ANGLIA RUSKIN UNIVERSITY

INFLUENCE OF BIOMETRIC PARAMETERS AND THE EFFECTS OF LASER PERIPHERAL IRIDOTOMY AND ARGON IRIDOPLASTY ON ANGLE CLOSURE IN CAUCASIAN SUBJECTS

LAURA SANCHEZ-PARRA

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FACULTY OF SCIENCES AND TECHNOLOGY

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Thesis Abstract

The purpose of this study was, first, to evaluate the intraocular pressure characteristics in eyes with occludable anterior chamber angles and the influence of Peripheral Anterior Synechiae (PAS). Second, to further investigate the hypothesis that smaller values for Angle Opening Distance (AOD), Angle Recess Area (ARA), Trabecular-Iris Space Area (TISA) and Trabecular-Iris Angle (TIA), are associated with greater diurnal intraocular pressure fluctuation and extent of PAS. Third, to additionally investigate the effect of Laser Peripheral Iridotomy (LPI) and Argon Laser Peripheral Iridoplasty (ALPI), in treated eyes versus untreated, on the diurnal intraocular pressure fluctuation, the angle parameters aforementioned and the corneal endothelial cell density, polymegethism and pleomorphism.

40 Caucasian patients with a gonioscopic diagnosis (less than 180 degrees posterior pigmented trabecular meshwork visible) of bilateral Primary Angle Closure (PAC), Primary Angle Closure Suspect (PACS) or a combination of both conditions and no ocular co-morbidity were recruited.

After recruitment one eye was randomized to receive LPI and the fellow remained untreated as a control eye. Three months after LPI, those eyes in which the anterior chamber angle remained occludable were further randomized into either receiving ALPI or no further treatment. The follow up visits were set at 1 day, 1 week, 1.5 months, 3 months and 6 months after LPI. For ALPI, the treated eyes were assessed at 1 day, 1 week, 1.2 months and 2.5 months.

Intraocular pressure (IOP) was measured hourly from 9.00 am to 4.00 pm with Goldmann applanation tonometry by the same examiner at the baseline and final visit. Diurnal intraocular pressure (DIOP) fluctuation was defined as the difference between the maximum and minimum IOP during that period.

Angle parameters were measured using the novel non-contact three-dimensional AS-OCT (CASIA) in dark (0.3-0.5 lux) and light (170-200 lux) conditions at every follow up visit. AOD, ARA, TISA and TIA were quantified in 8 different sections of the angle (Superior, Superior-Nasal, Nasal, Inferior-Nasal, Inferior, Inferior-Temporal, Temporal and Superior-Temporal) and at 500 and 750μm from the scleral spur. All the scans were acquired and evaluated by the same examiner.

Measurements of DIOP in eyes with PAS were 1.5 mmHg ($p=0.043$) higher than in eyes without PAS.

DIOP fluctuation varied from 1.50 mmHg to 14.50 mmHg (mean 5.99 mmHg, SD 2.70 mmHg). There was a statistically significant relationship between this fluctuation and the majority of angle parameters in Superior and Superior-Nasal sections, showing standardized coefficients from -254 to -438, demonstrating an inverse relationship between angle parameters and DIOP in these sections. Additionally, the higher contribution to the multiple predictor models also demonstrated negative standardised coefficients showing a similar inverse relationship between magnitude of fluctuation and angle dimensions. These models were statistically significant ($p<0.05$) for AOD 750 (light), ARA 750 (light and dark), TISA 500 (light), TISA 750 (light), TIA 500 (light) and TIA 750 (light and dark). The circumference of PAS (measured in degrees) and DIOP showed a statistically significant association (calculated using single factor or univariate regression) at every time measurement of the DIOP.

There was a statistically significant widening effect of the parameters found in the Inferior-Temporal section of the angle of those eyes treated with LPI, but no effect was found on the diurnal intraocular pressure fluctuation. After ALPI, the parameters found in Superior, Inferior-Temporal and Superior-Temporal significantly increased 2.5 months after the treatment when compared to the untreated eye. Additionally, ALPI was associated with a reduction in the diurnal intraocular pressure fluctuation of 1.60 mmHg (SD 0.78 mmHg) that was of borderline statistical significance ($p=0.056$).

There was not a clear effect on the endothelial cells density, polymegethism or pleomorphism after the LPI or ALPI treatments.

Substantial changes in IOP occur throughout the day in patients with occludable anterior chamber angles. Narrower angle parameters and the presence of PAS are associated with greater diurnal fluctuation.

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CHAPTER 1 General Introduction

1.1 Burden of Angle Closure Glaucoma

The World Health Organisation (WHO) rates glaucoma as the second leading cause of blindness worldwide, after cataract. Glaucoma is the principal cause of irreversible blindness (Resnikoff, et al., 2004).

The number of people with glaucoma worldwide is increasing substantially. In 2005, Quigley and Broman (2006) estimated that, in 2010, 60.5 million people would have glaucoma worldwide which would increase by approximately 20 million by 2020. Their model suggested that over 8.4 million people would be bilaterally blind from glaucoma in 2010 and 11.1 million in 2020. Although angle closure glaucoma is less common than open angle glaucoma, it causes greater morbidity and is estimated to be responsible for half of the blindness caused by glaucoma worldwide. It is predicted that approximately 10 million Chinese, 5 million Indians, 3 million South East Asians, 1.6 million Europeans, 0.5 million Latin Americans, 0.34 million Japanese, 0.32 million Africans and 0.25 million of the Middle Eastern population would suffer from angle closure glaucoma (ACG) by 2020 (Quigley and Broman, 2006).

1.2 Definitions of Primary Angle Closure Suspects (PACS), Primary angle Closure (PAC) and Primary Angle Closure Glaucoma (PACG)

As primary angle closure glaucoma (PACG) is regarded as the final stage in a series of pre-glaucomatous stages of angle closure, namely Primary Angle Closure Suspects (PACS) and Primary Angle Closure (PAC), described by Foster, Buhrmann, Quigley and Johnson (2002).

There is a variation in opinion about the circumferential extent of the posterior pigmented trabecular meshwork (TM) that needs to be obscured in order to meet a definition of an 'occludable' angle. For example, we can find PACS/PAC diagnosed in those eyes with TM obscured in ≥ 270 degrees in some reports (Devereux, et al., 2000; Foster, 2002; Nolan, et al.,2003; Lei, Wang, Wang, and Wang, 2009) or in ≥180 degrees in others (Thomas, Arun, Muliyil and George, 1999; Thomas, et al., 2003; Thomas, Parik, Muliyil and Kumar, 2003; Kumar, et al., 2008; Lavanya, et al., 2008; Jiang, et al.,2010; Lee, Kim and Choi, 2011).

For the purpose of this research project, the definition of an occludable angle was chosen to match that of the Zhongshan Angle Closure Prevention Trial (Iridotomy for the Prevention of

Angle Closure in Southern China- currently on-going), (Jiang, et al., 2010), which will permit comparison between results. PACS has been diagnosed in those eyes with posterior pigmented TM obscured in ≥180 degrees of the irido-trabecular angle. PAC, additionally includes adhesion of the peripheral iris over the TM (peripheral anterior synechiae, PAS*) and/or a raised intraocular pressure (IOP).

An IOP of 21mmHg or more is generally accepted as the IOP criterion, and for the purposes of this study thesis this was fulfilled if the IOP achieved this level at any point during office hours at the baseline visit for the study.

*PAS defined as: abnormal adhesions of the iris to the angle extending to the anterior TM or more anteriorly (Kumar, et al., 2008)

1.3 Mechanism of angle closure

It is believed that the predominant mechanism for anterior chamber angle narrowing in the Caucasian population is pupil-block (He, Foster, Johnson and Khaw, 2006). Lowe (1964) indicated that pupillary block was due to contact between the posterior plane of the iris and the anterior surface of the lens. A differential of intraocular pressure could therefore build between anterior and posterior chambers. As a result, the iris root profile would bow forward and the peripheral iris would then narrow or occlude the irido-trabecular space. In a further theory developed in 1966, the same author stated that the conflict of forces between dilator and sphincter pupil muscles could lead to the iris-lens contact explained by the earlier assertion (Lowe, 1966). Lowe observed that those angle closure eyes dilated with homatropine (muscarinic receptor antagonist- acts blocking the parasympathetic innervations in the sphincter muscle) presented a lower risk of an acute episode than those dilated with phenylephrine (α agonist- acts stimulating the sympathetic innervations in the dilator muscle). The author observed that when the homatropine was acting on the sphincter muscle, the iris was experiencing a more peripheral posterior force for dilating and, although it was narrowing the angle, the aqueous humour flow through the pupil was not impaired. However, when the pupils were dilated with phenylephrine, the dilator muscle forces where acting over a tonic sphincter muscle and the posteriorly directed forces would be placed closer to the pupil. This would increase the contact between the anterior surface of the lens and the posterior iris leading to pupillary block mechanisms (Lowe, 1966). If the pupil block takes place, pressure accumulates in the posterior chamber bowing the iris forward and narrowing the angle (Mapstone, 1976). Pupillary block mechanisms may occur without pharmacological inducement and relative pupillary block is present in most phakic eyes due to the

natural curvature of the lens. Additionally, the normal convex shape of the iris in a mid-dilated pupil narrows the trabeculo-iris space. This space can further decrease or close in eyes with a more anteriorly positioned lens leading to angle closure (Quigley, et al., 2003).

Mechanisms other than pupil-block may be present such as an anteriorly positioned ciliary body where iris processes press the peripheral iris against the drainage area. This is known as iris plateau configuration (Salmon, 1999; Pavlin and Foster, 1999). Plateau iris syndrome refers to an episode of angle closure in an eye with plateau iris configuration (Ritch, Liebmann and Tello, 1995).

1.4 Prevalence of Primary Angle Closure Glaucoma (PACG)

There is considerable variation in the prevalence of PACG worldwide. In the Greenland and Alaskan Inuit populations, the prevalence of PACG was estimated to be the highest with 5.1% for females and 1.6% for males older than 40 years (Alsbirk, 1976; Arkell, et al., 1987; Van Rens, Arkell and Doesburg, 1988). Prevalence rates for PACG in other populations are different, for example: Taiwan at 3% (Congdon, et al., 1996), South Africa (Cape-Malay) at 2.3% (Salmon, 1993), China (calculated through statistical models based in published literature) at 1.11% (Foster and Johnson, 2001), South West Mongolia at 1.05% in subjects older than 50 years (Nolan, et al., 2003), Thailand with a 0.9% in population older than 50 years (Bourne, et al., 2003), Mongolia and Singapore with an equal prevalence of 0.8% (Foster, 2002), East Asians with 0.8% (Devereux, et al., 2000), Brazil with 0.8% (Sakata, et al., 2007), Central Sri Lanka with a 0.57% for inhabitants older than 40 (Casson, et al., 2009) , Japan with 0.2% for males and 0.4% for females older than 40 years (Shiose, et al., 1991), Australia with 0.1%-0.3% (Mitchell, et al.,1996; Wensor, et al., 1998), USA with 0.1% (Klein, et al, 1992) and 0.0-0.1% in the case of Europe (Hollows and Graham, 1966; Bankes, et al., 1968; Bengtsson, 1981; Coffey, et al., 1993; Dielemans, et al., 1994). These values for prevalence have been summarised in Table 1.1.

There is some contradiction between the European rates mentioned earlier and the rates Bonomi, et al. (2000) found in the Egna-Neumarkt Study of northern Italy. In this study, women were estimated to have a prevalence of PACG of 0.9%, with a prevalence of 0.2% in men. They noticed that not only were the PACG rates for women nearly 4 times higher than for men, but also that the percentage of narrow angles with predisposition to occlusion was 6% higher among women. The authors gave a possible explanation for these differences between their study and other European rates of prevalence. They mentioned that many of the previous prevalence studies

considered only acutely forms of PACG, which were less common. The authors also acknowledged a high incidence of endogamy within this population.

Author	Country	Age group	% PACG
Alsbirk, 1976	Greenland	> 40	1.6 % males -5.1% females
Arkell, et al., 1987	Alaska	> 40	2.7 %
Van Rens, Arkell and Doesburg, 1988	Alaska	> 40	2.1 % males -5.5% females
Congdon, et al., 1996	Taiwan	> 40	3.0%
Salmon, 1993	South Africa	> 40	2.3%
Foster and Johnson, 2001	China	> 40	1.11%
Bourne, et al., 2003	Thailand	> 50	0.9%
Foster, 2002	Mongolia and Singapore	> 40	0.8%
Devereux, et al., 2000	Mongolia	> 40	0.8%
Sakata, et al., 2007	Brazil	> 40	0.8%
Casson, et al., 2009	Sri Lanka	> 40	0.6%
Shiose, 1991	Japan	> 40	0.34%
Mitchell, et al., 1996	Australia	> 49	0.3%
Wensor, et al., 1998	Melbourne	> 40	0.1%
Klein, et al., 1992	United States	> 43	0.1%
Hollows and Graham, 1966	Wales	> 40	0.1%
Coffey, et al., 1993	Ireland	> 50	0.01%
Dielemans, et al., 1994	Netherlands	> 55	0.0%
Bankes, et al., 1968	England	> 40	0.2%
Bengtsson, 1981	Sweden	From 55 to 69	0.0%
Bonomi, et al., 2000	Italy	> 40	0.6%

Table 1.1. Examples of rate of PACG prevalence in different countries.

To summarise these prevalence studies, PACG is considered a relatively uncommon type of glaucoma among Europeans but is relatively common among Asians (Quigley, Congdon and Friedman, 2001; Quigley, 2010; Wang, Wu and Fan, 2002; Rotchford, 2005; He, Foster, Johnson and Khaw, 2006; Lavanya, et al., 2008; Cedrone, et al., 2008; Mansouri, Sommerhalder and Shaarawy, 2010).

1.5 Prevalence of Primary Angle Closure Suspects (PACS) and Primary angle Closure (PAC)

An estimated 28.2 million people living in China are believed to have narrow anterior chamber angles; this figure approximately represents 10% of the Chinese population older than 50 years. Of these, 9.1 million are believed to have PAC (approximate 2.2 % of prevalence) and 19.9 million to have PACS (approximately 4.9 % of the total population) (Foster, 2002). In an East Asian based study, PACS prevalence rates were higher than those found for PAC, 3.3% and 2.7%, respectively (Devereux, et al., 2000). A screening study for narrow angles (PACS, PAC and PACG studied as a group) in Singapore, reported a prevalence of 20.4% in at least one eye (Lavanya, et al., 2008). In

Mongolia, the prevalence of PACS and PAC was estimated to be 2.11% and 1.31% respectively (Nolan, et al., 2003); which was not dissimilar to prevalence estimates from Central Sri Lanka (Casson, et al., 2009).

Generally, the prevalence of PACS and PAC, the pre-glaucomatous stages of PACG, has not been as thoroughly studied as the prevalence of PACG. One possible reason being that these early stages have been described as "narrow angles" (Martinez, Campbell, Reinken and Allan, 1982; Lee, Brubaker and Ilstrup, 1984) or "occludable angles" (Tomey, Traverso and Shammas, 1987; Bonomi, et al., 2000) in the literature or may have been grouped together (Nolan, et al., 2003; Thomas, Arun, Muliyil and George, 1999). However, since 2002, when there was some consensus on definitions (Foster, Buhrmann, Quigley and Johnson, 2002), there has been an increasing tendency among studies to distinguish between these stages (Su, et al., 2008; Lavanya, et al., 2008; Mansouri, Burgener, Bagnoud and Shaarawy, 2009; Casson, et al., 2009; Ang and Wells, 2011; Lee, Kim and Choi 2011).

1.6 Prevalence of Primary Angle Closure in the United Kingdom

In 1963, a population survey carried out in three villages of South Wales showed a prevalence of primary angle closure glaucoma (PACG) of 0.09% (Hollows and Graham, 1966). Bankes, et al. (1968) found a prevalence of 0.2% of PACG in Bedford. However, Perkins (1973a) found no cases of PACG in a review carried out in the same town. Glaucoma was found in 0.93% of the Bedford population and there was no case described as angle closure. After 5 years, a re-screening of 'normals' (non-glaucomatous) again showed no evidence of angle closure among the additional 0.52 % found to have glaucoma (Perkins, 1973b).

Since then, there has been a lack of published data on the prevalence of PACG within the UK. A relatively recent retrospective review of the glaucoma clinic database at Moorfields Eye Hospital showed that from 7186 patients attending the clinic, 4.6% were diagnosed with angle closure glaucoma, 42.1% were primary open angle glaucoma, 15.4% were ocular hypertensive and 32.4% were glaucoma suspects (Morley and Murdoch, 2006). Another similar retrospective study was based in a glaucoma clinic in Scotland (Aberdeen Royal Infirmary glaucoma clinic). All the Caucasian patients newly diagnosed with PACS, PAC, PACG or acute primary angle closure during 2004 and 2005 were included in the report. It showed that of 104 patients, 23.1% had PACS, 28.8% had PAC, 48.1% had PACG and 11.5% presented with acute primary angle closure (Ng, Ang and Azuara-Blanco, 2008). It was interesting that this Aberdeen clinic noted a higher proportion of

PACG than the pre-glaucomatous stages. In their report, the authors mention poor follow up in the community as a possible reason.

This limited data from both population-based and clinic-based studies in the UK does not allow conclusions to be drawn about temporal trends in angle closure prevalence in the UK. However, a recent review of the PACG literature in Caucasian populations (UK, Europe and USA) has reported a predicted increase of cases in Caucasians (Day, et al., 2012). They estimated that the number of people, aged 40 or more, affected by PACG in UK was 130,000 in 2010 and that this number would increase to 195,000 cases by the year 2050 (Day, et al., 2012).

Additionally, in recent years there does appear to be better case detection within the ophthalmology/optometry with referral refinement systems that include measures to detect eyes at risk of angle closure in the community (Ratnarajan, et al., 2013 a; b). Another study by Day and Foster (2011) showed data suggesting that prophylactic treatment in angle closure cases has decreased the number of acute angle closure within the UK from 1998 to 2010.

An increase in immigration of individuals of Asian origin into the UK may also have an impact on angle closure prevalence.

1.7 Prevalence of Primary Angle Closure due to Plateau Iris

When angle closure is caused by a pupillary block mechanism, a peripheral iridotomy creates a new pathway for aqueous humour and relaxes the peripheral iris by restoring the pressure balance between the anterior and posterior chambers. However, as mentioned earlier, primary angle closure may be due to an anteriorly positioned ciliary body where an iridotomy may not resolve the peripheral apposition of the iris against the trabecular meshwork. This is known as plateau iris configuration. There is no published information on the circumferential extent of a plateau profile for a 'plateau iris' diagnosis to be made (Kumar, et al., 2008) nor is it known how much time is needed post-LPI for an angle to reach a configuration that remains stable. A lack of consensus on these issues probably explains the variation in reporting of "unsuccessful" LPIs (the angle remains occludable).

Several studies based in Asian populations have reported prevalence rates for plateau iris. Kumar, et al. (2008) studied a sample of 205 PACS eyes (majority Chinese). Gonioscopy was performed before and one week after the laser peripheral iridotomy (LPI), finding that 89 eyes remained gonioscopically occludable (≤ 180° of trabecular meshwork visible). When the same sample was assessed with Ultrasound Biomicroscopy (UBM), plateau iris pre-LPI was found in 55 eyes out of

167 eyes and 42 remained plateau post-LPI. Using the UBM criteria, the prevalence of plateau iris in the sample was 25.14%, while the same prevalence based on gonioscopy was 43.41%. It can be argue that one week post-LPI may not have been time enough for pupillary-block to completely resolve and gonioscopy may have overestimated this prevalence. Similar rates as those described by Kumar and colleagues using the UBM were found in another study carried out in South India where a mixed sample of PAC and PACG was studied. The LPI was unsuccessful in opening the angles in 26.6% of eyes one month after the treatment (≤ 180° of trabecular meshwork visible in applanation gonioscopy), (Thomas, Arun, Muliyil and George, 1999). He, et al. (2007) found lower rates in a study based in Guangzhou, China, with a sample of 72 PACS eyes that received LPI with a review two weeks after the treatment. The criterion for diagnosing narrowing angle was based on 270° or more of trabecular meshwork obscured on applanation gonioscopy. Quite a different rate, a 2% was found by Nolan, et al. (2000) in a Mongolian sample of PAC, PACS and PACG. They reviewed 141 cases in a period of time that ranged between 10 to 37 months and only 3 treated eyes were diagnosed as still occludable (based ≤ 270° of trabecular meshwork visible in applanation gonioscopy).

In a Caucasian population, Mansouri, Burgener, Bagnoud and Shaarawy (2009) studied a sample of 35 eyes presenting PAC or PACG. One week post-LPI, 22 eyes out of 30 were found unoccludable (>90° of trabecular meshwork visible). Similar rates were found in another study in a Caucasian population; Ang and Wells (2011) reporting that in a sample of 71 eyes with PAC, PACS or PACG nearly 24% of the eyes treated with LPI remained with narrow angles (≤ 180°of trabecular meshwork visible). The review was performed at a mean follow up of 5.9 weeks (SD 3.2 weeks).

Table 1.2 (below) summarises these findings.

Author	Ethnicity	Ocular Condition	Time since LPI	% Of occludable eyes after LPI (Possible Iris Plateau)
Kumar, et al. (2008)	Chinese	PACS	1 week	25.14% (UBM); 43.41% (Gonioscopy)
Mansouri, Burgener, Bagnoud and Shaarawy (2009)	Caucasian	PAC/PACG	1 week	26.7%
He, et al. (2007)	Chinese	PACS	2 weeks	19.44%
Thomas, Arun, Muliyil and George (1999)	Indian	PAC/PACG	4 weeks	26.6%
Ang and Wells (2011)	Caucasian	PAC/PACS/ PACG	6 weeks	24%
Nolan, et al. (2000)	Mongolian	PAC/PACS/ PACG	10 to 37 months	2%

Table 1.2. Summary of the rates of occludable angle despite of laser peripheral iridotomy in different ethnicities.

The literature search regarding prevalence of Primary Angle Closure Glaucoma, Primary Angle Closure, Primary Angle Closure Suspects and Iris Plateau was conducted by accessing the following databases: PubMed, Medline, AMED and EMBASE. The terms searched were "prevalence" and "angle closure" in the Title and Abstract.The aim of this literature search was to find studies that reported prevalence rates of these angle closure conditions in different geographical regions and ethnic groups worldwide. On occasion, some reports were obtained by searching references given in the reference list of some published studies.

1.8 Risk factors

Various genetic factors and ocular biometrical parameters may predispose individuals to angle closure.

Age:

It has been found that an increase in age is indirectly associated with occludable angles in different studies (Panek, et al., 1990; John, 1999; Bonomi, et al., 2000). This association is believed to be mainly due to the natural growth of the lens that would lead to a smaller anterior chamber depth and, consequently, to a narrowing of the irido-trabecular space (Rabsilber, Khoramnia and Auffarth, 2006).

Anterior chamber dimensions:

Anterior chamber depth plays an important role as a risk factor in the risk of developing angle closure. Among Sri Lankans, a 1mm decrease in anterior chamber depth was associated with a 2.6 times increase risk of angle closure (PACS, PAC and PACG were studied as a group), (Casson, et al., 2009).

Several reports indicate an association between the dimensions of the anterior chamber and its structures and narrow angles. Smaller dimensions of anterior chamber depth, volume and diameters have been associated with narrow angles (Lee, Brubaker and Ilstrup, 1984). In a study recently carried out in Singapore, it was reported that the average anterior chamber area and volume in patients with narrow angles were 5.5 mm^2 and 44.5mm^3 respectively, which were smaller in dimension than in those patients who acted as controls (in whom average anterior chamber area and volume measurements were 21.1 mm^2 and 142.1 mm^3, respectively (Wu, et al., 2011).

Other studies have reported thicker or more anteriorly placed lenses, shorter axial ocular length and anterior chamber length as risk ocular factors for developing PACG (Marchini, 2002; Lavanya, et al., 2008).

Iris configuration:

There is some evidence showing a relationship between iris configuration and narrow angles. A Singapore-based study showed that a higher sectional iris curve, area and thickness were significantly associated with gonioscopically narrow angles (Wang, Wu and Fan, 2010). Aptel and Denis (2010) suggested that an increase in iris volume after dilation was directly associated with eyes predisposed to acute angle closure. All the patients in this latter study were European. Following this work, Quigley (2010) proposed that irises in patients with angle closure are less able to function as a sponge (absorb and release fluid as the pupil dilates then constricts) than those without.

Gender:

PACG seems to be more common in women. Quigley and Broman (2006) estimated that in 2010 females would comprise 69.5% of the PACG cases worldwide. Other studies have also found higher number of cases among women (Shiose, et al., 1991; Bonomi, et al., 2000; Lavanya, et al., 2008). This higher prevalence in females may be due to the narrower anterior chambers found in this gender when compared to males for three different ethnicities studied (Afro-Americans, Caucasians and Far East Asians), (Oh, Minelli, Spaeth and Steinman, 1994).

In another community-based study conducted in Singapore it was found that women (Odds Ratio 1.43; 95% CI: 1.06%-1.92%), had shorter axial lengths (Odds Ratio 0.69; 95% CI: 0.58%-0.81%) and shallower anterior chamber depths (Odds Ratio 42.5; 95% CI: 27.4%-66.2%). Additionally Chinese ethnicity (Odds Ratio 3.58; 95% CI: 2.29%-18.2%) was a statistically significant predictor for angle closure (Lavanya, et al., 2008).

In a recent review of studies associating gender and glaucoma, the authors found that female gender is not only directly associated to a higher number of cases of angle closure but to a higher rate of blindness due to longer life expectancy among women (Vajaranant, Nayak, Wilensky and Joslin, 2010)

Genetics:

A genetics study performed in 563 pairs of young Chinese twins (357 monozygotic and 206 dizygotic whose ages were 7 to 15 years old) showed that there was a higher correlation for anterior chamber depth in the group of monozygotic twins (coefficient of 0.92) than in the dizygotic group (correlation coefficient 0.50). They found that 90% of the anterior chamber depth was due to heritability and the remaining 9.9% was due to unshared environment (He, et al., 2008). A second study by He et al. in 462 Chinese twins, investigated the heritability of different parameters used to quantify the irido-trabecular angle (the angle opening distance, angle recess area and trabecular-iris space). These parameters were measured in the Temporal and Nasal sections of the right eyes angles. They found that the correlation coefficient for the angle opening distance was higher in monozygotic than in dizygotic twins (0.73 and 0.36 respectively) while the coefficients for angle recess area and trabecular-iris space were similar in both groups. The heritability was determined as approximately 70% for the three parameters, the other 30 % being attributable to environmental factors (He, et al., 2008). These two studies suggested that parameters commonly defined as risk factors for angle closure seemed to be genetically shared in this Chinese sample.

