated angle. It should also be considered that the association between
smaller angles and greater DIOP fluctuation in our previous cross sectional
inter-subject analysis, may result from the inclusion of narrower angles that
have reached a more advanced stage of the angle closure process continuum
(and aqueous drainage impairment process). Pre-LPI, the mean diurnal
maximal IOP was found to be 18.9 mmHg, ± 4.2 mmHg. The baseline IOP in
our study is similar to that of pre-Nd:YAG laser treated eyes in a study by
Moster et al., where the mean IOP was found to be 17.1 mmHg, ±5.2 mmHg.
Their study reported that all the treated eyes showed a return of IOP to
baseline within one week after the laser was performed and that it remained
the same at one month and three months post-LPI. It is possible that in both
studies, the initial IOP may not have been sufficiently high enough to observe
statistically or clinically significant drop in IOP measurements following LPI.
However, Cumba et al.\textsuperscript{19} report similar findings in their patients (baseline IOP
19.6 ±5.5 mmHg), where no change in IOP was observed at 6 months.
Given the association between smaller angles and greater DIOP fluctuation
that we observed in a cross-sectional inter-subject analysis of patient’s
baseline in this study,\textsuperscript{11} we found no significant difference in DIOP fluctuation
between gonioscopically open and closed angles post-PI which one might
consider surprising. In the present study that reports intra-subject changes in
angle opening and DIOP fluctuation before and after iridotomy, we were
unable to demonstrate detectable DIOP change at 6 months compared to
baseline, despite statistically significant widening of the angle. The difference
in minimal IOP (0.59 mmHg, $p=0.021$) at 6 months, although statistically
significant, is unlikely to be of clinical significance at that particular time point.
The fact that the study excluded eyes which were later randomized to
undergo laser peripheral iridoplasty will have led to an element of selection
bias. Since the excluded eyes were those eyes where the angles were still
closed after LPI, a higher proportion of gonioscopically open angle eyes after
LPI remained in the analysis. Our earlier work concluded that narrower
anterior chamber angles were associated with greater IOP fluctuation.\textsuperscript{11}
However, the current study found no significant difference in diurnal IOP
despite the bias favoring the difference. This apparent difference in
conclusions is likely due to the smaller range of angle width or change in
width in the present study and the smaller number of eyes included in the present analysis (it should be noted that reduction in numbers of patients involved in the analysis (29 versus the 40 patients involved in the sample size calculation) may have meant that the study lacked statistical power to detect a true difference in the DIOP outcome). It may simply be the case that laser PI does not influence the long-term IOP profile. There was no statistically significant association between the presence and extension of peripheral anterior synechiae (PAS) and the DIOP fluctuation values.

A strength of our study involves the use of the fellow untreated eye as a control. We chose this study design following the need for better control for comparing the effect of an intervention due to dynamic characteristics of ocular physiology as discussed by Quigley in the LXVI Edward Jackson Memorial Lecture. Additional strengths lie in the use of the more advanced swept source OCT technology, which offered more sections to acquire and also such well-defined resolution of the scleral spur where all images were gradeable. This is in contrast with prior studies involving earlier OCT instruments have reported up to 30% of scans being unusable due to poor resolution.

There may be ethnic differences in the effect of the laser procedure on the biodynamics of the eye and therefore caution should be observed in comparing our DIOP fluctuation findings in this study with those of previous reports involving non-Caucasian subjects, such as in the study by Baskaran et al., where 89.1% were ethnically Chinese. In that study the highest DIOP fluctuation was found in the PACG diagnostic subtype. However, in our study, even those treated eyes that resulted in a gonioscopically open angle showed
higher DIOP fluctuations than those reported in PACS/PAC and PACG subtypes by Baskaran et al.\textsuperscript{12} There may be other reasons that account for differences between studies, for example, axial length. Loewen et al.\textsuperscript{22} reported an inverse correlation between axial ocular length and higher levels of 24 hour IOP fluctuation in healthy young adults of differing ethnicity.

**Conclusions:**

Our earlier work demonstrated that narrower anterior chamber angles were associated with greater DIOP fluctuation in a cross-sectional analysis. This current study demonstrates that although an LPI procedure widens the angle up to 6 months after treatment, this does not result in a reduction of DIOP fluctuation in PACS and PAC patients.

**Acknowledgments:** We wish to acknowledge the work of Laura Sanchez Parra in data collection and Paula Turnbull and Heather Pearman for administration of the study. Additionally, Professor Roger Buckley gave advice on aspects of the study design and Michael Parker provided statistical advice.

Tomey Corporation (Nagoya, Japan) loaned the instrument for the purposes of the study.
References:


**TABLE 1. Parameters (AOD) from swept-source OCT-measured anterior chamber angle sections before and after laser peripheral iridotomy**

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<tr>
<th></th>
<th>Pre- LPI*</th>
<th>1 week post-LPI†</th>
<th>6 months post- LPI†</th>
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<td>Superior AOD500</td>
<td>0.042</td>
<td>0.051</td>
<td>0.055</td>
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<td></td>
<td>(0.057)</td>
<td>(0.029)</td>
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<td></td>
<td>(0.005)</td>
<td>(0.001)</td>
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<td>0.147</td>
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<td></td>
<td>(0.013)</td>
<td>(0.003)</td>
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<td>(0.003)</td>
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<td></td>
<td>(0.0007)</td>
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<td>(0.008)</td>
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<td>(0.007)</td>
<td>(0.005)</td>
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<td>(0.054)</td>
<td>(0.006)</td>
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*Mean measurements are shown.
†Mean measurements (top) and p values from significance paired t-test comparing mean at the indicated time point with baseline bottom, in brackets) are shown.