Other similar studies to determine heritability of the anterior chamber depth and lens thickness have been carried out in older Caucasians twins. In a sample of 53 monozygotic twins and 61 dizygotic twins aged 20 to 45 years old, the heritability was defined as 0.88 and 0.94 for anterior chamber depth and lens thickness respectively (Lyhne, Sjølie, Kyvik and Green, 2001). Another study in Caucasian twins aged 18 to 88 years, found rates of heritability of axial length of 94% and 92% for male and females respectively (Dirani, et al., 2006). These findings further support the concept of genetic predisposition to angle closure.

<u>Environmental factors:</u>

Alsbirk suggested that the small anterior chamber depths found in Inuit and populations living in low temperatures were an adaptation to the climate. The explanation being that the warmly perfused iris would be closer to the cornea thereby reducing the risk of corneal freezing (Alsbirk, 1976).

Literature suggests no other association between PAC, PACS or PACG and environmental factors. However, environment appears to be associated with episodes of acute angle closure. A study carried out in Finland found an association between the number of acute episodes of angle closure and the number of hours without sunshine. Being in dark conditions would keep the pupils dilated for longer periods of time giving a rise in the intraocular pressure in eyes that were already predisposed (Teikari, O'Donnell, Nurminen and Raivio, 1991). Another study based in the

UK (Birmingham) found a direct association with hours of sunshine and acute episodes, but the authors could not fully explain the reasons for these results (Hillman and Turner, 1977).
A review about environmental factors in PACG, reported published evidences about the association of unpleasant weather conditions and acute episodes of angle closure. Stress and adrenaline were additionally reported as further environmental factors directly associated with acute episodes. Adrenaline may precipitate an angle closure crisis (Subak-Sharpe, Low, Nolan and Foster, 2010).

Ethnicity

As noted by the aforementioned section on prevalence rates, Inuit and Chinese ethnicity is a major risk factor for angle closure (Alsbirk, 1975; Arkell, et al., 1987; Van Rens, Arkell and Doesburg, 1988; Foster and Johnson, 2001; Lavanya, et al., 2008).

There have been very few comparative studies that have attempted to find biometric ocular factors that may predispose certain ethnic groups to angle closure. Shiose, et al. (1991) found that the mean intraocular pressure (IOP) in Caucasians was 3-4 mmHg lower than in Asians. Congdon, et al. (1997) observed that Chinese corneal radii were smaller than those studied in Caucasian subjects, and although it is certain that this would give a more crowded anterior chamber and a higher predisposition towards the angle closure, it does not fully explain the reasons for the marked variation in prevalence. A recent publication by Leung, et al. (2010), stating that Chinese eyes have a smaller anterior chamber width and a thicker iris than Caucasian eyes, may help explain some differences. Additionally, Wang, et al. (2012) studied a group of American Caucasian, American Chinese and Mainland Chinese without angle closure. They observed that the anterior chamber depth decreased with age in all groups. However, the speed of shallowing was greater in the Chinese group. Caucasians also had a wider and deeper anterior chamber than in the Chinese groups. These anatomical factors may explain the greater predisposition to angle closure in the Chinese population.

In addition, the rate of the disease among Chinese has been reported to be 10-15 times higher than Caucasians (Wang, Wu and Fan, 2002). This may be due to the fact that when compared to Caucasians, PACG among Asian ethnicities has been reported to be more frequently chronic and to have fewer symptoms (Lowe, 1988; Congdon, et al., 1996; Foster, et al., 1996; Rotchford, 2005). It must be mentioned this is in contradiction with a recent short review of the angle closure condition where acute presentations of angle closure were reported as approximately

three times more common in the Chinese population as compared to Caucasians (Friedman, Foster, Aung and He 2012). Friedman and colleagues also acknowledged the study by Day and Foster (2011) where the number of laser peripheral iridotomy procedures, phacoemulsification operations and incidence of acute angle closure (symptomatic rise of IOP) between 1998 to 2010 in the UK was reported. In this report there was evidence of an increase in number of peripheral iridotomy and lens extraction procedures and a decrease in the incidence of acute angle closure during that period in the UK. It is, therefore, possible that a higher access to angle closure prophylactic surgery in countries of majority Caucasian ethnicity may have influenced the incidence of the acute form of this disease.

1.9 Rate of progression of the angle closure condition, from PACS to PAC and PACG

The risk of conversion among the untreated different pathological stages of primary angle closure has been previously reported in a 5-year study based in an Asian population. They observed that 22% of their PACS participants progressed to PAC over a 5-year time period while 28.5% of PAC cases converted to PACG over the same period (Thomas, et al., 2003; Thomas, Parikh, Muliyil and Kumar, 2003). Another study in Asian patients showed that, despite prophylactic treatment with peripheral iridotomy, 28.9% of PACS eyes progressed to PAC in a period of two years (Kumar, Baskaran, Ronnie and Vijaya, 2009). The authors gave information about the mean opening rate of the angle quadrants at various follow-up visits, but did not mention how many of these eyes were considered to remain occludable after the LPI. It is possible that those eyes progressing to the PAC state were occludable regardless of a patent iridotomy.

Among the Inuit, the risk of progression from untreated PACS to PACG was estimated to be 35% over 10 years. Eight percent of those with anterior chamber angles diagnosed as non-occludable developed PACG (Alsbirk, 1992). While for Caucasians the lowest rates so far have been described; Wilensky found a rate of conversion of 19% from the PACS stage to PAC over a period of nearly 3 years (Wilensky, et al., 1993)

<u>Factors influencing the rate of progression:</u>

As explained above the rate of progression is different depending on the ethnicity and it seems to be directly related to their already predisposed ocular biometrical characteristics. However, there are some common factors that may affect the progression of the condition independently of the ethnicity. The difference in definition between PAC and PACS stages is the IOP level and the

evidence of appositional contact between the peripheral iris and the trabecular meshwork. Some authors support the idea of an existing inverse relationship between anterior chamber dimensions and higher levels of IOP fluctuation (Lowen, Liu and Weinreb, 2010).

It is not that clear which factors influence the transition from PAC to PACG. Salmon (1999) explained that one possible mechanism was the prolonged contact between iris and trabeculum. Peripheral anterior synechiae may spread to gradually seal the angle. The concept of 'creeping' angle closure has also been described in which narrowing of the angle starts from the inner structures. It is considered a type of plateau configuration. In both mechanisms, Salmon suggests a raised IOP as the additional causative factor for the glaucomatous stage (Salmon, 1999).

Raised IOP is considered to be highly associated with glaucomatous damage.

There is some evidence supporting a relationship between a higher IOP diurnal fluctuation (difference between diurnal IOP peak and trough) and glaucomatous change. Gonzalez, et al. (1996) studied 149 eyes of 149 patients diagnosed with ocular hypertension at baseline. They found that patients presenting a diurnal IOP fluctuation at baseline higher than 5 mmHg were more likely to develop visual field defects in the next 4 years than those with a diurnal IOP fluctuation lower or equal to 5 mmHg. There is also some evidence showing a relationship between a rise in IOP due to a period in the supine position and a deterioration of the visual field in normal-tension glaucoma (Kiuchi, Motoyama and Oshika, 2006).

It is possible that wide variations in IOP affect the progression towards a glaucomatous stage. However, there is no consensus on the effect the fluctuation of the mean IOP (mean of IOP measurement per follow-up visit) and the long-term IOP fluctuation (visit-to-visit fluctuation) might have. Asrani, et al. (2000) observed the diurnal IOP fluctuations for 5 days in 105 eyes diagnosed with open angle glaucoma. They found highest hazard ratios for severe visual field loss at baseline with maximal IOP standard deviation (18.38; CI 95%: 6.82%-49.50%) for the 5 days of study. When adjusting for visual field losses and age, the IOP still held important hazard ratios as shown by the diurnal IOP fluctuation (in this case, the difference between peak IOP minus the trough IOP; 5.69, CI 95%: 1.86%-17.35%) and the DIOP range for the 5 days (maximal mean DIOP minus minimal mean IOP; 5.76%, CI 95%: 2.21%-14.98%). The mean IOP measured (2 measurements with applanation tonometry at the beginning and at the end of the study) held no relationship with progression of the glaucomatous visual field. The Advance Glaucoma Intervention Study (AGIS) studied the long-term IOP fluctuation (defined as the standard deviation of the IOP measured until visual field worsening or end of follow up) and the mean IOP in a group of open angle glaucoma cases. They found that this fluctuation was associated with a

higher probability of visual field progression and the mean IOP was of borderline statistical significance (Caprioli and Colleman, 2008). On the other hand, The Early Manifest Glaucoma studied a group of cases diagnosed with open angle glaucoma, exfoliation glaucoma and normal-tension glaucoma. They found that the long-term glaucoma fluctuation was not an independent factor for glaucoma progression, but that the mean IOP was a strong predictor (Bengtsson, et al., 2007).

The aforementioned studies show that, while there is a significant amount of research in the area of IOP levels and their relationship with the onset or progression of glaucomatous changes in other types of glaucoma, there is a lack of information about the same factors in the case of angle closure. Furthermore, the only study about IOP diurnal fluctuation in primary angle closure has been performed in Asian treated eyes. Additionally, there is a lack of information about the effect of the laser peripheral iridotomy and laser peripheral iridoplasty for angle closure on the levels of diurnal IOP fluctuation. Given the importance of IOP fluctuation in the onset of glaucomatous changes in open and hypertensive glaucoma, this is a risk factor that needs investigation in angle closure.

1.10 Treatments for the stages PAC and PACS: Cataract surgery, Laser Peripheral Iridotomy and Argon Laser Peripheral Iridoplasty

All of these treatments in angle closure aim to widen the angle and consequently decrease the risk of progression of the condition. It is, therefore, of interest to investigate their effect on preventing the factors that influence progression.

1.10.1 Cataract surgery

Indicated when a PACS or PAC patient presents with a cataractous lens that has a significant impact on quality of life. Cataract surgery has been demonstrated to widen the angle as the crystalline lens is substituted by the much thinner intraocular lens. Additionally, cataract surgery has been demonstrated to have an effect on diurnal IOP reducing the diurnal maximums (peaks) and minimums (troughs) (Kim, et al., 2009).

Although the benefits of cataract surgery in a patient with a cataractous lens and narrow angle are obvious, it is still unclear whether performing cataract surgery in patients with angle closure and clear lenses is of benefit (Thomas, Walland and Parikh, 2011). Laser peripheral iridotomy remains the first step in the treatment of PAC and PACS. An ongoing study on the effectiveness of

lens extraction in patients with high-IOP PAC and PACG is expected to yield further evidence in this area (Azuara-Blanco, et al., 2011).

1.10.2 Laser Peripheral Iridotomy (LPI)

The principle, on which the peripheral iridotomy is founded, is to create a new pathway between anterior and posterior chambers, therefore normalising the difference in pressures between these chambers causing posterior relaxation of the peripheral iris and widening the trabeculo-iris space (Jin and Anderson, 1990).

There is some evidence that laser peripheral iridotomy performed as a prophylactic treatment has a positive effect in reducing the rate of progression of the angle closure condition (Nolan, et al., 2003). It is common practice to treat PAC and PACG with LPI in the absence of a cataractous lens (where cataract surgery may be indicated). However, when it comes to the PACS stage, the clinical guidelines are not that specific and some clinicians may opt for monitoring the condition until it progresses to PAC (American Academy of Ophthalmology Glaucoma Panel. Preferred Practice Pattern®, 2010). A recent UK national survey, in which all UK-registered consultant ophthalmologists were invited to take part (n=650), showed that 74.7% of the 408 participants performed prophylactic LPI in asymptomatic patients presenting with narrow angles (Sheth, Goel and Jain, 2005).

LPI is therefore used by the majority of consultant ophthalmologists in the cases of PACS and PAC in the UK. However, and as shown in the section above on prevalence of iris plateau, there is no consensus of when to review patients who have undergone LPI in different countries and ethnicities. This absence of guidelines may be due to the lack of information about the duration of the LPI widening effect. Presumably the longer the time that elapses between LPI and the review, the higher the likeliness of that eye to be diagnosed as unoccludable. Is there a relationship between rate of opening and time elapsed? Does this effect have a perennial duration? Is this relationship constant for all the quadrants in the angle or does it vary? The present study investigates these research questions.

Additionally, it has been mentioned earlier that cataract surgery appears to dampen the peaks and troughs of the diurnal IOP. It is possible that as both, cataract surgery and LPI, have a widening effect on the angle, LPI may have an effect on the diurnal IOP fluctuation. This also remains unknown and is addressed in the present study.

1.10.3 Argon Laser Peripheral Iridoplasty (ALPI)

When angle closure mechanisms other than pupillary block are present, the LPI alone may be insufficient to widen the irido trabecular space. ALPI may be indicated in these cases.

The laser is focused in order to create low energy burns in the most peripheral iris stroma. These burns are larger and of a longer duration than those created with the LPI. The aim is to contract the iris tissues and mechanically pull the iris root from the periphery (Ritch, Tham and Lamb, 2007).

In Asian populations, ALPI seems to be an effective treatment in widening angles that remained occludable after the LPI. Leung, et al. (2005) describes one case with PACG using anterior segment imaging technology. In cases of PACG in the same ethnicity, ALPI has been successful in changing the configuration of at least 180° of the angle in all the treated eyes (Chew and Yeo, 1995). In a Caucasian population, a long-term study in the treatment of plateau iris configuration, showed that ALPI is not only successful in opening the angle but that this effect is long standing in the majority of the eyes (Ritch, Tham and Lam, 2004). However, a recent review about the ALPI has pointed out that there is an absence of randomised trials showing the effect of this laser (Ng, Ang and Azuara-Blanco, 2012).

There is also some information regarding the IOP lowering effect (Chew and Yeo, 1995), but an effect of ALPI on the diurnal IOP fluctuation remains unknown.

The present study assesses the effect of ALPI on randomised eyes in comparison with eyes that, although remained occludable after LPI, did not receive ALPI. This effect is assessed in terms of widening of the angle together with the effect on IOP. Details about more specific gaps in the knowledge regarding ALPI and how to address them are given in the following section.

1.11 Gaps in the knowledge and how to address them

1.11.1 Diurnal and postural characteristics of intraocular pressure in Caucasian patients with angle closure

Raised IOP is a major risk factor for glaucoma and is the principal modifiable factor in the treatment of patients with and at risk of glaucoma. Measurement of IOP in the clinical setting usually involves a single measurement with the patient in an upright seated position. However, it is recognised that there can be considerable variability of IOP during the day (diurnal IOP fluctuation, DIOP fluctuation) in non-glaucomatous and glaucomatous eyes (Barkana, 2006;

Baskaran,et al., 2009; Realini, Weinreb, Wisniewski, 2010) and that changes in posture can also result in marked increase in IOP in eyes with (Yamabayashi, 1991) and without glaucoma (Lam and Douthwaite, 1997). The effect of a change in posture from seated to supine positions was measured in one of the research studies of this thesis (supine IOP test, SIOP), as was the effect of darkness in addition to a change in posture (the darkroom provocation test, DRPT). Given the considerable burden of patients diagnosed with angle closure in Caucasian populations, there is a need to investigate these IOP characteristics in individuals with occludable anterior chamber angles and the possible relationship with narrow angle features such as PAS. The research hypothesis and results for this investigation can be found in Section 3.1. (Chapter 3). These results provide clinicians with an evidence base to guide the diagnostic classification of patients and the management strategy associated with this.

Chapter 3- section 3.1. reports a study of the IOP characteristics and its relationship with the presence of PAS in Caucasian untreated PAC/PACS eyes.

1.11.2 Investigation of static and dynamic anatomical characteristics of eyes with gonioscopically occludable anterior chamber angles using ocular coherence tomography: Is there an association with IOP?

Many clinicians use anterior segment imaging in addition to gonioscopy as a screening or diagnosis tool for occludable anterior chamber angles. Most published literature involving Anterior Segment Ocular Coherence Tomography (AS-OCT) reports on the horizontal and vertical meridians of the eye when monitoring changes or making a diagnosis (Lavanya, et al., 2008; Mansouri, Burgener, Bagnoud and Shaarawy, 2009; Ang and Wells, 2010). It is unknown how representative these dimensions are of the entire circumference of the anterior chamber angle. After all, the established technique of gonioscopy, on which clinical management decisions are based, involves a decision made on visibility of the structures in each of the four quadrants of the angle. Therefore an important objective of this thesis was to investigate how meridians imaged by the OCT differed in dimensions within individual eyes. Additionally, the AS-OCT may be used to quantify the dimensions of the anterior chamber angle. Measurements of these dimensions allowed an investigation of the relationship between anterior chamber angle anatomy and characteristics of IOP (DIOP fluctuation, SIOP and DRPT) in the untreated occludable angle. These investigations can be found in Section 3.2. (Chapter 3) of this thesis.

1.11.3 Relationship between the degree of anterior chamber angle opening following laser peripheral iridotomy and time elapsed. Is there an association between angle widening and the intraocular pressure levels?

In general, the practice in the UK is to offer LPI as a prophylactic treatment for PAC and PACS (Sheth, Goel and Jain, 2005), although there is variability between centres in the gonioscopic cut-off used to denote an 'occludable angle' and some clinicians will postpone a decision on treatment of PACS in favour of awaiting the development of symptoms of PAC. There also exists variation in the time that is allowed to lapse between the LPI and the subsequent review of the patient in clinic to assess if the treatment has been effective in opening the anterior chamber angle. Published research studies in Caucasian populations have reviewed such patients at 1 week (Marraffa, et al., 1995; Mansouri, Burgener, Bagnoud and Shaarawy, 2009), 1 month (López-Caballero, et al., 2010), and another at approximately 6 weeks (Ang and Wells, 2010; 2011) post LPI. In a clinical-based environment, guidelines stating when to review these patients post LPI would be helpful. However, there may be considerable inter-individual variation in the degree of opening at different time points after LPI, with some anterior chamber angles remaining closed at 1 week post-LPI but subsequently opening at a later stage, perhaps after 1 month or even 6 months. ALPI is a laser procedure that may be offered to patients in whom the anterior chamber angle remains closed after LPI. Given that the clinical decision to perform an ALPI is based on the LPI outcome, it would be advantageous to know or to be able to predict from baseline data (angle parameters) when the degree of opening of the angle of a given eye has reached a maximal state following the LPI. Additionally, there has been no attempt to correlate an IOP change associated with the LPI with the change in angle parameters over time. This information would be of use in a clinical situation where a patient with PAC, in which the IOP is raised at the time point of the clinical examination, may be considered for the prescription of IOP lowering agents. Studies have shown lower (López-Caballero, et al., 2010) or baseline IOP levels (Moster, et al., 1986) after LPI is performed (finding observed at 1 month and 1 week respectively). Additionally, a drop in IOP levels has been related to a widening of the anterior chamber angle 1 month after the LPI (López-Caballero, et al., 2010). However, the relationship was not specified. One may hypothesise that IOP change and angular rate of opening are related. This is given consideration and investigated in Section 4.1. (Chapter 4) of this thesis.

1.11.4 Effect of the laser peripheral iridotomy on the diurnal intraocular pressure (DIOP) fluctuation after 6 months

Section 4.2. (Chapter 4) is devoted to the study of the effect of the LPI on the diurnal IOP fluctuation. LPI has been shown to affect the IOP; therefore, one may expect that it would also have an effect over the DIOP fluctuation. Previous studies have compared DIOP fluctuation following LPI at different stages of angle closure (Baskaran, et al., 2009). The effect however, of LPI on DIOP fluctuation by comparing treated and untreated eyes with occludable angles, has not been assessed.

1.11.5 Assessment of variability of the effect of the laser peripheral iridotomy depending on the angle section when using Ocular Coherence Tomography Technology

Mansouri, Burgener, Bagnoud and Shaarawy (2009) found a wider effect of the iridotomy on the Superior and Nasal sections of the angle (where the iridotomy was commonly placed) than in the Inferior and Temporal when measured in light conditions. These results were assessed with Ultrasound Biomicroscopy (UBM) and may suggest a different effect of the laser depending on the angular section. Section 4.3. (Chapter 4) is designed to test the hypothesis that sectors closer to the iridotomy site would show a greater widening.

1.11.6 Relationship between degree of angle opening post ALPI treatment and intraocular pressure and the effect of ALPI on the intraocular pressure diurnal fluctuation after 3 months

Section 5.1. (Chapter 5) reports the investigation of the effect of ALPI on the anterior chamber angle parameters and IOP characteristics in eyes that remained with a gonioscopically occludable angle post-LPI. Although there are minimal studies involving ALPI, it has been reported that ALPI is an effective treatment in opening those angles with a plateau iris configuration with a resultant lowering of IOP (Leung, et al., 2005). This procedure is also used in the treatment of acute angle closure (Lai, et al., 2002). It might also be expected that ALPI would have an additional effect of reducing IOP diurnal fluctuation and this is investigated in Section 5.2. (Chapter 5).

1.11.7 Assessment of variability of ALPI effect depending on the angle sector

It was hypothesised earlier that the effect of the LPI would be higher in those sections closer to the iridotomy site. The equivalent hypothesis for the effect of ALPI would be that the effect might be similar in all the sections when comparing with pre-ALPI baseline data. This is studied in Section 5.3. (Chapter 5)

1.11.8 Effect of argon laser iridoplasty in addition to laser peripheral iridotomy on the corneal endothelium

The effect of the Nd:YAG laser on the integrity of the corneal endothelium following LPI has been reported in several studies (Robin and Pollack, 1984; Kerr-Muir and Sherrard, 1985; Panek, Lee and Christensen, 1991; Marraffa, et al., 1995; Kozobolis, Detorakis, Vlachonikolis and Pallikaris, 1998). These studies have reported a decrease in cell density (Robin and Pollack, 1984; Panek, Lee and Christensen, 1991; Marraffa, et al., 1995; Kozobolis, Detorakis, Vlachonikolis and Pallikaris, 1998) and a change in cell morphology (Kozobolis, Detorakis, Vlachonikolis and Pallikaris, 1998) following LPI.

However, the integrity of the corneal endothelium that follows a LPI and then a subsequent ALPI laser has not been studied. This sequence of laser treatments is often followed clinically when the LPI does not successfully open the angle, when assessed by gonioscopy. The LPI involves an Nd:YAG laser delivering laser energy to the iridotomy site and the ALPI, performed 3 months later, involves argon laser energy (heat) delivered to 20 to 24 burn sites along the 360 degrees of the iris periphery. The recovery of the endothelium following this combination of procedures remains uninvestigated. This is of importance as a damaged corneal endothelium may lead to future visual sequelae for the patient such as reduced vision due to corneal decompensation, and the enhanced risk of this complication following intraocular surgery, such as cataract surgery. This is the subject of Section 6.1 (Chapter 6).

CHAPTER 2. General Methodology

2.1. Ethical Approval and National Institute for Health Research (NIHR) portfolio adoption

Ethical approval by Cambridgeshire Research Ethics Committee (REC) for this study was obtained on the 3rd August 2010. REC Reference 10/H0301/14. This approval was reviewed by the Hinchingbrooke Research and Development Steering Group and had agreement to proceed on the 25thAugust 2010.

This study progressed through the NIHR Coordinated system and entered on the National Institute for Health Research Clinical Research Network (NIHR CRN) Portfolio on 9th September 2010.NIHR CRN Study ID: 8955.

2.2 Study Design

This is a longitudinal, prospective, double randomised research study.

The following graph (Figure 2.1) gives a simple overview of the participant pathway.

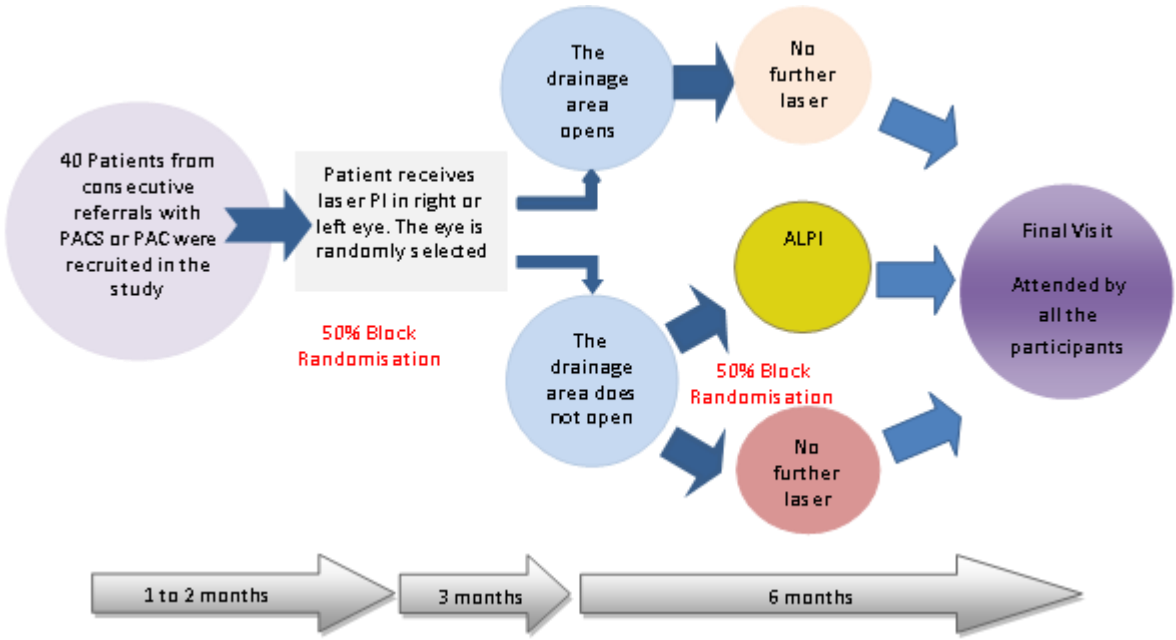


Figure 2.1. Participant's pathway in the study. Primary Angle Closure (PAC); Primary Angle Closure Suspects (PACS); Laser Peripheral Iridotomy (LPI); No Further Treatment (NFT); Argon Laser Peripheral Iridoplasty (ALPI).

Eligible patients were identified consecutively from new referrals to Hinchingbrooke Hospital Glaucoma Service and Moorfields Bedford Glaucoma Service from the community. A "Patient Information Leaflet" was given to the potential participant by the consultant ophthalmologist at the patient's first visit. The potential participants were contacted by telephone not earlier than twenty-four hours after the information was given. If the patient wished to participate, a visit was booked in order to answer possible questions about the research.

In the first visit of the study, Visit 1, and after clarifying any concerns, patients were asked to provide informed consent. Full details were given to the patients including their right to withdraw from the study.

A copy of the "Patient Information Leaflet" can be found in Appendix 4 of this document.

A letter was sent to each participant's General Practitioner to inform him/her about their patient's participation. A copy of this letter can be found in Appendix 4 of the present document.

Once the patient was decided to be eligible (eligibility criterion is specified in Section 2.5.3. of this chapter), both of his/her eyes were included in the sample. At baseline, Visit 1, 20 right eyes and 20 left eyes were included in the statistical analysis.

After the first visit the participants were randomised to receive LPI in either their right or left eye (Details about the randomisation process can be found in Section 2.7. of this chapter). Once these participants received the laser treatment they were booked into three further monitoring visits.

Three months after the LPI was performed, the consultant ophthalmologist made the clinical decision of whether the anterior chamber angle of the treated eye remained occludable by gonioscopy. An angle was considered to remain occludable if 180 degrees or less of the posterior pigmented trabecular meshwork was visible with applanation gonioscopy. If this was the case, the participant was further randomised into:

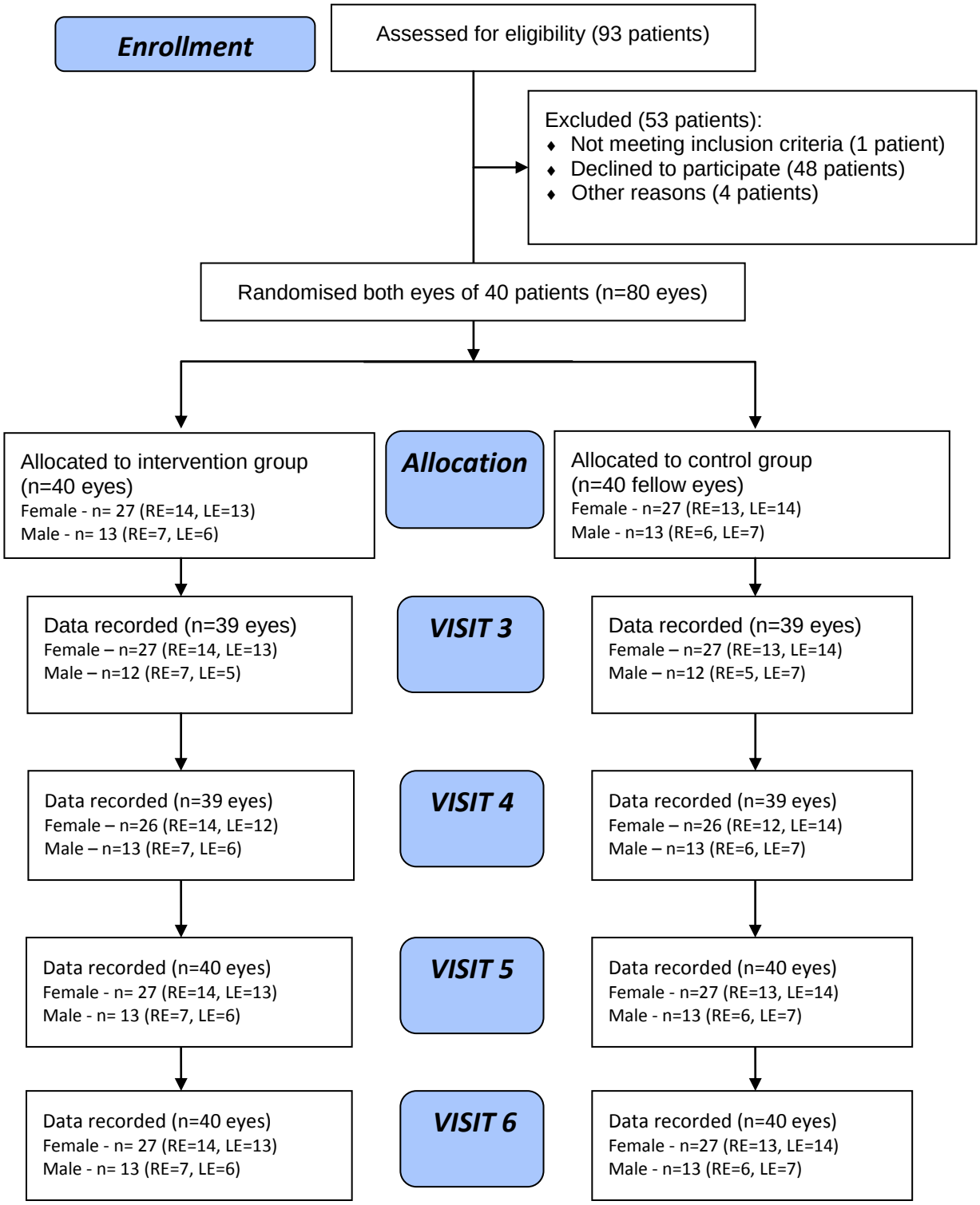
a. No further treatment. The participant came to the exit visit three months later

b. Argon Laser Peripheral Iridoplasty (ALPI). The participant received ALPI in the treated eye and was invited to attend three more monitoring visits

If the anterior chamber angle was not occludable three months after the LPI, the participant came to the exit visit three months later.

Further details about the visits are described in section 2.4 of this chapter.

The following CONSORT diagram shows a detailed pathway of how the participants and their eyes were followed through the study:



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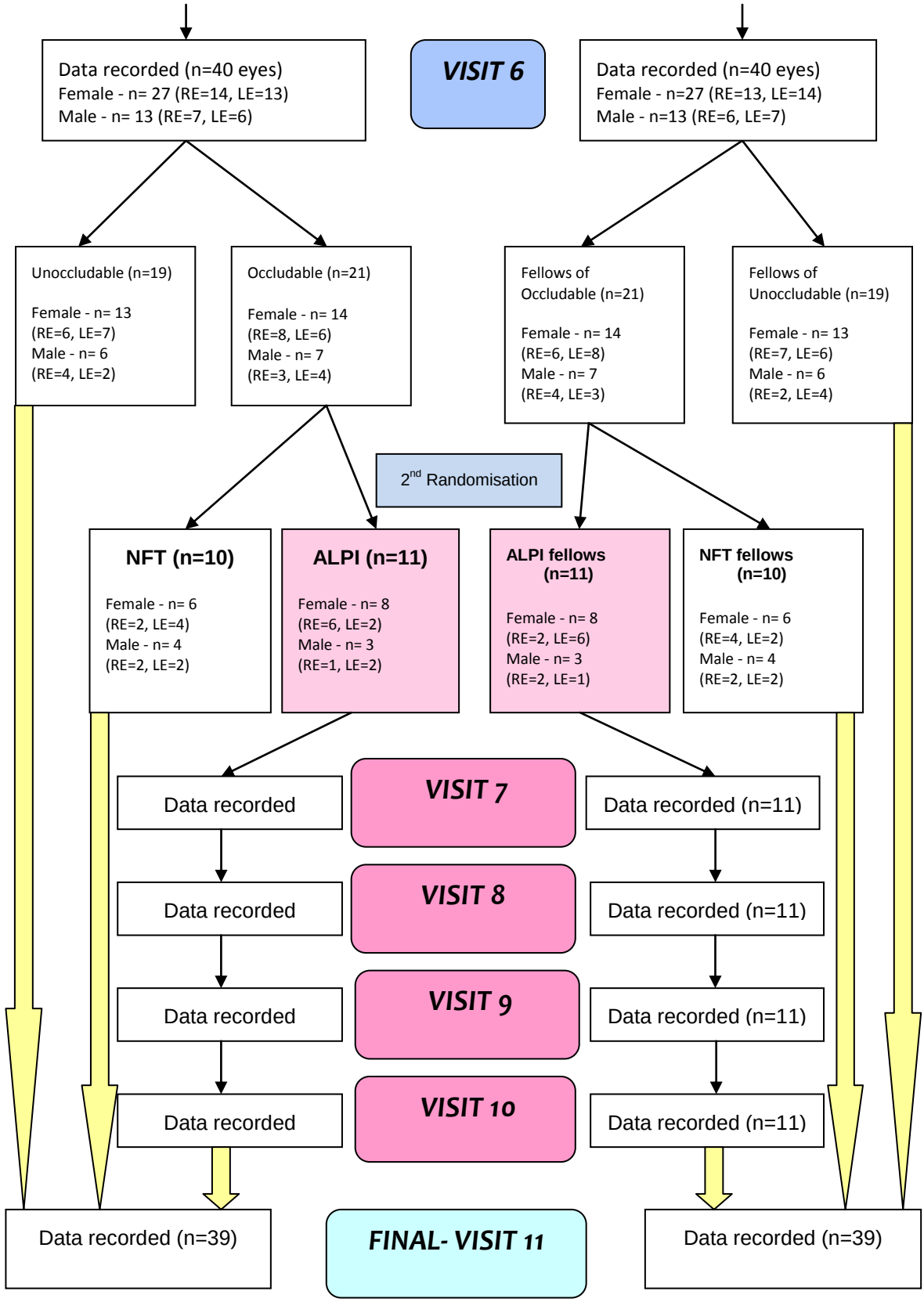

Figure 2.2. Consort Diagram showing the pathway of participants in the study. ALPI= Argon Laser Peripheral Iridoplasty, NFT= No Further Treatment, RE= Right Eye, LE= Left Eye.

2.3 Visits Description and Schedule, Time Windows and Visits Duration

Table 2.1 illustrate the tests and the visits when they were performed. Table 2.2 shows the approximate time frames* for the visit. (*Time windows: referred to the flexibility of timing of the visit either side of the intended date)

	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11
Visual Acuity Measurement	X	X	X	X	X	X	X	X	X	X	X
Autorrefraction and Keratometry	X					X					X
Subjective Refraction	X					X					X
Visual Field	X*										X
Non-dilated Biomicroscopy	X		X	X	X	X		X	X	X	X
Retinal Photography	X										X
Heidelberg Retina Tomography	X										X
Posterior Ocular Coherence Tomography	X										X
Supine Intraocular Pressure and Dark Room Provocation Test	X					X					X
Gonioscopy	X					X					X
Anterior Segment Optical Coherence	X	X	X	X	X	X		X	X	X	X
Specular Microscope	X	X	X	X	X	X	X	X	X	X	X
Biomicroscopy and Indirect Ophthalmoscopy (dilated pupils)	X					X					X
Monitoring Intraocular Pressure		X	X	X	X	X	X	X	X	X	
Diurnal Intraocular Pressure	X										X
Pre and Post Laser Intraocular Pressure		X					X				
Laser Peripheral Iridotomy		X									
Argon Laser Peripheral Iridoplasty							X				

Table 2.1. Tests and visits when they were performed. (X*- only carried out when the previous visual field was performed within more than one month or was unreliable).

	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11
TIME TO VISIT 2	4 to 8.5 weeks	REFERENCE	1 day	1 week	6 weeks	12 weeks	14 weeks	14 weeks + 1 day	15 weeks	20 weeks	24 weeks
TIME WINDOW			±0	±2 days	+/-1 week	+/-1 week	+/-1 week	±0	±2 days	+/-1 weeks	+6 weeks/ -5 days

Table 2.2. Time lines for the different visits with their corresponding time window.

2.3.1 Visit 1 (Training Visit)

The following tests were performed as part of this visit:

- Diurnal Intraocular Pressure (Every hour from 9:00 to 16:00 hours)

- Measurement of Visual Acuity (Unaided/Habitual and Pinhole)

- Autorefraction and Keratometry

- Subjective Refraction

- Measurement of the Best Corrected Visual Acuity

- Visual Field (only if the previous visual field performed in the Eye Clinic was unreliable or older than 1 month)

- Biomicroscopy (undilated pupil)

- Supine Intraocular Pressure

- Dark Room Provocation Test

- Gonioscopy

- Anterior Segment Optical Coherence Tomography (light and dark conditions)

- Instillation of Tropicamide 1%

- Retinal Photograph

- Heidelberg Retina Tomograph

- Posterior Segment Ocular Coherence Tomography

- Anterior Segment Optical Coherence Tomography (dilated pupil)

- Dilated Pupil Biomicroscopy

- Indirect Ophthalmoscopy (dilated pupil)

- Specular Microscope

- Post Dilation Intraocular Pressure

A further explanation of all these tests can be found in Section 2.4 of this chapter.

This visit took place 4 to 8.5 weeks prior to Visit 2

The duration of the visit was approximately eight hours.

2.3.2 Visit 2 (Laser Peripheral Iridotomy Visit)

This visit was set as a reference for timing the rest of the visits. Therefore, this visit was assigned time zero.

The following processes and tests were performed as part of this visit:

- Measurement of Visual Acuity (Unaided/Habitual and Pinhole)

- Monitoring Intraocular Pressure

- First Randomisation

- Instillation of Pilocarpine 2% in both eyes

- Anterior Segment Optical Coherence Tomography (constricted pupil)

- Laser Peripheral Iridotomy

- Post Laser Intraocular Pressure

- Specular Microscope

The duration of this visit varied from one and a half hours to three hours.

A further explanation of all these tests and the randomisation process can be found in Sections 2.4 and 2.7 of this chapter respectively.

2.3.3 Visits 3, 4 and 5 (Follow-up Visits)

The same sequence of tests was performed at each of these visits.

The tests aimed to monitor any biometrical or structural ocular changes occurring after the laser treatment. They were performed at one day, one week and one month after Visit 2, respectively.

No time window was allowed for Visit 3. There was a time window of plus/minus 2 days and plus/minus 1 week for Visits 4 and 5, respectively.

The following processes and tests were performed as part of this visit:

- Measurement of Visual Acuity (Unaided/Habitual and Pinhole)

- Monitoring Intraocular Pressure

- Biomicroscopy (undilated pupil)

- Anterior Segment Optical Coherence Tomography (light and dark conditions)

- Specular Microscope

The duration of the visit was one hour each.

A further explanation of all these tests can be found in Section 2.4.

2.3.4 Visit 6

Three months after Visit 2, the same consultant ophthalmologist determined if the anterior chamber angle of the treated eye was still gonioscopically occludable.

The angle of the eye was considered to remain occludable if 180° or less of the posterior trabecular meshwork was obscured on applanation gonioscopy.

Participants with a gonioscopically occludable anterior chamber angle post-LPI undertook the second randomisation process. This randomisation took place at the end of this visit (Visit 6), with assignment of these patients to receive ALPI or No Further Treatment (NFT). The participant was informed.

The following tests were performed as part of this visit:

- Measurement of Visual Acuity (Unaided/Habitual and Pinhole)

- Autorefraction and Keratometry

- Subjective Refraction

- Measurement of the Best Corrected Visual Acuity

- Monitoring Intraocular Pressure

- Biomicroscopy (undilated pupil)

- Supine Intraocular Pressure

- Dark Room Provocation Test

- Gonioscopy

- Second Randomisation Process (when was indicated)

- Anterior Segment Optical Coherence Tomography (light and dark conditions)

- Instillation of Tropicamide 1%

- Anterior Segment Optical Coherence Tomography (dilated pupil)

- Dilated Pupil Biomicroscopy

- Indirect Ophthalmoscopy (dilated pupil)

- Specular Microscope

- Post Dilation Intraocular Pressure

The duration of this visit was three and a half hours approximately.

A further explanation of all these tests and the randomisation process can be found in Sections 2.4 and 2.7 of this chapter respectively.

2.3.5 Visit 7 (Argon Laser Peripheral Iridoplasty- ALPI)

Participants with a post-LPI gonioscopically occludable angle who were randomly placed into the group which was going to undertake ALPI attended Visit 7 to receive the procedure. This visit took place 14 weeks after Visit 2. The time window for this visit was plus/minus 1 week.

The duration of this visit varied from two to four hours

The following tests were performed as part of this visit:

- Measurement of Visual Acuity (Unaided/Habitual and Pinhole)

- Monitoring Intraocular Pressure

- Instillation of Pilocarpine 2% in the treated eye

- Argon Laser Peripheral Iridoplasty

- Post Laser Intraocular Pressure

- Specular Microscope

A further explanation of all these tests can be found in Section 2.4 of this chapter.

2.3.6 Visits 8, 9 and 10 (Follow-up Visits)

These visits were only attended by participants who received ALPI; taking place one day, one week and 6 weeks after ALPI respectively.

If these times are related to Visit 2, these visits were then performed fourteen weeks and one day, fifteen weeks and twenty weeks after Visit 2 respectively.

These visits were a mirror of Visits 3, 4 and 5 and, as such, they were aimed to monitor changes following the ALPI.

The time windows and tests of these are equal to those specified for Visits 3, 4 and 5, in the same order.

2.3.7 Visit 11 (Final Visit)

Taking place six months after Visit 2, this visit was designed as a replica of Visit 1 and the same data was collected. Every participant attended this visit.

The duration was similar to that set for Visit 1 and the time window was plus 4 weeks /minus 1 week.

2.4 Tests and Instrumentation

The following tests and instrumentation were used in this research project:

2.4.1 Visual Acuity (VA): Distance and Near

2.4.1.1 Distance VA (DVA)

Four types of DVA were measured at the different visits:

- Unaided VA (UVA), measured in those participants who were not wearing any refractive correction. Performed in these participants at every visit
- Habitual VA (HVA), only assessed in those participants who were wearing a spectacle/contact lens correction. Performed in these participants at every visit
- Optimal VA (OVA) or Best Corrected VA (BCVA). This VA was measured after subjective refraction and with the results placed in a trial frame. Performed in every patient in Visits 1, 6 and 11
- Pinhole VA (PHVA), performed in every patient at every visit

A logMAR chart was used as it is widely accepted for clinical research (Ferris and Bailey, 1996) and it has been proven to give more accurate visual acuity measurements than Snellen chart (Lovie-Kitchin, 1988). The continuous nature of the scaling of visual acuity means that LogMAR results are more suited for statistical analysis than Snellen visual acuity.

Examination room lighting was set for the luminance of the chart to be between 80 and 320cd/m² (Elliot, 2007). This chart was placed 3 meters from the participant. Distance and illumination were kept constant throughout the study.

The DVA was always measured monocularly. Right eye measurements were taken first. The untested eye was covered with an opaque handheld occluder.

Distance visual acuity was measured at every visit during the research.

2.4.1.2. Near VA (NVA):

The NVA was measured with the optimal near distance subjective refraction result worn by the participant while performing this test.

An N-print chart was used as a near vision adequacy measurement was considered to be sufficient. The chart was held by the patient at his/her usual reading distance. No angle poise lamp was used and the illumination of the room was kept the same throughout the study.

NVA was measured monocularly and the right eye was always tested first.

The NVA was measured in every patient after subjective refraction was performed. This took place in Visits 1, 6 and 11.

2.4.2 Autorefraction and Keratometry:

The Topcon Auto Kerato-Refractometer N141276 was used on account of its automated function and the fact that it was non-contact.

At least three measurements were taken per eye. Each measurement contained information of the two corneal ratios (power/millimetres) and the auto refraction. The device gives an average of the measurements.

The keratometry readings were necessary to obtain accurate measurement from the Heidelberg Retinal Tomograph (HRT). The use of the HRT will be explained later in this section.

The autorefraction data was used to guide the start of the subjective refraction.

2.4.3 Subjective Refraction

The trial frame method using the plus/minus technique was chosen for best vision sphere determination and the Jackson cross-cylinder technique to accurately determine astigmatism.

The subjective refraction was performed monocularly with the exception of the near assessment where a binocular tentative reading addition technique was used.

Subjective refraction was performed in every participant in Visits 1, 6 and 11.

2.4.4 Visual Field

Humphrey- Field Analyser was used. MODEL 745 S/N:7451-5247. Carl Zeiss. Meditec Inc. Dublin, CA.USA

Two 24-2 SITA Fast Visual Field (VF) tests were performed as part of the study.

The first VF was performed at the time of recruitment, during Visit 1, or within the previous month. The second VF was performed at the end of the study, during Visit 11.

The aim of performing the first VF test was to decide whether the patient was eligible to participate in the study and for use as base line data. The aim of the second VF test was to determine repeatability of the first VF test.

If the VF was unreliable*, the test was explained again to the participant and it was repeated. If the VF was unreliable a second time, the participant was booked for an alternative date as soon as possible for repeat testing.

*A VF plot was considered reliable when:
- Fixation Losses (FL) <20%
- False Positives (FP) <15%

2.4.5 Biomicroscopy

The device used was a BQ 900 mobile slit lamp, Haag-Streit International. The same device was used throughout the study for all participants.

2.4.5.1 Undilated Pupil Biomicroscopy examination:

- Assessment of eyelids: to evaluate if there was upper eyelid retraction (exclusion criterion)
- Assessment of cornea: to grade anomalies such as Krukenberg´s spindle or posterior embryotoxon.
- Assessment of iris: in terms of thickness, colour, transillumination or any other relevant information
- Assessment of pupils: to assess for the presence of a Relative Afferent Pupillary Defect (RAPD)
- Assessment of the angle using the Van Herick Technique. This measurement was performed and recorded using the modified Van Herick Technique proposed by Foster, et al., 2000)

This test was performed in every visit with the exception of Visits 2 and 7.

2.4.5.2 Dilated Pupil Biomicroscopy examination:

- Assessment for the presence of pseudoexfoliative material
- Cataract assessment using the LOCS III, (Chylac, et al., 1993):

Degree of nuclear, cortical and posterior subcapsular cataract

This test was performed in conjunction with the fundus examination (Section 2.6.14 of this chapter) and when the participant had her/his pupils dilated on Visits 1, 6 and 11.

2.4.6 Intraocular Pressure (IOP) measurement:

The IOP was measured with the Goldman Tonometer HS Haag-Street International AT900.

The Goldman Tonometer is considered the benchmark tonometer for research studies.

Only disposable probes were used to reduce the risk of cross-contamination.

The same tonometer was used for every IOP measurement for every participant. Care was taken in checking the tonometer was calibrated at the beginning of every week. No calibration errors were found throughout the study.

Every measurement was taken twice in the same eye. In order to maintain the reliability of the results, the measurements must have been only 1 mmHg difference between them.

One drop of Proxymetacaine 0.5% and Fluorescein 0.25% was instilled prior to every IOP measurement.

As is the case with other topical ocular anaesthetics, proxymetacaine can cause an inhibition of the blinking reflex and make the eye vulnerable to trauma. To decrease this risk one drop of saline was instilled in each eye after every IOP measurement.

2.4.6.1 Monitoring IOP

This test was performed once at the beginning of the Visits 3, 4, 5, 6, 8, 9 and 10.

2.4.6.2 Diurnal IOP

In Visit 1 and Visit 11, IOP was measured every hour from 9:00h to 16:00h. A time window of $\pm$ 15 minutes around the o'clock times was considered acceptable.

2.4.6.3 IOP 45 minutes post laser

In Visit 2 and Visit 7, the IOP was measured before and 45 minutes after the laser procedure. This was considered a safe measurement as IOP has been reported to achieve a peak 1 hour after this type of laser intervention (Moster, et al., 1986).

2.4.6.4 IOP 40 minutes post dilation

An additional measurement was taken 40 minutes after instilling Tropicamide 1 % at the end of the same visits. This was considered a safe measurement as IOP has been reported to achieve a peak 40 minutes after instillation of this drug (Marchini, et al., 2003).

2.4.7 Dark Room Provocation Test

The room luminance was adjusted to less than 0.1 lux. The level was measured with the ISO-Tech RS-1332A Digital Lux Meter (Range 0.01-20000 lux)

The patient was precisely instructed on the dynamics of this test as measurements of the IOP needed to be taken immediately before and after the test. A single IOP per eye was measured while the participant was seated, no more than 1 minute after this measurement, the participant laid prone for 15 minutes. The IOP was then immediately measured in each eye in the seated position.

Participants were awake during the test.

Several studies have used a longer version of this test as a diagnostic tool for acute attacks of angle closure; Wilensky, et al. (1993) 45 minutes; Ishikawa, et al. (1999) 1 to 2 hours. However, a shorter duration was chosen to be able to compare results with the ZAP study (The Zhongshan Angle Closure Prevention Trial, Iridotomy for the Prevention of Angle Closure in Southern China), (Jiang, et al., 2010).

This test was performed in Visits 1, 6 and 11.

2.4.8 Supine Intra Ocular Pressure (SIOP) measurement:

Measured with the Perkins Tonometer MK2 by HS Clement Clarke International SN T12360.

The participant was asked to lay supine. After 5 minutes, the IOP was measured while the participant was resting in the same position.

Only one measurement per eye was taken.

This test was performed in Visits 1, 6 and 11.

2.4.9 Gonioscopy and Angle Evaluation

Gonioscopy was performed with and without indentation; the Zeiss Four Mirror lens and the Magnaview lens were used respectively.

As a more detailed gonioscopy was required for this thesis study, the Spaeth Gonioscopic Grading System was used (Marsh and Cantor, 2005).

The same consultant ophthalmologist, with extensive gonioscopy experience, performed this gonioscopy, as the interpretation of the gonioscopical view can be extremely subjective.

This test was performed in Visits 1, 6 and 11.

2.4.10 Anterior Segment Imaging:

Cornea/Anterior Segment Optical Coherent Tomography: CASIA SS-1000, Tomey GmbH.

This device is a three-dimensional corneal and anterior segment optical coherence tomography (ASOCT) based on Swept Source OCT techniques which provide a faster acquisition of scans (30000 A Scans/second). This increase in speed provides a higher resolution of the two-dimensional images and the possibility of building three-dimensional ones. This system achieves high resolution imaging of 10 μ m (Axial) and 30 μ m (Transverse).

This technology and its advantages over time domain (used in the Visante OCT Carl Zeiss Meditec, Inc.) were explained in a study by Yasuno, et al. (2005; 2009). In the case of our study, this new resolution was translated in a more accurate identification of the scleral spur by the examiner. The CASIA OCT is equipped with storage and analysis software (Version 6H). This software provides angle analysis (semi-automated analysis) with the possibility of assessing the angle opening distance (AOD), the trabecular-iris angle (TIA) (Pavlin, Harasiewicz and Foster, 1992), the angle recess area (ARA) (Ishikawa, et al., 1999) and the trabecular iris space area (TISA) (Radhakrishnan, Huang and Smith, 2005). These parameters were measured at 500 and 750 microns from the Scleral Spur. A visual representation can be found in the following figure (Figure 2.3).

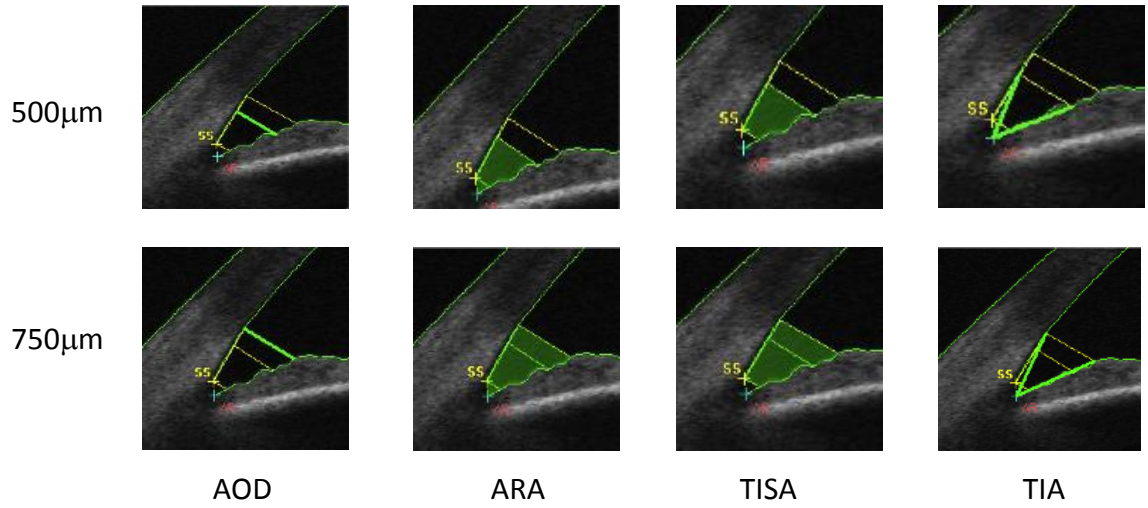

Figure 2.3. Irido-trabecular angle parameters as measured with the CASIA AS-OCT analysis software. AOD (Angle Opening Distance), ARA (Angle Recess Area), TISA (Trabecular-Iris Space Area) and TIA (Trabecular-Iris Angle) at 500 and 750µm are highlighted in bright green colour. SS (in yellow ink)=Scleral Spur; AR (in red ink)=Angle Recession.

These dimensions can be analysed in up to 360° of the irido-trabecular angle. For an example of a scan taken with the CASIA, please see Figure 2.4.

The software automatically detects the front and posterior cornea and front iris profile. However, if this trace is not accurate, it can be manually modified.

The scan range was 16x16x6mm.

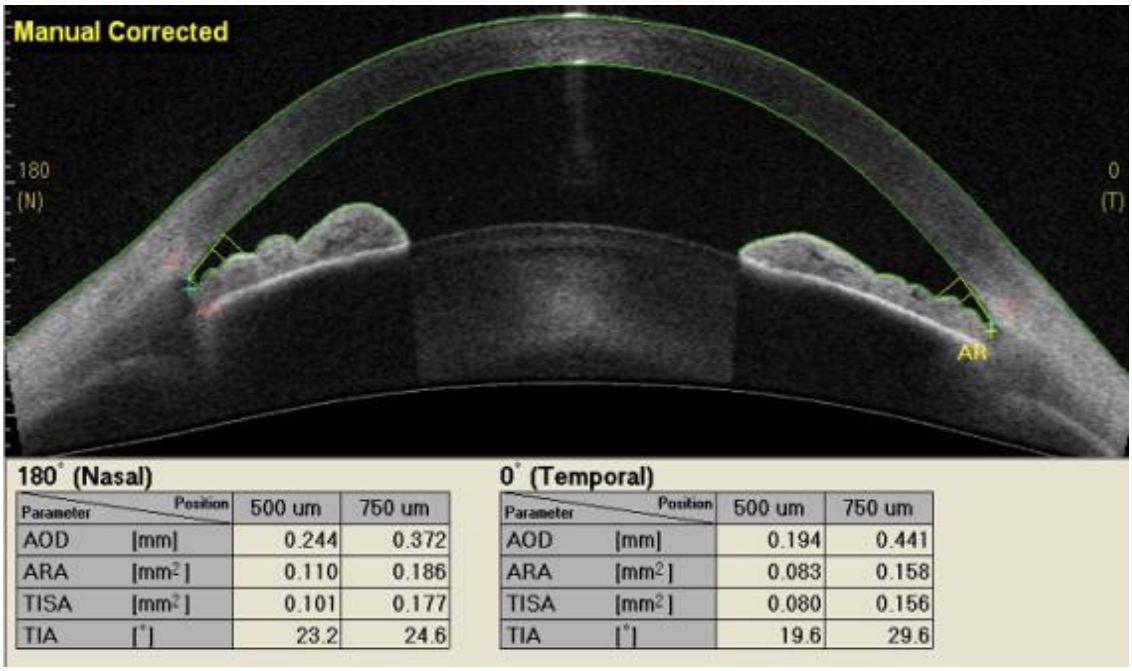

Figure 2.4. Image scan taken with the CASIA OCT. It shows a horizontal cut of the anterior chamber (Nasal and Temporal sections of the angle of a Left Eye). SS=Scleral Spur; AR=Angle Recession. AOD (mm)=Angle Opening Distance. ARA (mm^2)=Angle Recess Area; TISA (mm^2)= Trabecular Iris Space Area; TIA (°)= Trabecular-Iris Angle.

Testangle Radial Scan was set as default analysis as it was the scan providing the highest resolution, 10µm. This scan consisted in 512 A/B scans plus 256 B/C scans

The duration of the acquisition was 4.6 seconds and the participant's upper eyelid was held during the test. Care was taken to not to put any pressure on the eyeball as this would have modified the result. Proxymetacaine 0.5% and Fluorescein 0.25% was used only if the participant experienced difficulty maintaining his/her eye open for the required image acquisition time.

A scan was considered valid only if the scleral spur was visible throughout 360 degrees of the angle circumference. This was assessed immediately after every scan. If the scan failed in the validity criteria, it was re-taken after allowing the participant to recover for several seconds.

A scan sequence per eye was performed in the following light conditions:

2.4.10.1 Non dilated pupil in dark conditions

Dark conditions were set as a luminance of no higher than 0.5 lux. A lower luminance level was not possible due to the residual light coming from the device computer screen.

To accurately measure the luminance, the lux meter (described in section 2.4.8) was placed in the same location where the participant´s eye was going to be situated. The luminance was measured prior to every measurement and it was maintained throughout the study.

This scan was taken in every visit with the exception of Visits 2 and 7.

2.4.10.2 Non dilated pupil in light conditions

Light conditions were set as 150-200 lux (Recommended by CIBSE (2002) as Places of Public Assembly and General Areas Illumination). To achieve this level of luminance an extensible ceiling-attached angle poise lamp was used. The angle of the lamp was modified until the desired luminance was achieved.

The procedure of how the light was measured is equal to that described in section 2.4.10.1

This scan was taken at every visit with the exception of Visits 2 and 7.

2.4.11 Imaging of the Corneal Endothelium

For this propose a non-contact device was chosen, the EM-3000 Specular Microscope by Tomey GmbH. This testing unit was formed by 2 systems:

A. Tomey EM-3000 Specular Microscope (SM)

This is the microscope that acquires the images of the corneal endothelium

B. Tomey Analysis and Storage Software: VS-100

External software connected to the EM-3000 SM.

This instrument is a non-contact auto focus device. 7 images per eye were taken. The participants were asked to look in the following directions (Figure 2.5):

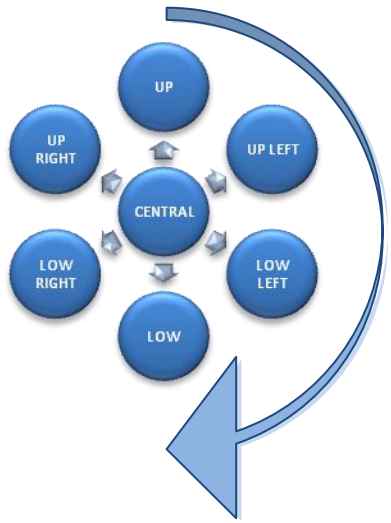

Figure 2.5. Sequence followed by the examiner when testing with the specular microscope.

The endothelial sampling was always started with the participant looking at the central target followed by the sequence indicated by the arrow in the previous figure.

For every position tested, the device gave 15 different images that were temporarily recorded for the examiner to make a choice. Only one shot per position could be stored, therefore the decision

on which image to retain was made immediately after taking the measurement. The image with the highest number of cells images and the highest contrast was chosen.

Once the image is selected the information is saved in the storage device in three different formats:

- Jpeg picture of the EM-3000 SM automated analysis (Figure 2.6). This analysis provided the following information:

Number : The number of analysed endothelial cells

CD : The density of the analysed endothelial cells

(Number of cells per mm2)

AVG : The average dimension of the analysed endothelial cells

SD : The standard deviation of the analysed endothelial cell dimensions

CV : The coefficient of variation of the analysed endothelial cells, derived by dividing the average dimension by the standard deviation

Max : The dimension of the largest analysed endothelial cell

Min : The dimension of the smallest analysed endothelial cell

Area (Polymegathism): expressed as a percentage

Apex (Pleomorphism): expressed as a percentage

Corneal Thickness: only given when testing central corneal endothelium

- CSV file containing the information shown in the Jpeg file
- Exam data storage file. Only to be read with the Tomey Analysis and Storage Software VS-100

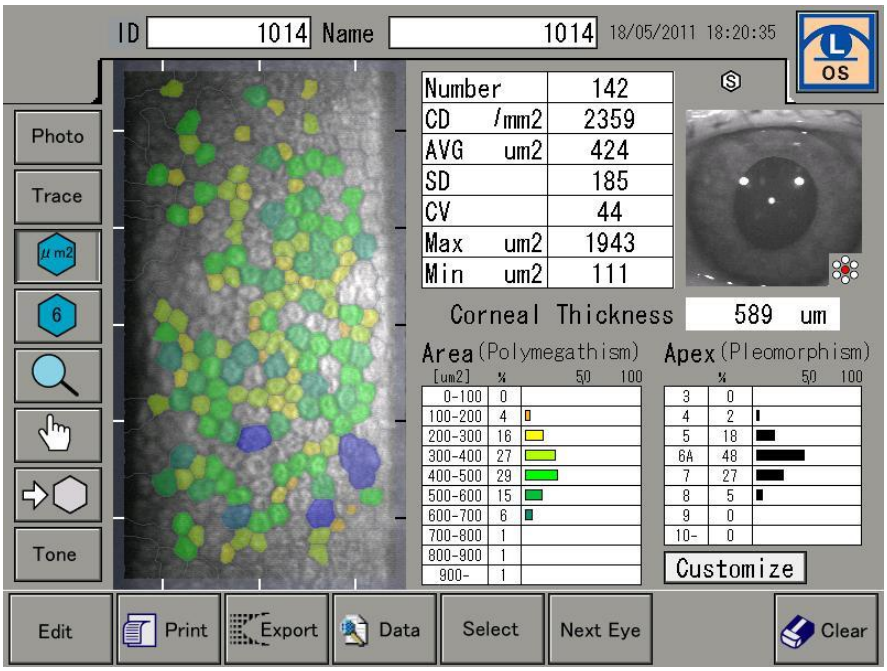

Figure 2.6. Screen shot of the specular microscopy performed with the Tomey 3000 in central cornea of the left eye of the participant. The abbreviations in this image have already been discussed in the previous page.

Specular Microscopy of the corneal endothelium was performed at every visit. This means that some participants had this test performed on 7 and some on 11 different occasions. These testing times were chosen following the findings of the study by Kozobolis, Detorakis, Vlachonikolis and Pallikaris (1998) that reported changes to the endothelium following laser.

2.4.12 Indirect Fundus Examination

Performed in both eyes when the participant had dilated pupils (Tropicamide 1%). The same slit lamp described in section 2.4.6 was used in conjunction with a fundoscopy lens of 66 Diopters.

The assessment included:

2.4.12.1 Assessment of the Optic Nerve Disc:

Cup/disc ratio

ISNT rule

Vertical Disc Diameter

Presence of Nerve fibre layer haemorrhages

Presence of Nerve Fibre Layer Defect

Presence of Neuroretinal Rim (NRR) Thinning

2.4.12.2 Assessment of the Macular area:

Presence of any abnormality

2.4.12.3 Assessment of the peripheral Retina:

Presence of any abnormality

2.4.13 Posterior Segment Imaging

2.4.13.1 Fundus photography:

Topcon TRC NVV65 Non-Mydriatic Retinal Camera

2.4.13.2 Retinal Tomography:

Heidelberg Retinal Tomograph (HRT) by Heidelberg Engineering HRTI

2.4.13.3 Posterior Segment Optical Coherent Tomography:

OCT Spectralis by Heidelberg Engineering HRTI

Posterior segment imaging was performed on Visits 1, 6 and 11.

The aim of these imaging tests was to be able to keep an objective record of the retinal and optic nerve function.

2.4.14 Laser Peripheral Iridotomy (LPI)

Nd:YAG Laser VISULAS YAG II plus Zeiss ZIP by Zeiss Meditec

The LPI was always performed by the same consultant ophthalmologist (RB) throughout the study.

The dynamics of this procedure are explained as follows:

2.4.14.1 Prior to the LPI:

- Pilocarpine Hydrochloride 2% was instilled in both eyes at least 20 minutes before the laser
- Consent for the laser procedure was taken by the consultant
- One drop of Iopidine was instilled in the eye that randomly selected to undergo the laser treatment

2.4.14.2 During the LPI, the following information was recorded:

- Time the procedure took place at
- Power range (Minimum/Maximum)
- Total power used
- Number of shots
- Complications during the procedure
- Name of the professional who performed the test

2.4.14.3 After the LPI:

- 250mg Diamox tablet was given to the patient immediately after the laser was performed
- Maxidex was prescribed to be applied every hour the first day and every four hours during the following week

This procedure dynamic complies with that describe in the Nd:YAG Peripheral Iridotomy clinic guidelines developed by the Department of Ophthalmology at Hinchingbrooke Hospital NHS Trust, November 2008, Version 3.

Information regarding the concentration of the drugs used can be found in section 2.6.18. A brief description of possible secondary effects of the drugs was given to the participant.

This laser took place in Visit 2.

2.4.15 Argon Laser Peripheral Iridoplasty (ALPI)

Lumenis Novus Specta by Lumenis Gmb.

This laser device was formed by two units:

- The laser power generator
- The laser link, which was adapted into a Haag Streit Bern M90045409 Slit Lamp

The laser ALPI was always performed by the same consultant ophthalmologist (RB) throughout the study.

The dynamics of this procedure are explained as follows:

2.4.15.1 Prior to the ALPI:

- Pilocarpine Hydrochloride 2% was instilled only in the eye that was going to receive the procedure. This drop was administrated at least 20 minutes before the laser
- Consent for the laser procedure was taken by the consultant

2.4.15.2 During the ALPI, the following information was recorded:

- Time the procedure took place at
- Power range (Minimum/Maximum)
- Spot size
- Duration of each shot
- Number of shots
- Complications during the procedure
- Name of the professional who performed the test

2.4.15.3 After the ALPI:

- Pred Forte was prescribed to be instilled 4 times/day for a week
- Pilocarpine Hydrochloride 2% was prescribed only if peripheral anterior synechiae were present. To be instilled 3 times/day for a week

2.4.16 Eye Drops and Pre/Post-laser Medication

- Minims ® Proxymetacaine 0.5% and Fluorescein 0.25%(B&L)

- Minims® Saline (B&L)
- Minims ® Tropicamide 1% (B&L)
- Pilocarpine Hydrochloride 2% (Non- Proprietary)
- Maxidex ® Dexamethasone 0.1% and Hypromellose 0.5% (Alcon)
- Diamox ® (Acetazolamide 250mg)- Oral administration
- Iopidine ® (Apraclonidine 1%)
- Pred Forte ® (Prednisolone acetate 1%)

The use and doses of these drugs has been described in previous sections of this chapter.

This laser procedure is identical to that used in the Clinical Safety of Hinchingbrooke Hospital Guidelines.

2.5 Participants

2.5.1 Sample size calculation

At the time this study was designed (January 2010), the literature review related to this study aims showed very few studies in this subject area

In order to justify a sample size of 40 participants, the most similar published studies to the present aims and their sample size are specified in the following table. The sample power was set at 80% as this was considered reasonable and the alpha was set at 0.05 to achieve statistical significant differences of 5%.

The mean differences to be detected were chosen either from the published literature when it was available, or if unavailable, it was decided to consider the minimal detectable difference for the given parameter in a clinical setting (the minimal difference detectable in IOP with Goldmann tonometer is 1mmHg). None of the publications mentioned in the table below showed standard deviations or standard errors for the mean differences found in their outcomes, therefore the widest standard deviations (SD) specified in the publication descriptive statistics were chosen to calculate the effect on the sample size calculation.

When several parameters for the same outcome could have been chosen from the same publication, only those giving the larger sample size are shown in Table 2.3.

Present Study Research Outcome	Sample required	Mean difference to be detected (SD)	Author	Sample characteristics
Diurnal Intraocular Pressure Profile	n=12 eyes	1mmHg (0.5)	Liu, et al., 1999	21 healthy individuals of mixed ethnicity without ocular pathologies
Supine Intraocular Pressure	n=52 eyes	2mmHg (2.25)	Lam and Douthwaite, 1997	33 Chinese healthy individuals without ocular pathologies
Dark Room Provocation Test	n=12 eyes	6mmHg (3.27)		
Diurnal Intraocular Pressure Fluctuation	n=12 eyes	4.53 mmHg (2.33)	Baskaran, et al., 2009	119 participants enrolled after LPI. Most subjects were Chinese (32 PACS, 34 PAC and 32 PACG
Change in angle parameters due to change in lighting conditions	n=12 eyes	AOD 500=146μm (82)	Leung, 2007	18 Chinese subjects with narrow angles
	n=24 eyes	TISA 500=0.05mm^2 (0.04)		
Change in angle parameters due to the effect of the LPI	n=70 eyes	Superior TIA= 4.29° (6.3)	Mansouri, Burgener, Bagnoud and Shaarawy, 2009	35 eyes of 28 European participants: 19 PAC 16 PACG
		Superior AOD 500= 0.056μm (0.08)		
Change in the Intraocular Pressure due to the effect of the LPI	n=100*	1.9 mmHg (3.3)	Lei, Wang, Wang and Wang, 2009	15 eyes of 15 Chinese PAC patients
Change in the Intraocular Pressure Fluctuation due to the effect of the LPI	n=?	No publications	No publications	
Change in angle parameters due to the effect of the ALPI	n=?	No publications	No publications	
Change in the Intraocular Pressure due to the effect of the ALPI	n=18	8.57 mmHg (5.94)	Chew and Yeo, 1995	11 PACG eyes already treated with LPI. All the eyes were under ocular β-blockers and pilocarpine.
Change in the Intraocular Pressure Fluctuation due to the effect of the ALPI	n=?	No publications	No publications	
Change in Central Corneal Thickness due to the effect of the LPI	n=20	0.011mm (0.008)	Kozobolis, Detorakis, Vlachonikolis and Pallikaris, 1998	10 eyes of 10 participants (AAC fellow eyes; No ethnicity specified)
Change in Endothelial Cell Density due to the effect of the LPI	n=46	170 cells/mm^2 (199.67)		
Change in Endothelial Polymegathism due to the effect of the LPI	n=220	46.2 μm^2 (120.295)		
Change in Endothelial Pleomorphism due to the effect of the LPI	n=68	5% (7.177)		
Change in Central Corneal Thickness due to the effect of the ALPI	n=?	No publications	No publications	
			Table continues in next page	

Change in Endothelial Cell Density due to the effect of the ALPI	n=78	106 cells/mm^2 (161)	Thoming, Van Buskirk and Samples, 1987	Rates reported for Argon laser Trabeculoplasty. -20 eyes of 17 participants with Open Angle Glaucoma -No statistically significant differences were found
Change in Endothelial Pleomorphism due to the effect of the ALPI	n=106**	5% (9.08)		
Change in Endothelial Polymegathism due to the effect of the ALPI	n=58	18μm^2 (24)	Hong, Kitazawa and Tanishima, 1983	10 eyes with Open Angle Glaucoma

Table 2.3. Sample size calculation for statistically differences of 5% and a power of 80% for the different research outcomes.

*(n=100 as required sample); To have a sample of 70 eyes in this case reduces the power of the sample to a 65%.

** In this publication a change of 0.041% was reported as a non-statistically significant change in hexagonality rate after the Argon Laser Trabeculoplasty when compared to baseline. To detect a statistically significant difference of this magnitude a sample of 1550396 eyes would be needed. A change of 5% was decided to be sufficient for detection of change in hexagonality rates.

As can be observed in Table 1, the sample size required often exceeded the sample of the present study (80 eyes at baseline; 40 eyes for assessing LPI effect (after 1st Randomisation); 7-8 eyes for assessing ALPI effect (After 2nd Randomisation)). In spite of this, the published studies from which this data was withdrawn had a smaller sample than the present study, the main reason for this being the lack of information about standard deviations for the mean differences in published literature. It is additionally rare to find the mean differences published even when these are reported as statistically significant. In the case of the studies listed in the table above, only the descriptive statistics and the p values were given. The standard deviation used for calculating the sample size required in the present study for every outcome was the highest specified by the descriptive statistics of the same reported outcomes. Therefore, it is possible that this sample calculation was overestimating the sample required.

It was of interest for the present study to have an approximation of what would be the power of detection given by a sample of 80 eyes at baseline. This was calculated only for those outcomes in which the “calculated sample” was larger than the present sample. The results can be found in Table 2.4 (bellow). For the outcomes related to the effect of the LPI the sample size of the present study was adequate. The sample of eight eyes for the study of the effect of the ALPI on the

endothelium may have been insufficient for the study of the endothelium. At the outset of the study, the number of eyes to be randomised into the ALPI allocation was unknown.

Outcome	Present Sample	Power of detection
Change in angle parameters due to the effect of the LPI	n=40	67% to 70%
Change in the Intraocular Pressure due to the effect of the LPI	n=40	55%
Change in the Intraocular Pressure due to the effect of the ALPI	n=8	56%
Change in Endothelial Cell Density due to the effect of the LPI	n=40	84%
Change in Endothelial Polymegathism due to the effect of the LPI	n=40	32%
Change in Endothelial Pleomorphism due to the effect of the LPI	n=40	69%
Change in Endothelial Cell Density due to the effect of the ALPI	n=8	21%
Change in Endothelial Pleomorphism due to the effect of the ALPI	n=8	24%
Change in Endothelial Polymegathism due to the effect of the ALPI	n=8	17%

Table 2.4. Power of detection by a sample size of 80 eyes at baseline. The minimal clinical difference is the same as described in Table 2.3 and the levels for statistical significance remain at 5%.

2.5.2 Enumeration of participants

Participants recruited for this research study were identified from consecutive eligible patients attending as new referrals to the Department of Ophthalmology at Hinchingbrooke Hospital NHS Trust, Huntingdon, Cambridgeshire, UK (the study centre).

To facilitate recruitment, permission was granted for Moorfields Bedford to act as a Patient Identification Centre patients to the ophthalmology department at Hinchingbrooke Hospital, Huntingdon. The recruitment for this site started on 30th of March 2011.

The total recruitment period took place from 25th of August 2010 to 25th of April 2011. The first participant was recruited on 6th of October 2010 and the last on 15th of April 2011.

Ninety-three patients diagnosed with PACS and/or PAC in either eye were invited to participate in the study. Fifty-three of these patients declined participation. The recruitment period, initially set at three months, was extended to eight months in order to achieve a sample size of at least forty participants.

From the 40 participants recruited, 27 were female and 13 were male. The average age in the group was 59,6 years at the time of recruitment (range 25-77 years).

All were Caucasian.

At the time of recruitment, 23 participants were diagnosed with bilateral PAC, 14 with bilateral PACS and 3 with a combination of both conditions.

2.5.3 Inclusion and exclusion criteria:

2.5.3.1. Eligibility and Inclusion Criteria

Consecutive patients newly diagnosed with either PACS or PAC in both eyes (or PACS in one and PAC in the fellow eye) according to the gonioscopic definition of an occludable angle (posterior pigmented trabecular meshwork visible in 180 degrees or less of the circumference of the anterior chamber angle on applanation gonioscopy) were invited to participate in the study.

2.5.3.2. Exclusion Criteria

- Patients with any ophthalmic co-morbidity other than cataract with an important influence on visual field deterioration or optic nerve head damage
- Patients included in other glaucoma therapeutic studies
- Patients with PAC with an IOP of ≥30 mmHg in either eye
- Patients with upper eyelid retraction
- Patients who have undergone cataract surgery
- Inability to give consent (where applicable)
- Patients with no capacity to consent (Mental Capacity Act)

2.6 Study endpoints

2.6.1 Intraocular Pressure

If the IOP was higher than 35mmHg in either eye measured on two successive occasions the participant was subsequently withdrawn from the study.

This cut-off was chosen with respect to the Guidelines for the Management of Open Angle Glaucoma and Ocular Hypertension, 2004, Royal College of Ophthalmologists. “A constant IOP over 35 mmHg merits treatment as at these levels mechanical damage occurs to the optic nerve head”.

2.6.2 Glaucomatous Optic Neuropathy

The second study endpoint was described as a glaucomatous visual field defect or glaucomatous optic nerve appearance as defined in the UK Glaucoma Treatment Study.

2.7 Randomisation Process

The randomisation process was designed prior recruitment and it was formed by two different randomisations.

For doing this, the following information was taken in account:

70 potential participants to be recruited

(Data obtained through estimation of flow of patients diagnosed with bilateral PAC/PACS at The Department of Ophthalmology at Hinchingbrooke Hospital NHS Trust)

Only one eye of these subjects to be treated

Participants to be randomised into Right Eye treated or Left Eye treated with LPI

FIRST RANDOMISATION

Based on previous studies 20% to 43% of the irido-trabecular angles would not open (Thomas, et al., 1999; Kumar, et al., 2008)

Taking in account the most restrictive scenario (20% do not open), this would have given 14 participants

Participants to be randomised into “Further treatment (ALPI)” or “No further treatment”

SECOND RANDOMISATION

2.7.1 First Randomisation

A random sampling of numbers was generated by computer software.

This random sampling unsorted set of unique numbers ranged from number 1 to number 70.

As an example, the following set was generated by the software:

SET : 43, 52, 18, 32, 17, 21, 62, 31, 56, 20, 46, 22, 28, 13, 64, 66, 51, 45, 48, 54, 53, 44, 9, 29, 30, 34, 4, 65, 49, 10, 37, 7, 50, 27, 19, 35, 67, 59, 61, 26, 24, 15, 60, 57, 39, 14, 23, 3, 36, 16, 11, 55, 2, 40, 38, 12, 41, 42, 33, 6, 68, 69, 1, 25, 8, 63, 47, 58, 70, 5

Right Eye was identified with the even numbers and the Left Eye with odd numbers.

Random Set Number	Participant’s study number	Eye to be treated
43	1001	Left Eye
52	1002	Right Eye

18	1003	Right Eye

The information relating to the “Participant’s number” associated to the “Eye to be treated” was placed in envelopes at the beginning of the study and before the recruitment.

The envelope was only identifiable by the participant’s study number.

The “Form 1”was kept inside the envelope. The only information written in this form at that point was the patient study number and the eye which was assigned the laser procedure.

A copy of Form 1 can be found in the Appendix 4.

A person external to the research team carried out the randomisation. This person had no knowledge of the study and wrote only the “Patient Study N°” and the “Eye which was undertaking LPI”. The investigator who opened the envelope at the pertinent time completed the remaining details.

The corresponding envelope was attached to the participant’s file at the moment of the recruitment and was opened at VISIT 2 pre-laser.

The participant was informed of the result at the same time.

2.7.2 Second Randomisation

As in the First Randomisation, a random sampling unsorted set of unique numbers was generated by computer software.

It was not possible to predict how many participants would remain with occludable angles after LPI. However, we proposed a randomisation process in blocks of 14 participants was decided. This number was based on previous studies which state that approximately 20% of the post-LPI angles would remain occludable (Thomas, Arun, Muliyil and George, 1999).

As an example, the following 5 sets were generated by the software:

SET 1: 12, 11, 8, 14, 5, 13, 9, 7, 1, 10, 6, 3, 2, 4

SET 2: 23, 20, 18, 28, 21, 25, 17, 19, 27, 16, 15, 24, 22, 26

SET 3: 36, 41, 42, 37, 40, 38, 30, 29, 33, 31, 34, 32, 35, 39

SET 4: 53, 44, 51, 50, 56, 52, 46, 48, 45, 54, 43, 47, 49, 55

SET 5: 60, 70, 65, 67, 59, 57, 58, 62, 68, 69, 64, 61, 63, 66

Odd numbers corresponded to “ALPI” and even numbers to “no further treatment”.

As an example:

SET 1 Randomisation Number	Participants with occludable angles after LPI	Outcome
12	A1	No further treatment
11	A2	ALPI
8	A3	No further treatment

In this case, participants with a post-LPI occludable angle were named as A1, A2, A3… A70. The number was assigned following the order of diagnosis. These new notation was used only for randomisation proposes and it did not modify the patient identification number.

The envelope was only identifiable by the randomisation “A-numbers” written on them.

A second type of form, “Form 2”, was kept inside the envelope. In this case the external person in charge of preparing the randomisation will write only the “Randomisation Patient A-Number” and the “outcome”.

A copy of Form 2 can be found in the Appendix 4 of this thesis.

The investigator who opened the envelope completed the remaining details.

The corresponding envelope for each participant was attached to his/her file at the moment of diagnosis of post-LPI occludable angle in Visit 6 and was opened at the end of the same visit. The participant was informed of the result at the same time.

2.8 Data Collection and Confidentiality

In order to maintain the confidentiality of the participants, patients were identified with a 4-digit code at the time of the recruitment. The first two digits identified the centre, and the last two identified the patient. The key list translating patients' study numbers to their true identities remained at the investigator's master trial file. This file was kept in a location only accessible by hospital identification and access key.

The information collected from the different tests in the different visits was recorded into a Case Report Form (CRF). Which was transferred into a SPSS *file afterwards.

*SPSS: Statistical Package for the Social Sciences (SPSS Inc)

Participants' visual field and imaging data were kept confidential by recording study identification number and date of birth only.

2.9 Statistical analysis and assumption of normality

Statistical Package for the Social Sciences (SPSS) was chosen as the analysis software to be used in with this thesis. The collected data was transferred from paper record onto a pre-prepared SPSS database.

The SPSS package was used for the majority of the statistical analyses.

Prior to the statistical plan, the distribution of the data was checked for normality. Probability-probability plots were produced to visually inspect the assumption of normality for every type of measurement under study. It was observed that the majority of these plots showed a normal distribution to a very good approximation. It was therefore justified to use parametric methods.

P values less than or equal to 0.05 were considered statistically significant.

The statistical analysis used in every chapter is specified as follows:

Chapter 3- All the eyes (80 eyes) were included in the statistical analysis of this chapter.

Section 3.1:

- To test the slope present in the Diurnal Intraocular Pressure (DIOP), the analysis Repeated Measures of Variance was performed. This same analysis was used to test the relationship between presence of Peripheral Anterior Synechiae (PAS) and DIOP.
- The relationship between PAS and higher levels of DIOP and furthermore its relationship with higher DIOP fluctuations was tested with Linear Regression.
- The Supine Intraocular Pressure (SIOP) and Dark Room Provocation Test (DRPT) results were calculated using Paired Samples T-Test. Independent Samples T-Test was used to show the differences in the results of both tests for eyes with and without PAS. A further relationship between the results of these tests and presence of PAS was investigated with Univariate Regression.

Section 3.2:

- To find which of the 8 angle sections was the widest and which one was the narrowest, analysis of variance followed by Tuckey HSD multiple comparisons was performed. The same analysis was used to investigate the differences between the Superior, Nasal, Temporal amd Inferior sections and their adjacent sections (Superior-Nasal, Inferior-Nasal, Superior-Temporal and Inferior-Temporal).
- Paired Samples T-Test was performed to find the dimensionsl differences in the angular parameters between light and dark conditions.
- The confidence limits for the Sensitivity and Specificity tests were performed with Wilson's method.

Chapter 4- At this point of the study 40 eyes had been treated with LPI and 40 fellow eyes were acting as controls.

Section 4.1-The statistical analysis was divided in two sub-sections depending on the hypothesis to be tested:

- 1st Hypothesis: "The treated eye angle parameters would experience a widening effect after the LPI while the untreated eyes parameters would remain unchanged.

Furthermore, in the case of the treated eye, this widening would be directly associated with time elapsed since the procedure"

To statistically show the effect of the LPI on the angle parameters of treated and untreated eyes, two different statistical models were performed. The first statistical approach was to use paired samples t-test to compare Visit 4, Visit 5, Visit 6 and Visit 11 against Visit 1 (baseline) for the treated eye angle parameters and a separate analysis for the untreated ones. These analyses would show differences through time for both groups, but not differences between groups. A second analysis was designed to show differences through time between treated and untreated eyes adjusted for differences at baseline. Analysis of covariance was used with this aim. Both groups were compared against each other at Visits 4, 5, 6 and 11 while these differences were adjusted for the differences between the same groups at Visit 1.

The association with time was investigated with mixed effects models (Using "R") between time elapsed since the LPI and the adjusted mean differences in the parameters found between the treated and untreated groups.

- 2nd Hypothesis: "There may be an association between, first, the widening effect on the angle and time elapsed since LPI (direct association) and, second, between this effect and a decrease in IOP levels (inverse association)"

  These associations were investigated using mixed effects models (Using "R"). The adjusted mean differences between the parameters for the two groups (treated and untreated) were associated to adjusted differences in time elapsed (first regression model) and IOP (second regression model) for both groups.

Section 4.2- Diurnal IOP fluctuation data of 29 participants who only received LPI (no subsequent ALPI treatment) during the study were analysed. The study design involved random selection of one eye of each participant for LPI treatment and the fellow eye was left untreated. Three months after the LPI was performed in these 29 randomly selected eyes, 19 eyes were considered to be open and 10 to be occludable using gonioscopy.

- 1st Hypothesis Methodology

To test this objective's first hypothesis of a reduction in DIOP fluctuation in those eyes treated with LPI, DIOP fluctuation 6 months (Mean 5.85 months; SD 0.37 months) after the LPI treatment was compared with their fellow untreated eyes. Analysis of covariance was used as this gave the advantage to adjust the model to the differences found at Visit

1 between the treated and their fellow untreated eyes. Three statistical models were carried out:

- 1st statistical model: Aimed to test if LPI reduced the DIOP fluctuation 6 months after the LPI independently of the outcome of the treatment (gonioscopically occludable or unoccludable eyes as diagnosed 3 months post-LPI, n=29). This was achieved by comparing the DIOP fluctuation of those treated eyes with their fellows at Visit 11 and adjusted for the data found at Visit 1.

- 2nd statistical model: To test if there was a reduction of DIOP fluctuation in those eyes with post-LPI unoccludable angles (n=19) when compared with their fellow eyes (n=19). This was achieved by comparing those treated eyes with gonioscopically open post-laser angles with their fellow eyes at Visit 11 (6 months after LPI) and adjusted for baseline data (Visit 1).
- 3rd statistical model: Comparing treated eyes that remained with occludable angles (n=10) with their fellow eyes (n=10) at Visit 11 and adjusted for baseline data (Visit 1).
- 2nd Hypothesis Methodology

To test the second hypothesis, which is that those eyes with occludable anterior chamber angles (established using gonioscopy, n=10), would show a higher diurnal IOP fluctuation than those with open anterior chamber angles after the LPI treatment (n=19), analysis of covariance was used. DIOP fluctuation, peaks and troughs were compared between those eyes with gonioscopically occludable angle (3 months post-laser) and those with an open angle (3 months post-laser). Only the data for the treated eyes was used and the statistical model was adjusted for Visit 1 differences (baseline, pre-LPI).

Section 4.3- Data from 24 eyes of 24 participants who only received LPI in the randomised eye were used in this analysis. Ten angle sections of the scans (light and dark conditions) of each of these eyes were analysed. These 10 sections account for the ones already described (Superior, Superior-Temporal, Nasal, Inferior-Nasal, Inferior, Inferior-Temporal, Temporal and Superior-Temporal) plus 2 new sections which are the sections on both sides of the angle in the meridian of the iridotomy, one on the side that incorporates the iridotomy and the other on the opposing side

Only two time points Visit 1 and Visit 11 were compared.

Chapter 5:

Section 5.1- The statistical analysis was split into two statistical sub-analyses.

The first analysis was aiming to assess the difference through time in the angle dimensions when assessing solely the eye that was treated with ALPI. This analysis used the paired samples t test to compare the parameter dimensions assessed at baseline (Visit 6, 12.55 days, SD 5.24 days, prior to ALPI) with the same data collected at Visit 8 (1 day after ALPI, SD 0.00 days), Visit 9 (7 days after ALPI, SD 0.89 days), Visit 10 (1.43 months after ALPI, SD 0.18 moths) and Visit 11 (2.39 months after ALPI, SD 0.30 months). Secondly, it was of interest to assess the differences in angle parameter dimensions between those participants whose angle remained gonioscopically occludable 3 months after LPI but did not receive further treatment (NFT group; n=10 eyes) compared to those whose angles were treated with ALPI (n=11 eyes). The comparison was carried out at two time points, Visit 6 (12.55 days, SD 5.24 days, before ALPI) and Visit 11 (2.09 months, SD 0.30, months after ALPI). Only those scans taken in dark conditions were quantified. The statistical analysis was performed using analysis of covariance to assess the differences in angle parameter dimensions depending on the group at Visit 11 while being adjusted for differences at Visit 6 (ALPI or NFT). For more schematic information please see Figure 5.1.

The second analysis, performed with mixed effects refression models, aimed to assess how the angle dimensions (parameters) change through time and if a relationship between this change and the IOP exists. The data those eyes whose angles were treated with ALPI (n=11 eyes) were used. To assess the relationship between IOP and time was not possible as the IOP for these participants were measured at different times of the day.

IOP and parameters dimensions data (scans in darkness) collected in Visit 6 (12.55 days, SD 5.241 days, before laser), Visit 8 (1 day, SD 0.00, after ALPI), Visit 9 (7 days, SD 0.894, after ALPI), Visit 10 (5.91 weeks, SD 0.944, after ALPI) and Visit 11 (3 months after ALPI) for those eyes treated with ALPI and NFT (when applicable) was statistically studied using analysis of covariance.

Section 5.2- To test the hypothesis that ALPI would decrease the DIOP fluctuation

The statistical analysis was designed to investigate the differences in DIOP fluctuation within the same eye before and after the ALPI (time lines: Visit 1 and Visit 11). As this group of eyes was already treated with LPI, it was necessary to isolate the effect of the ALPI. The way this was done was using the NFT (group of eyes with similar features as the ALPI group with the exception that they did not receive the ALPI). This was carried out using analysis of covariance at Visit 11 and

adjusted for the differences in DIOP fluctuation for the two groups. If a statistically difference was to be found, this would have been due to the effect of ALPI solely.

The mean time between ALPI, carried out in Visit 7, and Visit 11 was 2.39 months, SD 0.29 months.

Section 5.3- Analysis of variance followed by Tukey HSD was used to statistically test the differences in angle parameters for the different 10 sections in light and dark conditions and before and after the ALPI (time points: Visit 6 (12.55 days, SD 5.24 days, before ALPI) and Visit 11 (2.09 months, SD 0.302, after ALPI)) in the 11 eyes that received the treatment.

Chapter 6: The assessment of cell density and degree of polymegethism and pleomorphism in 7 different regions of the corneal endothelium (1 central and 6 peripheral: Superior, Superior-Nasal, Inferior-Nasal, Inferior, Inferior-Temporal and Superior-Temporal) were obtained with the TOMEY- 3000 non-contact specular microscope analysis software.
The statistical analysis was carried out in several statistical comparisons and divided in two parts.

The first part of the analysis was aimed to investigate the effect of the LPI on the corneal endothelium in terms of density of endothelial cells, pleomorphism and polymegethism compared to baseline. The measurements were taken before LPI was performed at Visit 1 (2.31 weeks; SD 2.34 weeks, pre-LPI) and after LPI at the following visits: Visit 2 (1:54 hours; SD 25 minutes, post-LPI), Visit 3 (1 day; SD 0.00, post-LPI), Visit 4 (1.10 weeks; SD 0.13 weeks, post LPI), Visit 5 (1.44 months; SD 0.18 months, post-LPI), Visit 6 (3.05 months; SD 0.27 months, post-LPI) and Visit 11 (5.83 months; SD 0.37 months, post-LPI).

The second part of the analysis aimed to investigate the effect of the ALPI on the corneal endothelium (same parameters studied as for the LPI and specified in the paragraph above). The data used in this part of the analysis was collected from eyes whose angles remained occludable 3 months after the LPI. Only 11 of these 21 eyes were randomised to receive the ALPI and the analysis focused on this group. Data from baseline, in this case Visit 6 (1.79 weeks; SD 0.75 weeks, pre-ALPI), and consecutive posterior visits, Visit 7 (1:32 hours; SD 31 minutes, post-ALPI), Visit 8 (1 day; SD 0.00, post-ALPI), visit 9 (1 week; SD 0.13 weeks, post-ALPI), Visit 10 (1.43 months, SD 0.18 months, post-ALPI) and Visit 11 (2.39 months; SD 0.29 months, post-ALPI) were used for the statistical analysis.

The objective was studied in two groups of eyes:

Group 1- Forty eyes treated with LPI and their untreated fellow eyes. The data for those eyes that had received the ALPI were excluded in Visit 11.

Group 2- Twenty-one eyes with occludable angles after LPI, for which eleven received ALPI. Their fellow eyes were not included, but those occludable eyes that were randomised to not to receive ALPI (n=10) acted as the control eyes for the evaluation of the ALPI effect.

With the aim of studying the effect of the lasers through time, paired samples t-test was performed between the baseline visit and each of the consecutive visits. This analysis was performed in the treated and in the untreated fellow eye, using this latter as a control.

A second aim was to find if there were differences in the effect of these lasers when treated and untreated eyes were compared. This was achieved through analysis of covariance and adjusting all the models for the data found at baseline.

CHAPTER 3. Diurnal and postural characteristics of IOP in Caucasian patients with angle closure and the relationship with the anatomy of the anterior chamber angle

3.1 Study of the diurnal and postural characteristics of IOP in Caucasian patients with angle closure

3.1.1 Introduction

Raised IOP is an important risk factor for glaucoma, and is the principal modifiable factor in the treatment of patients with and at risk of glaucoma. Measurement of IOP in the clinical setting usually involves a single measurement with the patient in an upright seated position. However, it is recognised that there can be considerable variability of IOP during the day (diurnal fluctuation) and that changes in posture can also result in marked increase in IOP. IOP and the presence or absence of peripheral anterior synechiae (PAS) is used by clinicians to categorise a patient into differing disease categories that reflect a differing risk for glaucoma and which can be categorised into PACS and PAC (Foster, Buhrmann, Quigley and Johnson, 2002). It is important therefore to understand how such a single IOP measurement in the seated position, is reflective of the diurnal seated IOP variation. The majority of studies that have investigated such IOP characteristics have been conducted in individuals with open anterior chamber angles. Given the considerable burden of patients diagnosed with angle closure in Caucasian populations, there is a need to investigate these IOP characteristics in individuals with occludable anterior chamber angles. Diurnal measurement of IOP is an important management tool when diagnosing or treating patients with open angle glaucoma, and there is therefore an interest in understanding these IOP characteristics in those with closed angles.

Several studies have reported diurnal fluctuation of IOP for normal (non-glaucomatous) and glaucomatous eyes (Barkana, et al., 2006; Baskaran, et al., 2009; Realini, Weinreb and Wisniewski, 2010). A literature search failed to identify a study of diurnal IOP fluctuation among untreated individuals with angle closure in the absence of glaucoma. In a study of patients whose eyes had previously been treated with LPI with a diagnosis of PAC or PACG, Baskaran, et al. (2009) reported higher levels of fluctuations in these patients (fluctuation defined as the difference between peaks and troughs of diurnal intraocular pressure). PAC and PACG patients presented a level

diurnal fluctuation of 5.4±2.4 and 4.5±2.3 mmHg respectively, (IOP measured every hour from 8:30 to 16:30h) compared to those with PACS and normal subjects with open angles, 3.7± 1.2 and 3.8.±1.1 mmHg, respectively. The same study reported an association between the degree of PAS and the diurnal fluctuation of IOP in same eye of patients of Chinese origin. Like IOP, the presence or absence of PAS is used as a criterion to classify patients into diagnostic categories that are considered to indicate different risks of glaucoma. PAS are areas of iridotrabecular contact and have been shown by a histological study to be accompanied by surrounding damage to the trabecular meshwork (Sihota, et al., 2001).

Given the limited evidence described above, one might hypothesise that eyes with occludable angles in the absence of glaucoma would exhibit a greater range of IOP (greater IOP 'fluctuation') within the diurnal period than healthy eyes with open angles. One might also hypothesize that the presence of PAS, a sign of damage to the trabecular meshwork, would be associated with greater IOP fluctuation.

IOP is known to change with a change in posture, with a higher IOP measured in the supine position than the upright seated position, the latter posture being the usual position of the patient in clinical practice. This postural difference in IOP has been reported in patients with glaucoma (Yamabayashi, 1991) and without glaucoma (Lam and Douthwaite, 1997), the explanation being most probably a rise in episcleral venous pressure associated with a supine posture (Blondeau, Tetraul and Papamarkakis, 2001; Friberg, Sanborg and Weinreb, 1987). These aforementioned studies have been conducted in patients with eyes that have open anterior chamber angles. It may be hypothesised that eyes with angle closure would exhibit different postural changes in IOP, given the anatomical relationship of the iris in relation to the trabecular meshwork. The darkroom provocation test involves placing a patient in a prone position in a dark environment. This test is used to guide clinicians as to the likelihood of an acute rise in IOP, given that the gravitational effect of the prone position and pupil dilation would accentuate the narrowing of the angle. It was hypothesised that eyes, in which PAS are present, may have a more marked rise in IOP following the dark room provocation test.

3.1.2 Methodology

Intraocular pressure measurements performed on the participants' first visit were used. Diurnal Intraocular Pressure (DIOP) data was available for all 40 participants. Two participants were unable to perform the Dark Room Provocation Test (DRPT) and one could not undergo the Supine

Intraocular Pressure (SIOP) investigation, on account of difficulties adopting a prone or supine position.

The intraocular pressure (IOP) was performed every hour from 9:00h to 16:00h, a total of 8 measurements formed the DIOP. The SIOP was performed as close to noon as possible (SD around 12:00 was 1:16h) and it was defined as the difference between the earlier DIOP measurement (seated measurement) and the IOP in a supine position measured 5 minutes after adopting this posture.

The DRPT was performed after the SIOP at approximately noon (variation around this time, SD 1:14hours), and it was defined as the difference found between the IOP measured in the seated position before and 15 minutes after the participant had adopted a prone posture in a dark environment (lux $\leq$ 0.5).

Gonioscopy was performed by the same consultant ophthalmologist for all participants.

For further information about the methodology and instrumentation used in these tests, please refer to Chapter 2 of this thesis.

3.1.3 Results

Diurnal Intraocular Pressure (DIOP)

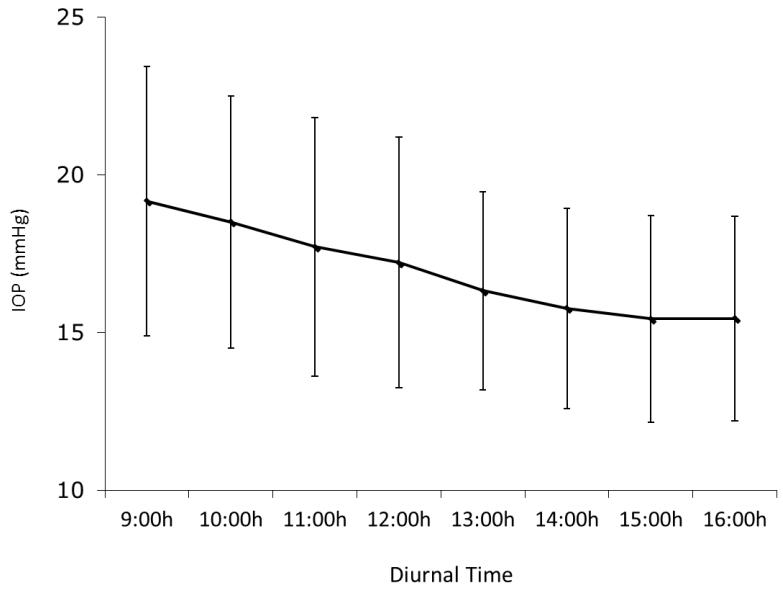

Figure 3.1. Mean values and standard deviation for 80 eyes with gonioscopically occludable anterior chamber angles (40 patients)

The mean peak of DIOP for the 80 eyes of the sample at every diurnal hour of measurement is represented in Figure 3.1. The peak for this sample of means was 18.5 mmHg (4.27SD; Range: 12.0- 30.5) and was found to be at 9:00 hours.

Inspecting the individual DIOP peak for every participant, this was found to be at 9:00h for 28 participants, at 10:00h for 5 participants, at 11:00h for 4, at 13:00h for 1, at 14:00h for 3 and at 15:00h for 1. In summary, the maximal IOP was measured in the morning (9:00 to 11:30h) for the majority of participants. The maximum IOP value between eyes of every participant was chosen to decide the final participant's DIOP peak.

Effect of the presence of Peripheral Anterior Synechiae (PAS) in the Diurnal Intraocular Pressure (DIOP)

Figure 3.2 shows DIOP measured for two groups of eyes, those with PAS (n=31) and those without (n=49). The mean IOP at each time point appears higher in eyes with PAS.

A repeated measures analysis of variance showed a significant decline in IOP as the day progressed ($p<0.001$), which was independent of whether an eye had PAS or not. In other words, there was no significant interaction between Presence/Absence of PAS and time of measurement ($p=0.458$).

However, there was an overall significant effect of presence of PAS on IOP across all time points of the DIOP. An average of difference between means was found to be 1.5 mmHg higher for those eyes with PAS, $p=0.043$. This effect was independent of the time of measurement. Therefore eyes with PAS would exhibit higher average DIOP than those eyes without PAS.

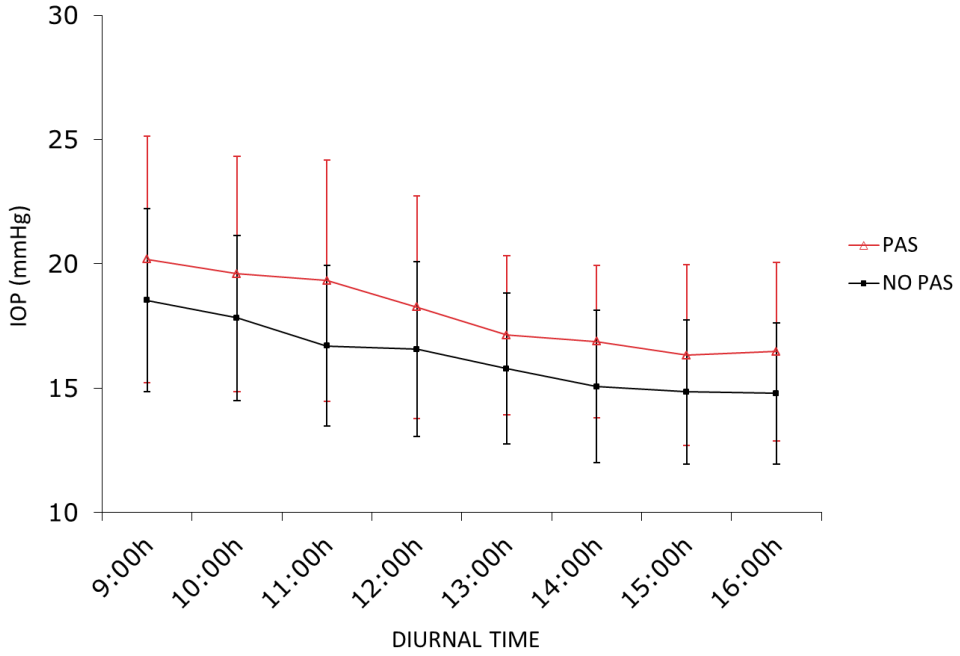

Figure 3.2. Mean IOP differences between Presence of PAS and Absence during the DIOP times.

The circumference of PAS (measured in degrees)* and DIOP showed a statistically significant association (calculated using univariate regression), at every time measurement of the DIOP. These models showed a similar relationship between the dependent (IOP at different times-DIOP) and the predictor (degree of PAS), which were all statistically significant except the measurement taken at 12:00h. Please see Table 3.1 for p values, standardized coefficients and R^2. All the standardized coefficients showed a direct association between IOP levels and degree of PAS, meaning that an eye with a higher degree of PAS would exhibit higher levels of IOP.

*The variable circumference of PAS included eyes without PAS (cero degree of PAS).

	Univariate Regression Analysis Degree of PAS (independent)		
	Standardized Coefficients	Adj. R^2	P value
IOP at 9:00h	0.341	0.105	0.002*
IOP at 10:00h	0.341	0.105	0.002*
IOP at 11:00h	0.332	0.099	0.003*
IOP at 12:00h	0.197	0.026	0.080
IOP at 13:00h	0.312	0.086	0.005*
IOP at 14:00h	0.282	0.068	0.011*
IOP at 15:00h	0.261	0.056	0.021*
IOP at 16:00h	0.288	0.071	0.011*

Table 3.1. Univariate regression over IOP measurements adjusted for degree of PAS at every time-hour of the diurnal IOP. Statistically significant p values have been flagged with an asterisk.

Diurnal Intraocular Pressure Fluctuation (DIOP Fluctuation) and the presence of Peripheral Anterior Synechiae (PAS)

The average fluctuation in DIOP was defined as the difference between the average for the maximum value of IOP attained during the DIOP (20.03 mmHg; SD 4.18) and the minimum for a given eye (14.04mmHg; 2.82). The mean fluctuation for this sample of eyes was found to be 5.99 mmHg (2.70 SD); paired samples t test $p<0.001$. An interesting finding was the range of fluctuation, showing a variation from as little as 1.50 mmHg to as much as 14.50 mmHg.

A regression model was fitted in order to investigate an association between DIOP fluctuation and age, gender, presence/absence of PAS and circumferential degrees of PAS.

When this model was fitted with age and gender adjusted (univariate and multivariate model), no association among factors was found for presence/absence of PAS or circumferential degrees of PAS and range of fluctuation of DIOP. For p values, standardised coefficients and R^2 please refer to Table 3.2.

	Univariate Regression Analysis			Multivariate Regression Analysis		
	Standardized Coefficients	P value	Adj. R^2	Standardized Coefficients	P value	Adj. R^2
Gender	-0.061	0.590	-0.009	-0.043	0.705	-0.014
Age	0.114	0.316	0.000	0.150	0.242	
Presence/Absence of PAS	-0.055	0.625	-0.010	-0.178	0.251	
Degree of PAS	0.045	0.691	-0.011	0.182	0.242	

Table 3.2 Univariate and multivariate regression models over DIOP fluctuation with age, gender, presence/absence of PAS and degree of PAS adjusted.

Supine Intraocular Pressure (SIOP)

The difference between mean values of IOP measured in the supine versus the upright position was 1.7mmHg (2.12 SD; paired samples t-test, $p<0.001$). Supine and upright posture IOP was highly associated (Standardised Coefficient 0.868, $p<0.001$). This is represented in Figure 3.1. The majority of eyes (50 eyes out of 78 eyes, 64.10%) were found to have higher pressures after the participant adopted a supine position for 5 minutes.

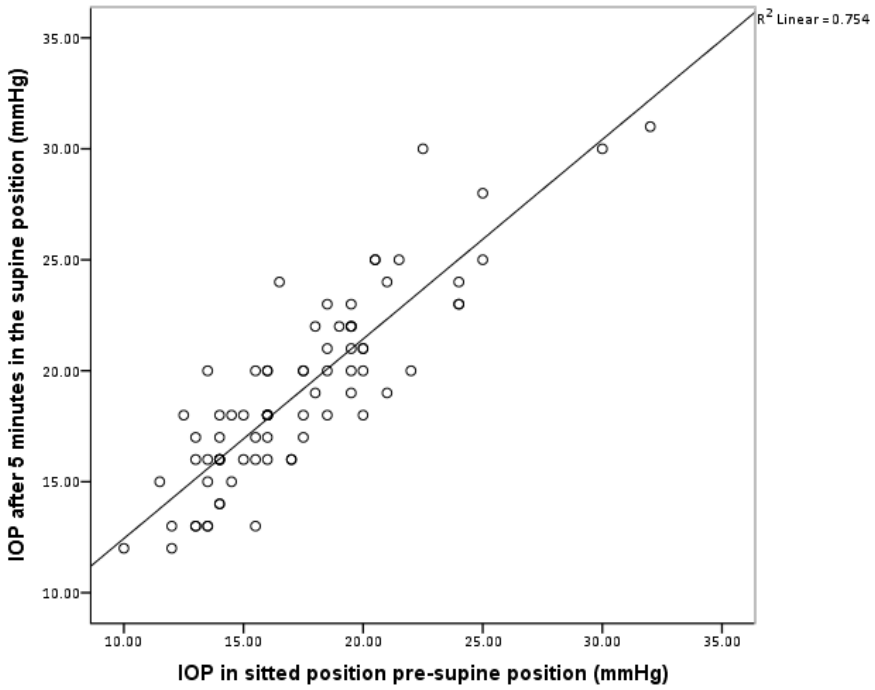

Figure 3.3. Scatter plot of the IOP measured in 78 eyes of before and after the adoption of a supine posture from a seated position (SIOP)

Association of Peripheral Anterior Synechiae (PAS) with the Supine Intraocular Pressure (SIOP)

The mean value for the Supine Intraocular Pressure (SIOP) found in those eyes with presence of Peripheral Anterior Synechiae (PAS), (n=31), was 1.50 mmHg (SD 2.50 mmHg) while for those without PAS (n=47) it was slightly higher 1.83 mmHg (1.85 mmHg). An independent sample t-test showed no statistically significant difference between the mean values for postural difference in IOP between eyes with PAS and without PAS (Mean difference between groups 0.33 mmHg; p=0.116).

When univariate regression was used to test the association between circumferential degrees of PAS and postural change in IOP, no statistically significant association was found (Univariate regression: Standardised Coefficient 0.109; Adjusted R^2 0.012; p value=0.341). This is visually represented in the graph below (Figure 3.4)

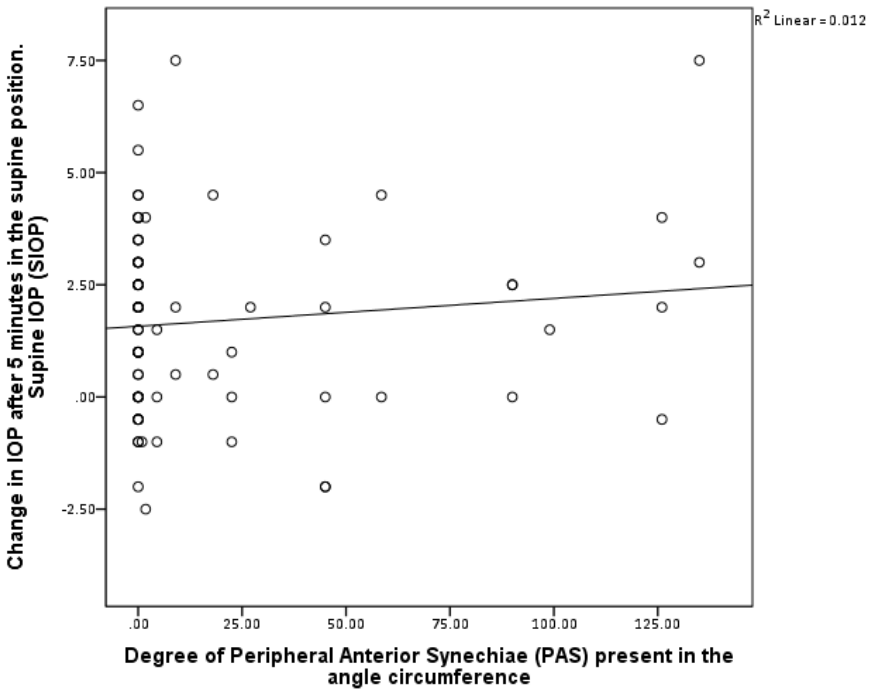

Figure 3.4. Scatter plot of the resulted SIOP measured in 78 eyes against the degree of PAS found in the same eyes.

The plot above shows the lack of relationship between the amount of PAS present in an eye and the difference of IOP found as a result of being in the supine position for 5 minutes.

The Dark Room Provocation Test (DRPT)

The mean difference in IOP before and after the dark room provocation test was 3.05mmHg (SD, 2.85 mmHg, paired samples t-test, $p<0.001$). IOP measured before and after this test was highly associated (Figure 3.5, Standardised coefficient, 0.802; $p=0.003$). Higher IOP post-provocation was noted in 63 eyes (82.9%).

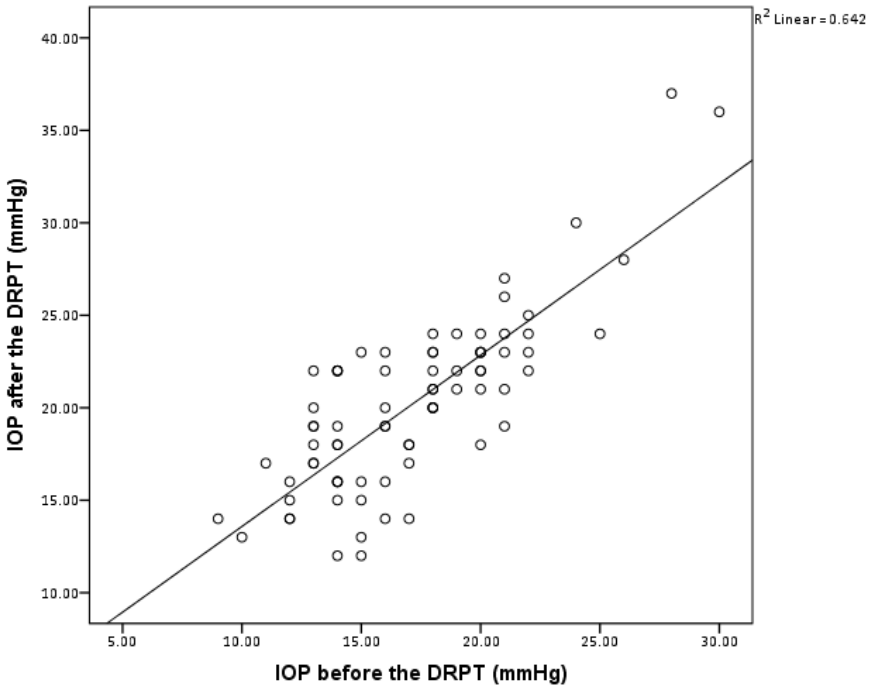

Figure 3.5. Scatter plot of the IOP measured in this sample showing the relationship in IOP levels found before and after the DRPT

Association of Peripheral Anterior Synechiae (PAS) and the Dark Room Provocation Test (DRPT)

Of the 76 eyes in this analysis, there was no statistically significant difference between eyes with PAS (n=31) and eyes with no PAS (n=45) before and after dark room provocation (independent samples t test, p=0.895). Furthermore, the circumferential degrees of PAS present in an eye was not statistically significantly correlated to higher levels of IOP after the DRPT (Univariate regression; Standardised Coefficient – 0.127; Adjusted R^2 0.016; p value=0.274). A visual representation of this regression can be found in Figure 3.6 (next page).

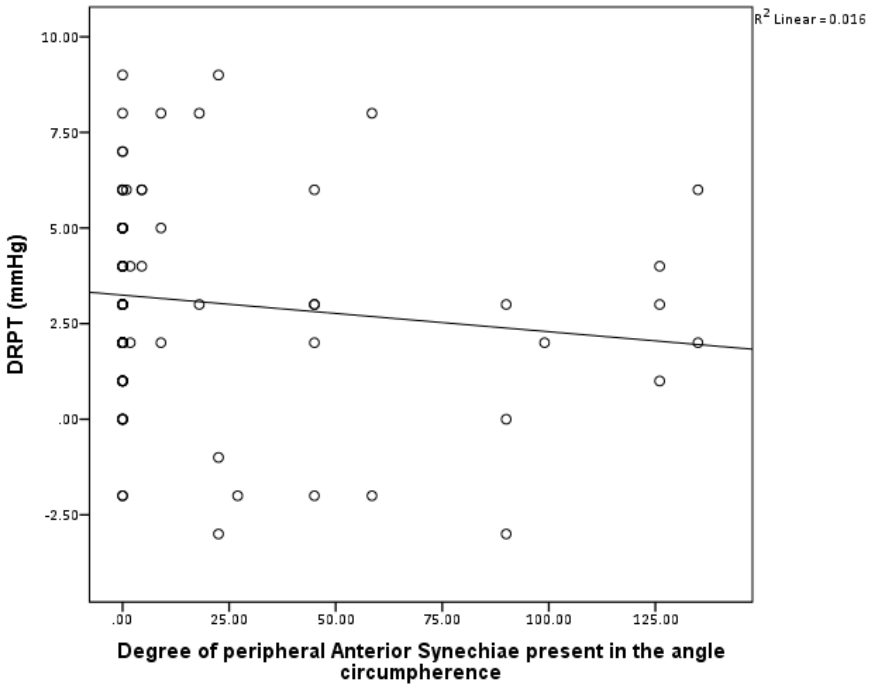

Figure 3.6. Scatter plot of the resulted SIOP measured in 78 eyes against the degree of PAS found in the same eyes

3.1.4 Discussion

Of 80 eyes of 40 patients examined at Visit 1, 49 were diagnosed as PAC and 31 as PACS. From those eyes diagnosed as PAC, 17 were due to presence of PAS only and 18 were due a raised IOP only (IOP higher or equal to 21mmHg at any time between 9:00 and 16:00 hours) and 14 were due to a combination of PAS and IOP criteria. Of the 18 eyes diagnosed with PAC due to IOP levels only, 15 would have been diagnosed as PACS had the IOP measurements been taken in the afternoon (12:30h to 16:00h). This highlights the observation that the timing of a single IOP measurement by a clinician is of importance when considering what diagnosis to ascribe a patient with angle closure. In this case, 6 participants might be ascribed the lower risk PACS diagnosis, had the single afternoon IOP measurement been the only measure used to reach a diagnosis. The management and follow-up of patients may be very different with patients with PAC than with those with a diagnosis of PACS.

Wilensky (1991) observed that 65% of normal subjects (defined as subjects with normal IOPs, normal visual acuity, healthy optic nerve heads and no history of ocular disease) had diurnal IOP peaks between 8:00 and 14:00h while 30% exhibited a peak IOP between 04:00 and 08:00. Differing results were reported for those diagnosed as ocular hypertensive (IOP >22mmHg and no signs of glaucoma) where 51% presented their peaks between 4:00 and 8:00 and 42% between

8:00 and 14:00. In the case of the present study, if an equivalent IOP based criterion (cut off of 22mmHg) to that of Wilensky et al. is used and PAS presence is not taken in account, 28 of 40 participants (70%) had IOP≤ 22mmHg in both eyes during the DIOP. Of these 28 participants, 27 (96%) exhibited an IOP peak between 9:00 and 14:00h. From the participants showing IOP>22mmHg in at least one eye (n=12), 100% showed their peak between 9:00h and 11:00h. To summarize, in both this study and that of Wilensky, diurnal peaks are more frequently found in the morning than in the late afternoon (after 14:00h) and this was independent of a particular IOP cut off.

The DIOP curve profile found for this group of subjects is similar to that in a study described in the literature for 21 healthy individuals in a similar age group and ethnicity (15 out of 21 were Caucasian), (Liu, et al., 1999). There was a peak in the early morning of approximately 18mmHg, decreases through the morning to levels of 17mmHg, with a moderate increase in the middle of the day (12:00h) of about half a mmHg, decreasing to levels of 17 mmHg in the early evening (16:00h). It is curious that, despite the fact that the participants in the present study had narrow angles and higher DIOP fluctuation, the DIOP curves behaved similar to patients with open angles from other studies.

To date there have not been any studies published that report the association of PAS with the DIOP curve. The present study has found a statistically significant effect of presence of PAS over the DIOP curve. An eye with PAS would exhibit an average of nearly 1.5 mmHg higher than an eye without PAS. Furthermore, the degree of PAS present in an eye was found to be directly associated with an increase in IOP at the majority of the diurnal times.

The fluctuation of DIOP was not related to age, gender or PAS. This result differs from a report by Baskaran, et al. (2009), where association was found between fluctuation and degree of PAS. In the case of the present study the lack of an association is not unexpected given that the DIOP curves of those eyes with presence of PAS and those eyes without were very similar (Figure 3.2). Although there may have been differences between the peaks and troughs between curves, the fluctuation obtained would have been similar. It has to be mentioned that in Baskaran's study, the data showed a high degree of variation and, although the association was reported as statistically significant (p= 0.013), the association was weak (R^2, 0.139). However, this does not fully explain the differences between studies.

Lam and Douthwaite (1997), using non-contact tonometry, found that after 8 minutes in the prone position the IOP increased from 13.5±2.01 mmHg (sitting position) to 20.0±3.27 mmHg (prone position) in individuals without any ocular pathology. An increase from 12.7±1.90 mmHg

(sitting position) to 14.1±1.92 mmHg (supine position) was found when the same individuals adopted a supine position for the same period of time (illumination 370lux). Even higher levels of IOP measured in the prone position were reported in individuals with normal eyes by Walick, Kragh, Ward and Crawford, (2007), where levels of IOP increased from 19.3±2.9 mmHg (sitting position) to 29.7±4.1 mmHg (prone position) after 10 minutes. Buchanan and Williams (1985) found a difference between the mean IOP measured for upright and post-supine postures of 4.11±1.82 mmHg with contact tonometry, but the duration of the test was not specified. When individuals remained for a longer duration in the supine position (30 minutes), the result was found to be higher; increases of 4.4mmHg (2.0 SD), 4.1 mmHg (1.8 SD) and 4.0 mmHg (SD 2.0) were found for normals (no ocular pathologies influencing IOP), low tension glaucoma and ocular hypertensive individuals, respectively (Yamabayashi, et al., 1991). It is interesting that the glaucomatous and ocular hypertensive individuals exhibited lower differences in IOP due to change in position as these individuals were not taking ocular hypotensive medication prior to or during the study. In the present study, a direct association has been found between the IOP levels prior and post supine; meaning that the higher the first, the higher the second. As ocular hypertensive eyes are diagnosed based on high IOP measurements made in the seated position, it might be expected that this group would exhibit the highest IOP variation.

When comparing published IOP results with those found in this study thesis, the rise in IOP level following adoption of a prone posture (DRPT) from the seated position is approximately half of that found by Lam and Douthwaite. However, the change in IOP from seated to supine postures was very similar. The differences between this study and those of Yamabayashi might be due to differences in instrumentation. They used the Alcon Pneumatonograph and, although care was taken in checking the calibration of this device on a regular basis, comparison with the Goldmann tonometer was not performed. It is further unlikely that these differences were caused by the duration of the tests as the change in IOP in the supine position was immediate and remained stable for the next 30 minutes.

The DRPT results differences between the present study and that performed by Lam and Douthwaite and Walick, Kragh, Ward and Crawford, may be explained on account of the different methods of measurement. In this study measurements were taken in the seated position before and immediately after the test while in these other published studies the second measurement was performed with the patient remaining in the prone position.

The IOP measurements after adopting a supine posture (SIOP) and following darkroom provocation (DRPT) were strongly and positively associated to the IOP measured at baseline in the seated position. Meaning that the higher the IOPs were prior the tests, the higher they were going to be after the tests. This was unsurprising as the majority of the eyes presented higher IOPs after the test.
However, and as explained previously, these postural changes in IOP were frequently lower than in previous literature.

3.1.5 Conclusion

Clinicians should be aware of changes in IOP that occur throughout the day in patients with occludable anterior chamber angles and that the circumferential extent of PAS is associated with higher IOP levels during the day compared to normals. In clinical centres where laser peripheral iridotomy is only applied to those individuals with a more advanced pre-glaucomatous stage (PAC), the present findings would support measuring IOP in the early morning to establish the maximal IOP.

It has been shown that adoption of a supine or prone position will raise the IOP of the majority of individuals. The data show that the presence of PAS was not associated with larger postural excursions of IOP with either the DRPT or the supine test.

3.2 Investigation of static and dynamic anatomical characteristics of eyes with gonioscopically occludable anterior chamber angles using ocular coherence tomography: Is there an association with IOP?

3.2.3 Introduction

Different anterior segment imaging devices have been used in the past to describe dimensions and structures of the anterior segment of the eye. These include the ultrasound biomicroscope (UBM), the Orbscan, the Pentacam with rotating Scheimpflug imaging and the 2 dimensional Anterior Segment Optical Coherence Tomography (2D AS-OCT) instruments.

There are certain advantages of one instrument over another depending on the structures that one wishes to image and the convenience of image acquisition. The AS-OCT offers images of the anterior chamber angle at a higher resolution than the UBM and the acquisition, of a non-contact character, is taken with the patient in a seated position. When comparing AS-OCT to the Pentacam and Orbscan, the three devices are non-contact, however, only the AS-OCT offers direct angle visualisation (Konstantopoulos, Hossain and Anderson, 2007), which is necessary for the quantification of the angle parameters.

In terms of depth of imaging, the UBM can provide visualization of more posteriorly located structures such as the retroiridial structures (Ursea and Silverman, 2010) and the Orbscan and Pentacam may also be used to monitor cataract formation in the crystalline lens (OCULUS Optikgeräte GmbH, 2008).

When evaluating the irido-corneal angle, one study suggested an excellent correlation with gonioscopical findings when using UBM and 2D AS-OCT. In the same study, sensitivity and specificity for detecting occludable angles when comparing to gonioscopy findings were found to be slightly better with 2D AS-OCT than with UBM (Radhakrishnan, Huang and Smith, 2005). Additionally, a more recent study showed poor agreement in the anterior chamber dimensions measurements taken with 2D AS-OCT and the UBM (Mansouri, Sommerhalder and Shaarawy, 2010). Between the Pentacam and the 2D AS-OCT there were no significant differences when the angle was estimated in degrees (Yi ,et al., 2008) or when comparing sensitivity for diagnosis of narrow angles between devices (Hong, et al., 2009).

Imaging techniques, such as those described above, have been frequently used in the past for monitoring changes in the angle. Specifically, the UBM (Marraffa, et al., 1995; Gazzard, et al., 2003; Kaushik, et al., 2007; He, et al., 2007, Mansouri, Burgener, Bagnoud and Shaarawy, 2009),

Pentacam (López-Caballero, et al., 2010; Antoniazzi, et al., 2010; Li, et al., 2010) and the 2D AS-OCT (Chalita, et al., 2005; Memarzadeh, et al., 2007; See, et al., 2007; Lei, et al., 2009; Ang and Wells, 2010) have previously been used to quantify anterior chamber dimensions following LPI. Additionally, the 2D AS-OCT has been used for screening and diagnosis of occludable angles (Nolan, et al., 2007) and in studies investigating the mechanism of angle closure (Leung, 2007; Liu, 2008; See, et al., 2007).

In summary, the AS-OCT does not involve contact with the eye which makes this a more acceptable technique than UBM for patients. When comparing the AS-OCT with the Orbscan and Pentacam in general terms, the main advantage of the AS-OCT is high-resolution visualization of the angle recess area and a more comprehensive quantification of the angle dimensions using the analysis software supplied with this instrument.

New advances in AS-OCT technology has made 3-dimensional (3D) swept-source OCT now possible. This technology based on the Fourier Domain technique gives the highest scanning resolution (11.6μm axial) for the angle space currently described (Yasuno, et al., 2009). As the analysis of the angle is based on the accurate detection of the scleral spur, it is expected that this higher resolution would give a more precise identification of its position. A study that compared 2D and 3D AS-OCT devices found no significant difference in central corneal thickness or anterior chamber width between them, but the intraclass coefficients of repeatability and reproducibility were marginally higher with the 3D AS-OCT device (Fukuda, Kawana, Yasuno and Oshida, 2010). These findings and the advantages of AS-OCT mentioned above, led to the decision to use this instrument for measurement of anterior chamber angle dimensions in this study.

Most published literature involving the 2D AS-OCT reports on the horizontal and vertical meridians of the eye when monitoring changes or making a diagnosis with the 2D AS-OCT (Nolan, et al., 2007; Lavanya, et al., 2008; Mansouri, Burgener, Bagnoud and Shaarawy, 2009; Ang and Wells, 2010). It is unknown how representative these dimensions are of the entire circumference of the anterior chamber angle. After all, the established technique of gonioscopy, on which clinical management decisions are based, involves a decision made on visibility of the structures in each of the four quadrants of the angle. Therefore an important objective of this thesis was to investigate how meridians differed in dimensions within individual eyes.

Peripheral anterior synechiae are believed to occur as a result of prolonged apposition of the root of the iris against the trabecular meshwork. Intuitively, one would expect more coverage of PAS in a given sector of the angle of an eye to be associated with smaller dimensions for that angle

section. Su, et al., (2008) reported a weak correlation between the angle width and the extent of PAS.

The relationship between degree of narrowing of an anterior chamber angle and fluctuation of diurnal IOP (during office hours) remains unexplored (Baskaran, et al., 2009). One may hypothesise that eyes with narrower anterior chamber angles would exhibit a greater diurnal variability in IOP. There may also be a relationship between degree of angle narrowing and the change in IOP associated with a change in posture between upright and supine positions, or in association with the changes in IOP associated with the darkroom provocation test. These relationships have not been tested previously.

Wang, et al. (2010) found a statistically significant association between numbers of closed sections in the angle of a given eye in dark conditions and a positive result in the dark room provocative test (DRPT). A possible association between higher IOPs after prone position in darkness and narrower dimensions of the anterior chamber angle parameters therefore deserves study and is an aim in this Section 3.2. These questions have important clinical relevance in terms of advice for patients and predictions of those eyes that have more risk with changes in posture or light levels.

3.2.2 Methodology

The collection of IOP data for the purpose of investigating IOP fluctuation, and the results of the dark room provocation test (DRPT) and supine IOP (SIOP) tests have been described previously. Three-dimensional AS-OCT (Casia device, Tomey, Japan) images were obtained on the same day as these IOP measurements. The scans were taken in darkness (between 0.3 and 0.5 lux) and in light conditions (between 170 and 199 lux) and the images taken were subsequently analysed using the commercially available software with this instrument. Acquisition and analysis of images was undertaken by the same examiner (LSP) throughout.

The analysis of AS-OCT images acquired in dark and light conditions involved calculation for each eye of the following parameters: the angle opening distance (AOD), the trabecular-iris angle (TIA)(Pavlin, Harasiewicz and Foster, 1992), the angle recess area (ARA) (Ishikawa, et al., 1999) and the trabecular iris space area (TISA)(Radhakrishnan, Huang and Smith, 2005). Figure 3.7 gives a visual representation of these angle parameters.

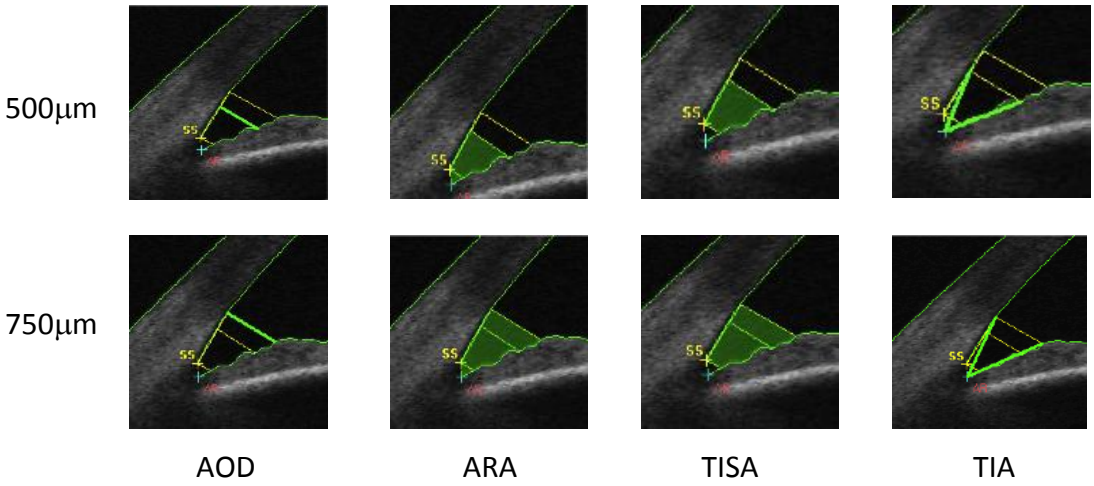

Figure 3.7. Irido-trabecular angle parameters as measured with the CASIA AS-OCT analysis software. AOD (Angle Opening Distance), ARA (angle Recess Are), TISA (Trabecular-Iris Space Area) and TIA (Trabecular-Iris Angle) at 500 and 750µm are highlighted in bright green colour.

These parameters were quantified in 8 different sections of the angle (Superior, Superior-Nasal, Nasal, Inferior-Nasal, Inferior, Inferior-Temporal, Temporal and Superior-Temporal) and at 500 and 750µm from the scleral spur. Figure 3.8 gives a schematic view of these angle sections:

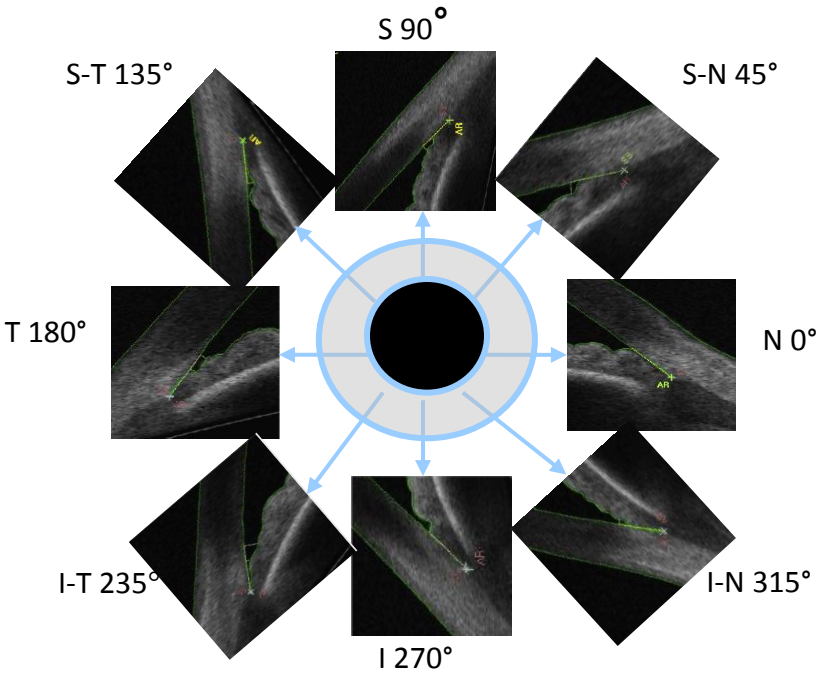

Figure 3.8. Schematic explanation of the eight irido-trabecular angle sections under study (please note that these are corresponding to a Right Eye). The abbreviations found in this figure are those corresponding to the sections and position-degree in the ocular circumference. Abbreviations: S=Superior (90 degrees), S-N=Superior-Nasal (45 degrees), N=Nasal (0 degrees), I-N= Inferior-Nasal (315 degrees), I=Inferior (270 degrees), I-T=Interior-Temporal (235 degrees), T=Temporal (180 degrees), S-T=Superior-Temporal (135 degrees).

To facilitate the interpretation of the results, these 8 sections were grouped into 3 independent sectors, Superior, Horizontal and Inferior. The Superior Sector incorporated Superior, Superior-Nasal and Superior-Temporal Sections; the Horizontal Sector the Temporal and Nasal Sections; while the Inferior Sector comprised the Inferior, Inferior-Temporal and Inferior-Nasal sections. Right and left eyes of 35 participants were included in the analysis. Five out of a total of 40 participants in the study were imaged with a different AS-OCT device at the beginning of the study therefore their results were excluded for this analysis. The justification for using both eyes of every participant is explained in detailed in the Appendix 2 of this thesis.

Diagnostic criterion for angles when using AS-OCT

A section of angle was diagnosed as closed if there was contact anterior to the scleral spur at any point between anterior iris surface and posterior corneal surface (trabecular meshwork or corneal endothelium). Therefore, as with the criterion followed for gonioscopy, an angle was diagnosed as closed if 2 or more sections were closed when using 4 sections for the diagnosis or if 4 or more sections were closed when using 8 sections for the diagnosis.

3.2.3 Results

Assessment of variability among the anterior chamber angle parameters for different angle sections

When comparing the mean (n=70 eyes) value for each of the angle parameters (AOD, ARA, TIA, TISA) in each imaged section of the eye, the lowest values (i.e. the narrowest section) in light and dark conditions for every parameter were found in the Superior section. The sections where angle parameters were largest (i.e. widest angle) were noted in Nasal and Inferior-Nasal sections for both light and dark conditions. Among the parameters investigated, only mean values for TISA 500 were found to be maximal in the Temporal section under light conditions. This can be visually observed in the following graphs (Figures 3.9 to 3.16).

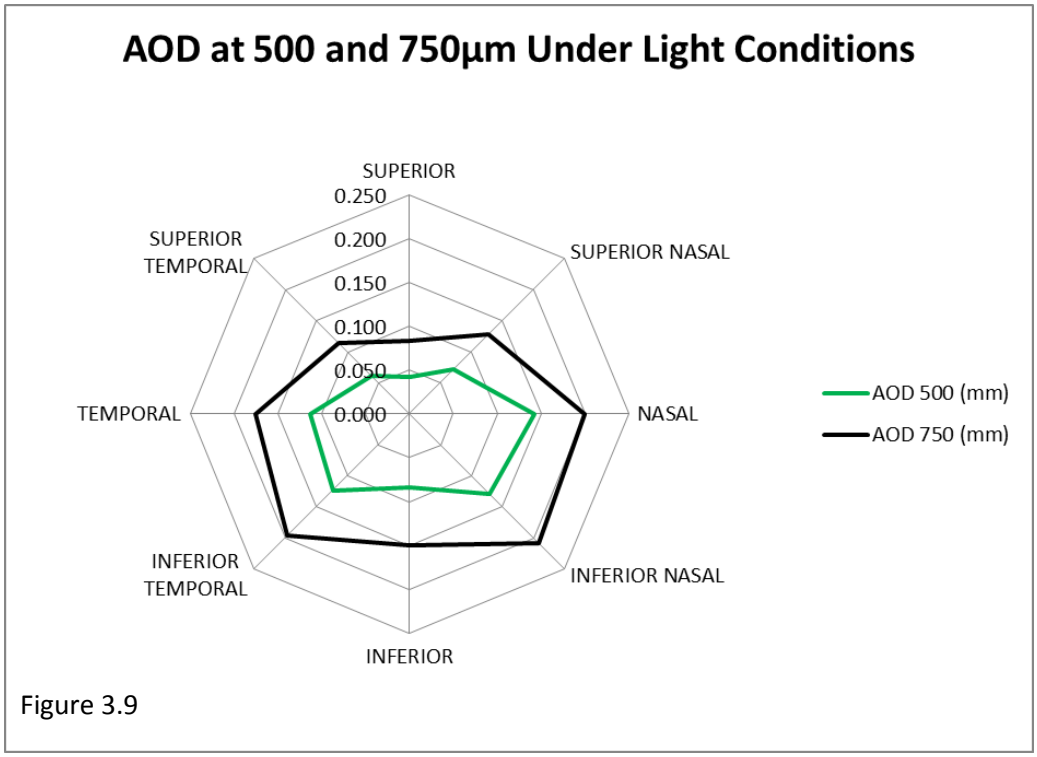

Figure 3.9

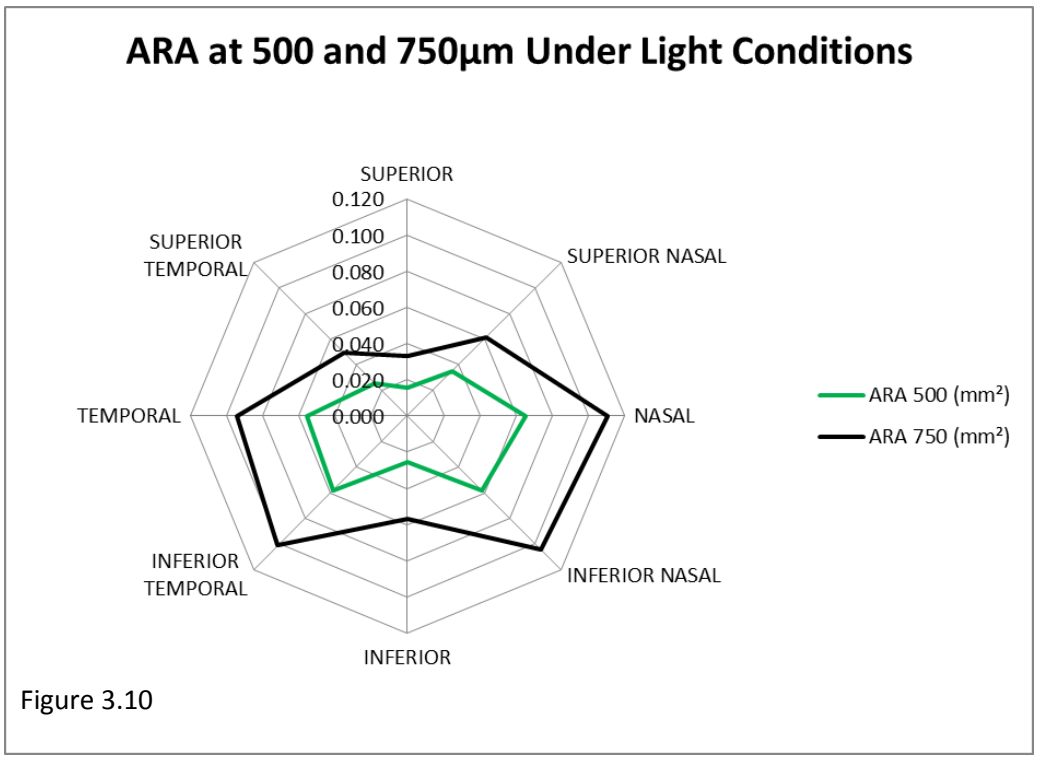

Figure 3.10

Figures 3.9 and 3.10. Mean value of AOD (Angle Opening Distance) and ARA (Angle Recess Area) at 500 and 750µm for 70 participants under light conditions for eight sections of the angle under light conditions

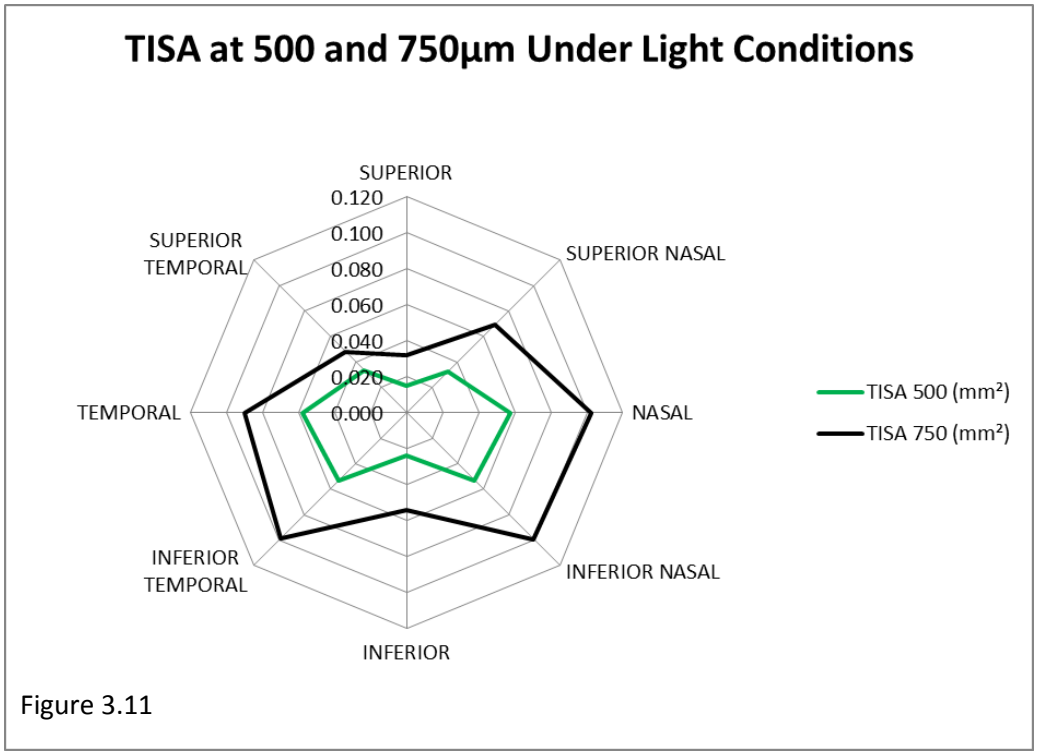

Figure 3.11

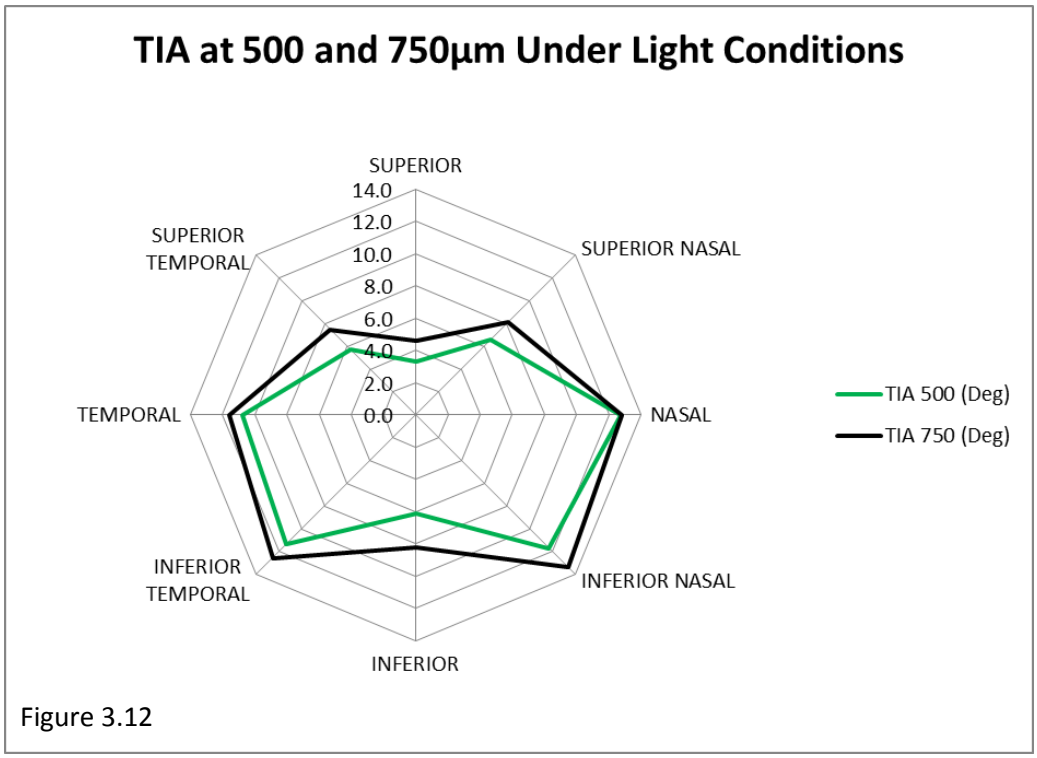

Figure 3.12

Figures 3.11 and 3.12. Mean value of TISA (Trabecular-Iris Space Area) and TIA (Trabecular-Iris Angle) at 500 and 750µm for 70 participants under light conditions for eight sections of the angle under light conditions.

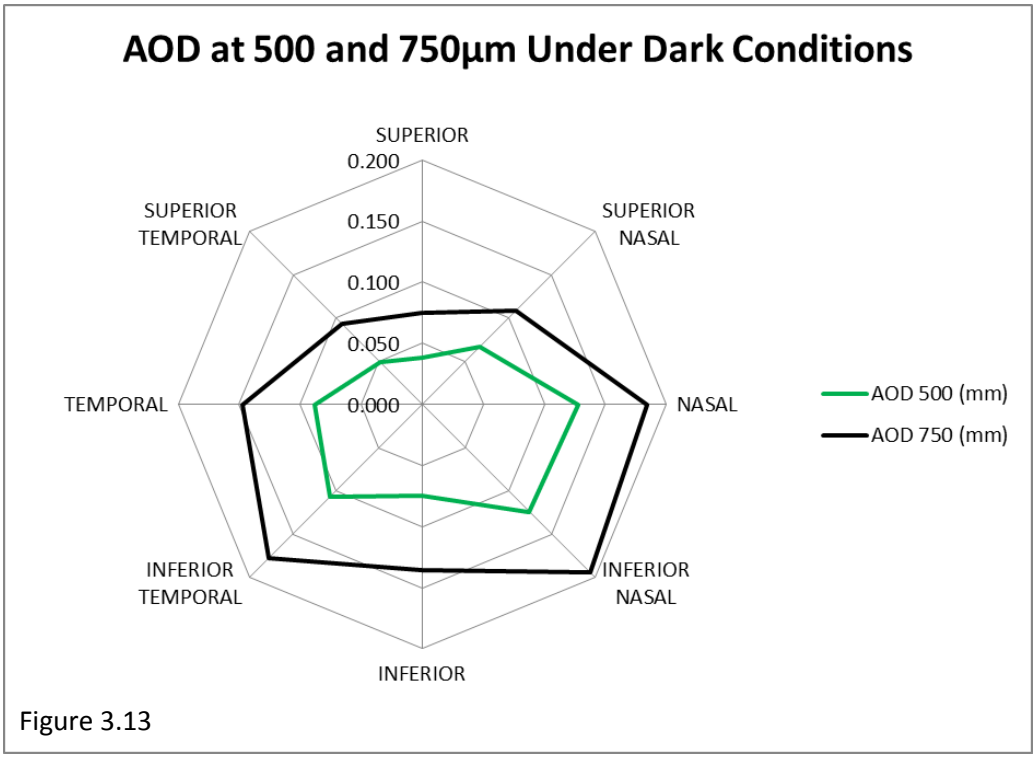

Figure 3.13

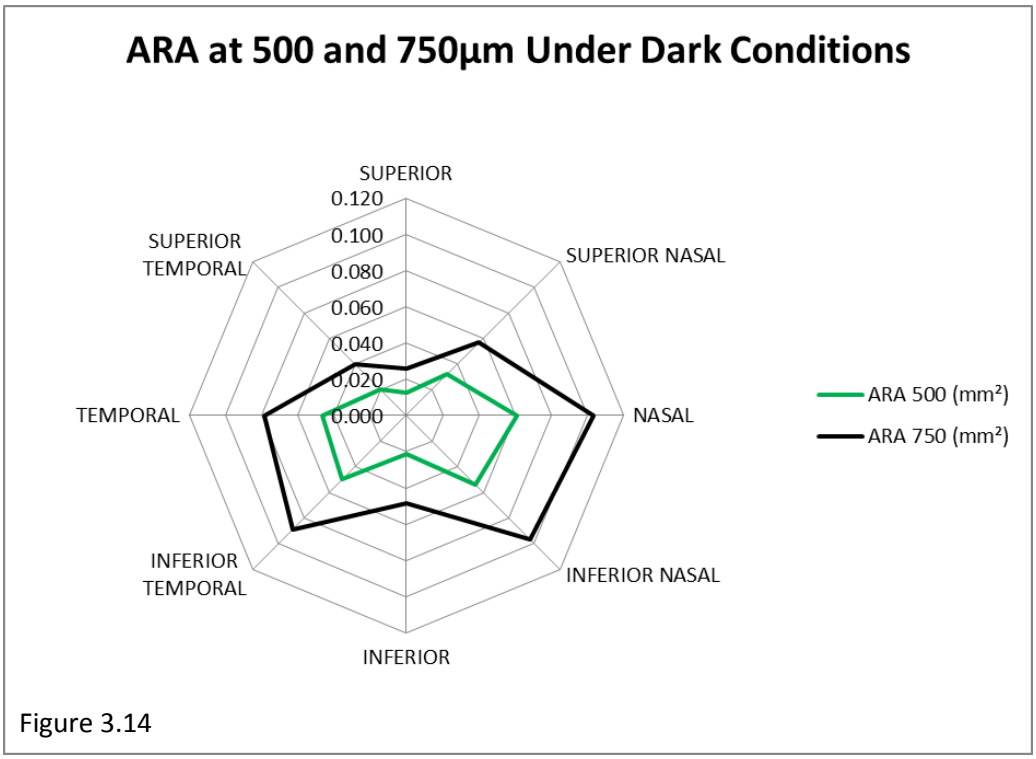

Figure 3.14

Figures 3.13 and 3.14. Mean value of AOD (Angle Opening Distance) and ARA (Angle Recess Area) at 500 and 750µm for 70 participants under dark conditions for eight sections of the angle under dark conditions.

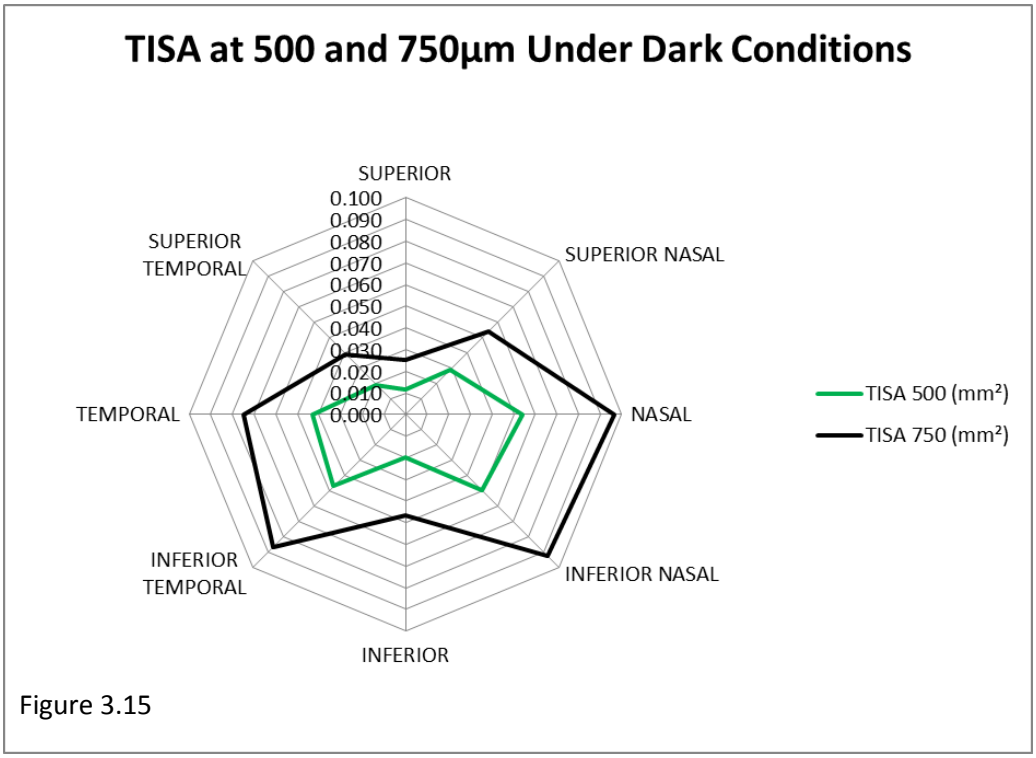

Figure 3.15

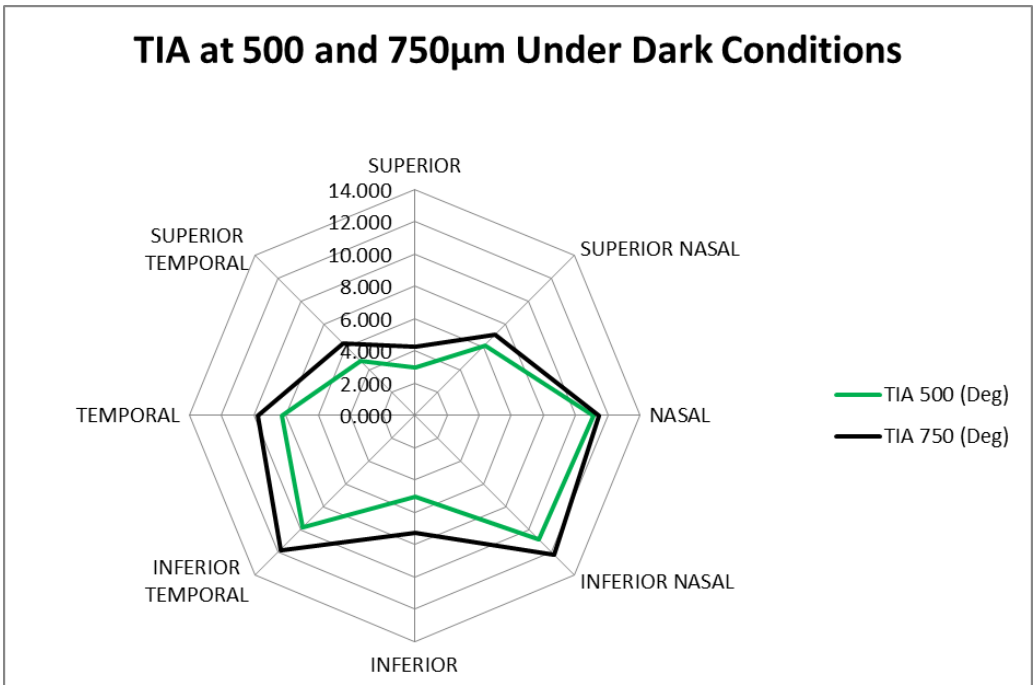

Figure 3.16

Figures 3.15 and 3.16 Mean value of TISA (Trabecular-Iris Space Area) and TIA (Trabecular-Iris Angle) at 500 and 750µm for 70 participants under dark conditions for eight sections of the angle under dark conditions.

The section in which minimum and maximum mean values for each angle parameter was found are given in Table 3.3, in both light and dark conditions.

CONDITION	LIGHT		DARK	
RANGE	MINIMUM MEAN VALUE (LOCATION)	MAXIMUM MEAN VALUE (LOCATION)	MINIMUM MEAN VALUE (LOCATION)	MAXIMUM MEAN VALUE (LOCATION)
AOD 500	0.0425 (Superior)	0.1419 (Nasal)	0.0378 (Superior)	0.1275 (Nasal)
AOD 750	0.0828 (Superior)	0.2082 (Inferior-Nasal)	0.0746 (Superior)	0.1943 (Inferior-Nasal)
ARA 500	0.0153 (Superior)	0.0652 (Nasal)	0.0126 (Superior)	0.0608 (Nasal)
ARA 750	0.0329 (Superior)	0.1105 (Nasal)	0.0261 (Superior)	0.1034 (Nasal)
TISA 500	0.0149 (Superior)	0.0577 (Temporal)	0.0117 (Superior)	0.0538 (Nasal)
TISA 750	0.0322 (Superior)	0.1022 (Nasal)	0.0250 (Superior)	0.0964 (Nasal)
TIA 500	3.2954 (Superior)	12.718 (Nasal)	2.9898 (Superior)	11,084 (Nasal)
TIA 750	4.6323 (Superior)	13.398 (Inferior-Nasal)	4.2911 (Superior)	12.182 (Inferior-Nasal)

Table 3.3. Maximum and minimum values and their section location for the angle parameters in light and darkness. AOD (Angle Opening Distance), ARA (angle Recess Area), TISA (Trabecular-Iris Space Area) and TIA (Trabecular-Iris Angle) measured at 500 and 750μm.

Differences between the narrowest and widest angle sections and the remaining sections

To assess the differences of every parameter in every section compared to maximum value and minimum value found for the same parameter (as described in Table 3.3), analysis of variance followed by Tukey HSD multiple comparisons was performed (the complete analysis performed using Tukey HSD can be found in the attached compact disc).

The minimum mean value was found to be in the Superior section for all the parameters; the difference between the Superior section's mean value and those corresponding to the same parameter in the other 2 sections of the Superior sector was statistically non-significant for all the parameters in the Superior-Temporal section in light or dark. However, when this mean was compared against the Superior Nasal section there was a statistical significant difference in dark for ARA 500, ARA 750, TISA 500 and TISA 750 and in light conditions for ARA 750, TISA 750 AND TIA 750.

When the parameters in the superior section were compared to the Horizontal and Inferior sectors parameters, the differences were all statistically significant ($P<0.05$) for light and dark conditions. The Inferior section was an exception, where ARA 500, ARA 750, TISA 750 and TIA 500

were not found to be significantly different from the minimum mean value in either light or dark conditions. Inferior section TISA 500 in dark condition was another exception. This is represented in Figure 3.17. The detailed analysis is presented in Tables 3.4 to 3.11 (Appendix 1, pages 1 to 2).

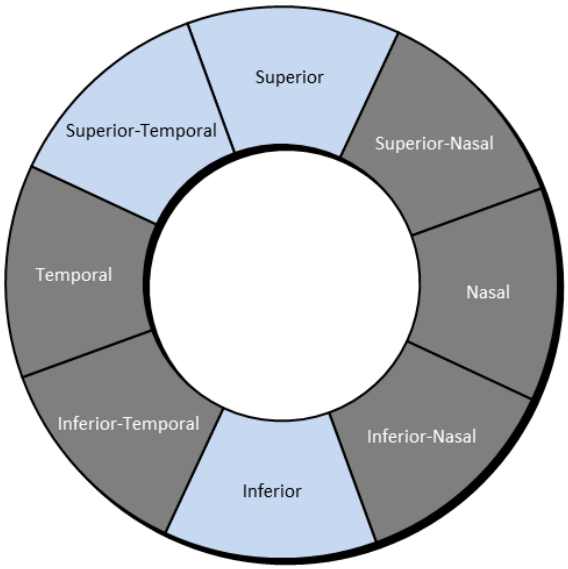

Figure 3.17. Representation of those sections in the angle whose majority of parameters were found **not** to be statistically significantly different to the narrowest section in the angle, the Superior section (these are represented in blue colour). Those other sections whose parameters were found statistically significant different are coloured in grey.

When comparing the maximum value for a given parameter (found in the Horizontal and Inferior sectors, more specifically in the Nasal, Temporal and Inferior-Nasal sections) with the rest of the means of the analysed parameter and for the other sections, the differences between the means found in the Superior sector (Superior, Superior-Temporal or Superior-Nasal) and the mentioned maximum mean value were all statistically significant ($p<0.05$). However, when the comparison was carried out between the maximum mean value and the rest of the sections found in the Horizontal and Inferior sector, these differences resulted non-statistically significant in the majority of the parameters. The Inferior section was an exception to this affirmation for all the parameters in light and dark conditions where the differences were statistically significant. AOD 500 (light) and ARA 750 (light) in the Temporal section were two other exceptions. Figure 3.18 shows a visual representation, but the detailed analysis is presented in Tables 3.4 to 3.11 (Appendix 1).

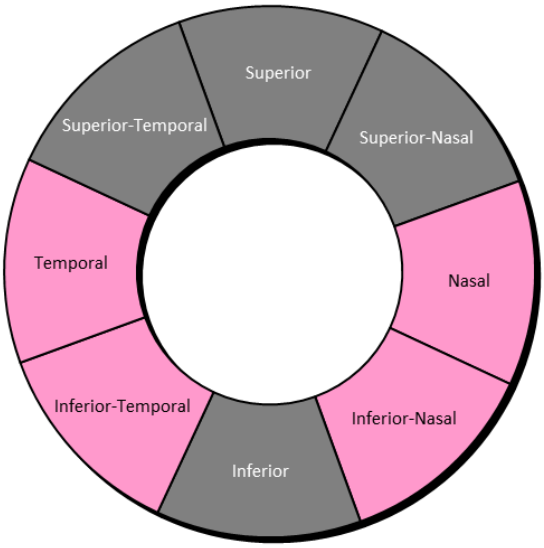

Figure 3.18. Representation of those sections in the angle whose majority of parameters were found **not** to be statistically significantly different to the widest sections in the angle, the Nasal, Temporal and Inferior-Nasal sections (these are represented in pink colour). Those other sections whose parameters were found statistically significantly different are coloured in grey.

Between the Inferior and temporal sections the majority of the parameters were statistically significantly different. Exceptions to this result were AOD 500 and 750 (light and dark) and TIA 500 and 750 in darkness.

<u>Comparison between the parameters found in the Superior, Nasal, Inferior and Temporal sectors and their adjacent sections (Superior-Nasal, Inferior-Nasal, Inferior-Temporal and Superior-Temporal)</u>

The same statistical analysis results were used when comparing the 4 most commonly described sections in the literature for quantification of the angle (Superior, Nasal, Inferior and Temporal) with their adjacent sections (Superior-Nasal and Superior Temporal against Superior, Superior-Nasal and Inferior-Nasal against Nasal, Inferior-Nasal and Inferior-Temporal against Inferior and Inferior-Temporal and Superior-Temporal against Temporal).

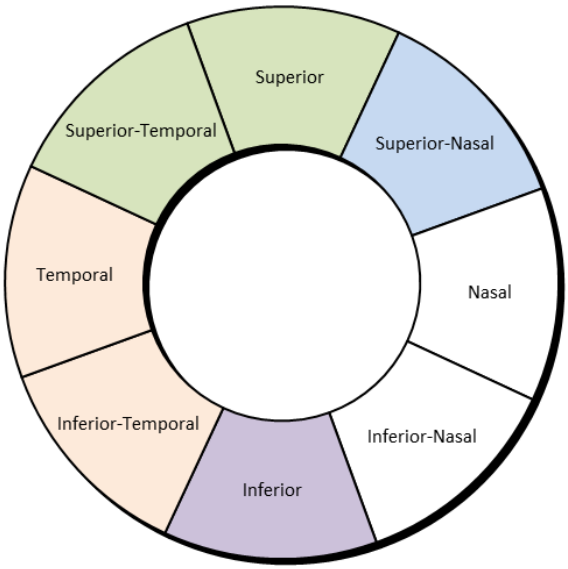

Figure 3.19. Representation of whether the differences between the four main four sections (Superior, Nasal, Inferior, Temporal) and their adjacent sections were statistically or not statistically significant. When no statistically significant differences were found between the sections, they were filled with the same colour (i.e. Superior and Superior-Temporal parameters were found to not to be statistically significantly different, therefore, both of them were coloured in green).

There were no statistically significant differences between the Superior and Superior-Temporal, for every angle parameter and for light and dark conditions. However, half of the parameters in the Superior-Nasal were statistically significant different to those in the Superior section.

In the case of the Inferior section, all the parameter mean differences found with the Inferior-Nasal section were statistically significantly different. When compared to Inferior-Temporal the majority of these differences (13 out of 16 parameters) were found as well to be statistically significant. This was the case for dark and light conditions.

Differences in Nasal section parameters were all significantly different from the Superior-Nasal section parameters in light and darkness (with the exception of TIA 500 light) but no statistical differences were found with the other adjacent section, Inferior-Nasal, independent of lighting conditions (with the exception of ARA 500 light). Differences in Temporal section parameters were all statistically significantly different from the Superior-Temporal section parameters in light and darkness (with the exception of TISA 500 light and TIA 500 dark) and not statistically different from those found in the Inferior-Temporal, independent of lighting conditions. Please, refer to

Table 3.12 for more information (Appendix 1). Figure 3.19 gives a visual representation of the results of this analysis.

The influence of light and dark conditions on dimensions of the anterior chamber angle

All the anterior chamber parameters were found to be smaller in darkness, as one would expect when the pupil is in a dilated position. A comparison between angle parameters in light and darkness was performed for each parameter using the Paired Samples t-test. The mean difference, standard deviation and p values are given in Table 3.13 (Appendix 1).

The most marked difference in angle opening as an effect of change of lighting was noted in the Temporal section. All the parameters in this section were significantly narrower in dark conditions. Additionally, Inferior-Temporal and Superior-Temporal sections showed statistically significant changes similar but smaller to those found in the Temporal section. The Superior section was least influenced by light conditions although this difference was not statistically significant. Figures 3.20 to 3.27 present the effect of light and dark conditions on these parameters

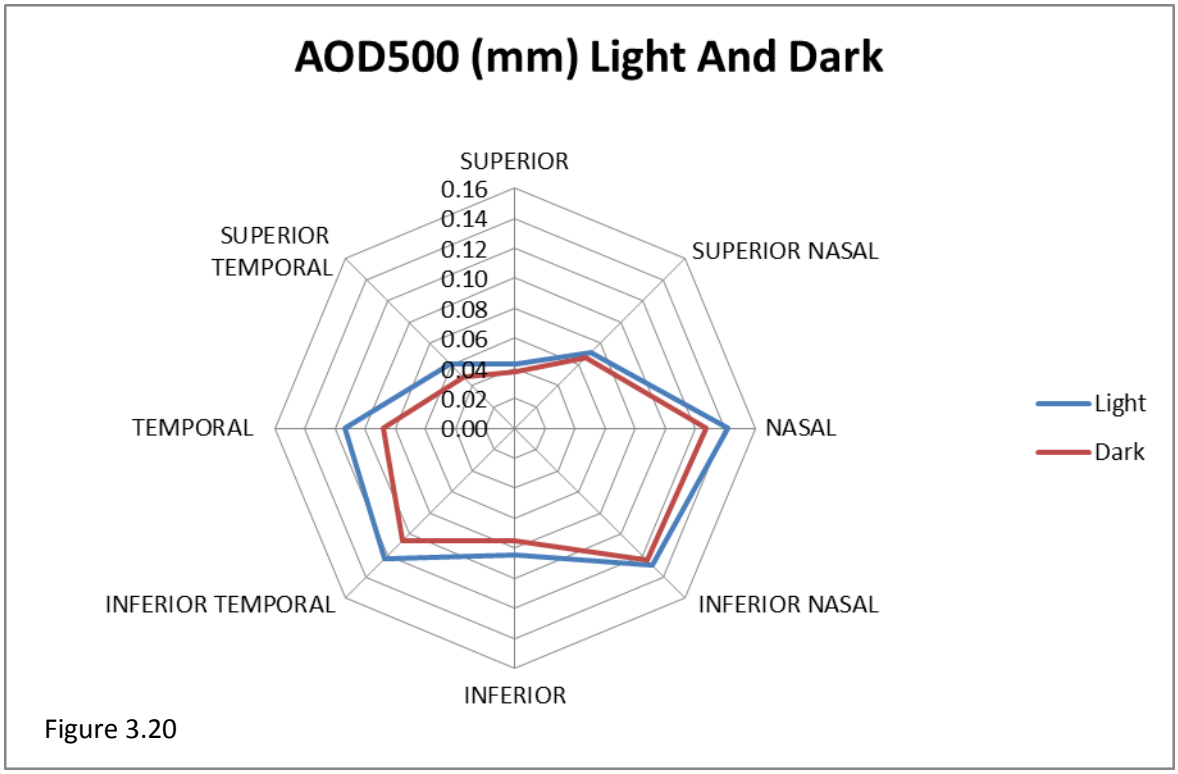

Figure 3.20

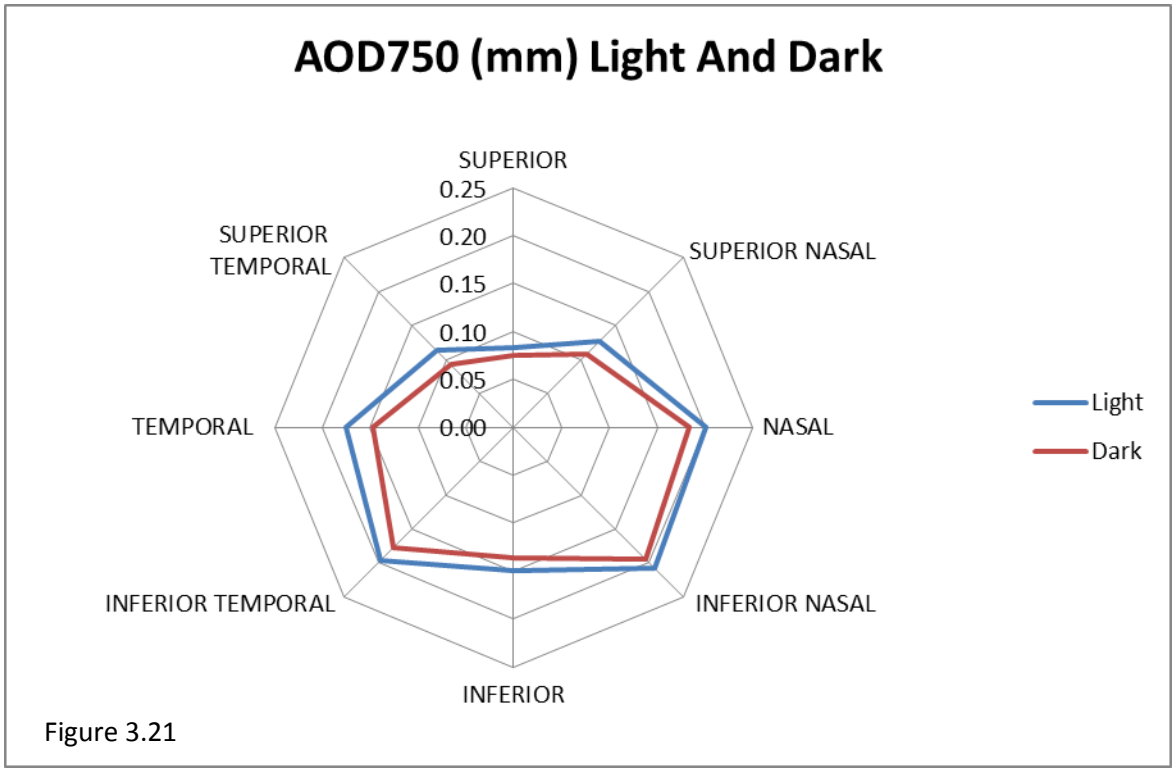

Figure 3.21

Figures 3.20 and 3.21 Mean value of AOD (Angle Opening Distance) at 500 and 750µm for 70 participants under light and dark conditions for eight sections of the angle.

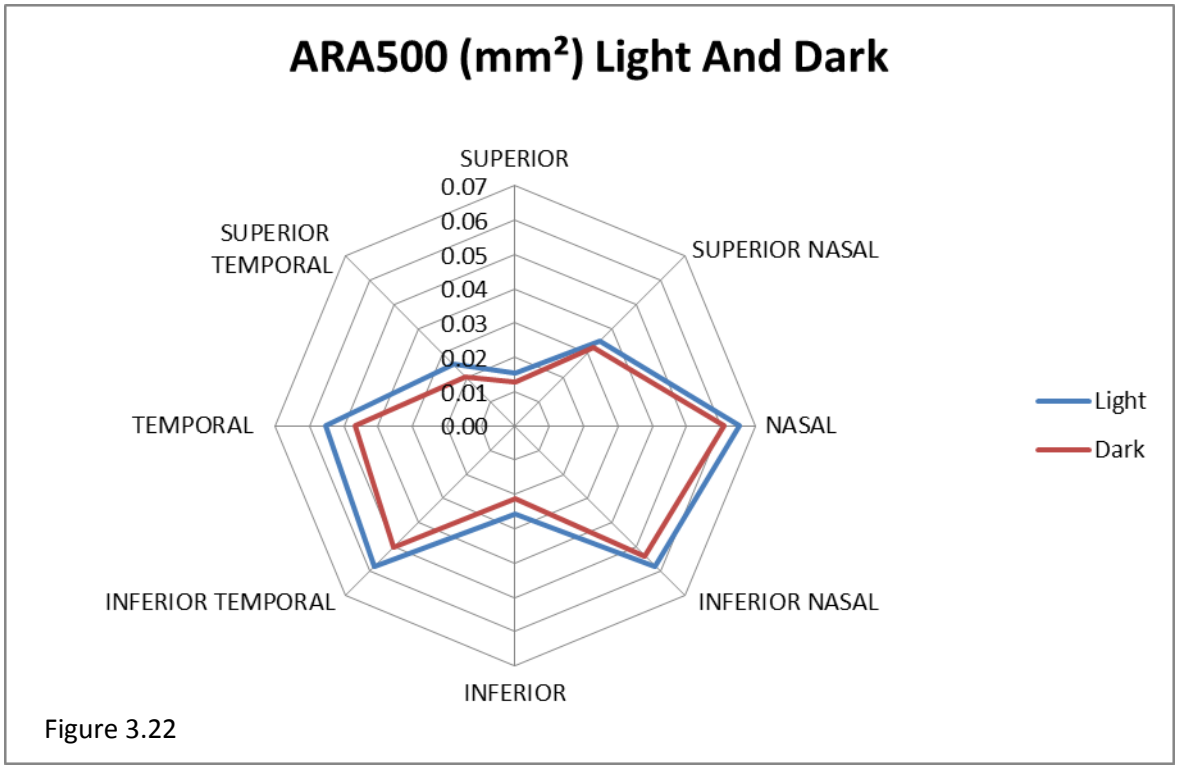

Figure 3.22

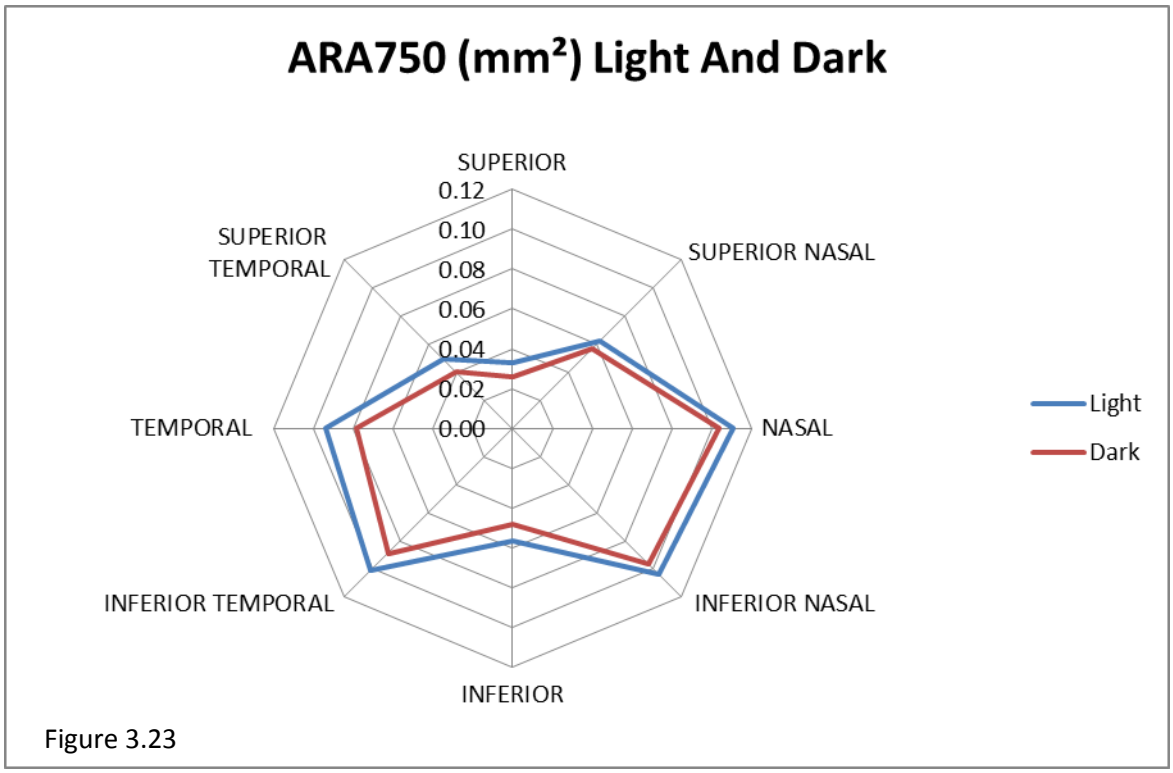

Figure 3.23

Figures 3.22 and 3.23. Mean value of ARA (Angle Recess Area) at 500 and 750μm for 70 participants under light and dark conditions for eight sections of the angle.

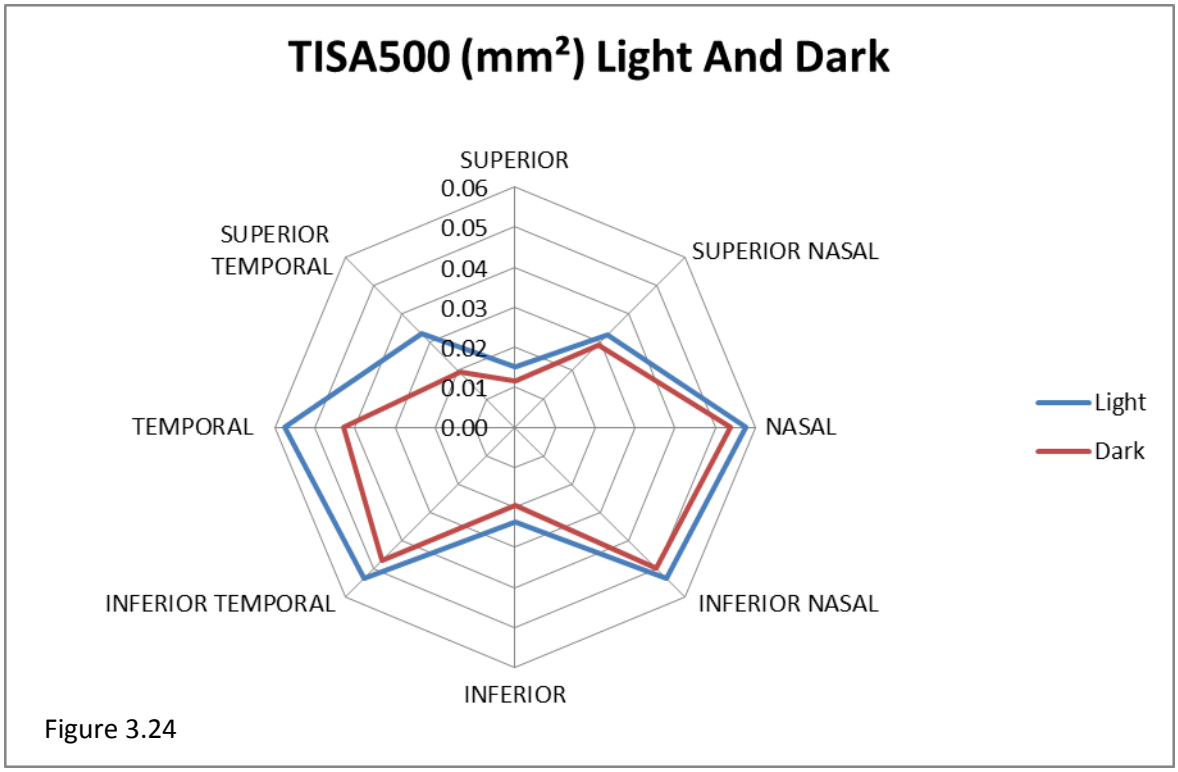

Figure 3.24

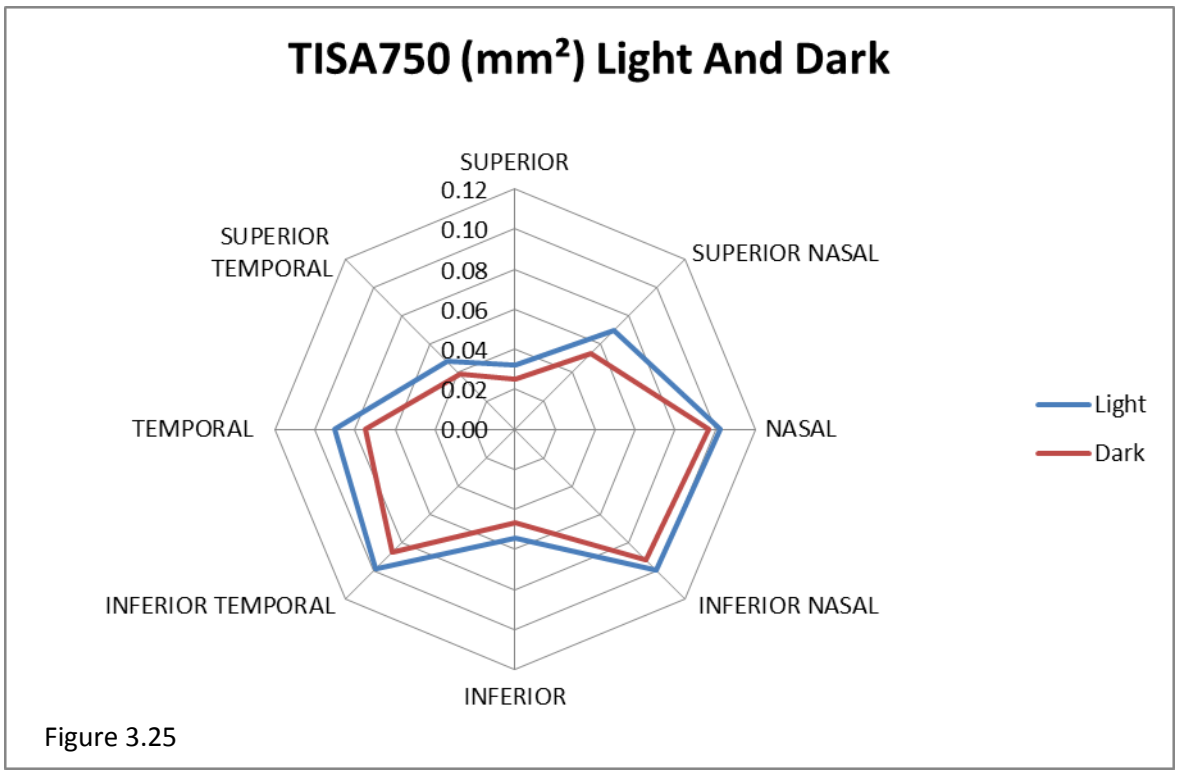

Figure 3.25

Figures 3.24 and 3.25. Mean value of TISA (Trabeculo-Iris Space Area) at 500 and 750μm for 70 participants under light and dark conditions for eight sections of the angle.

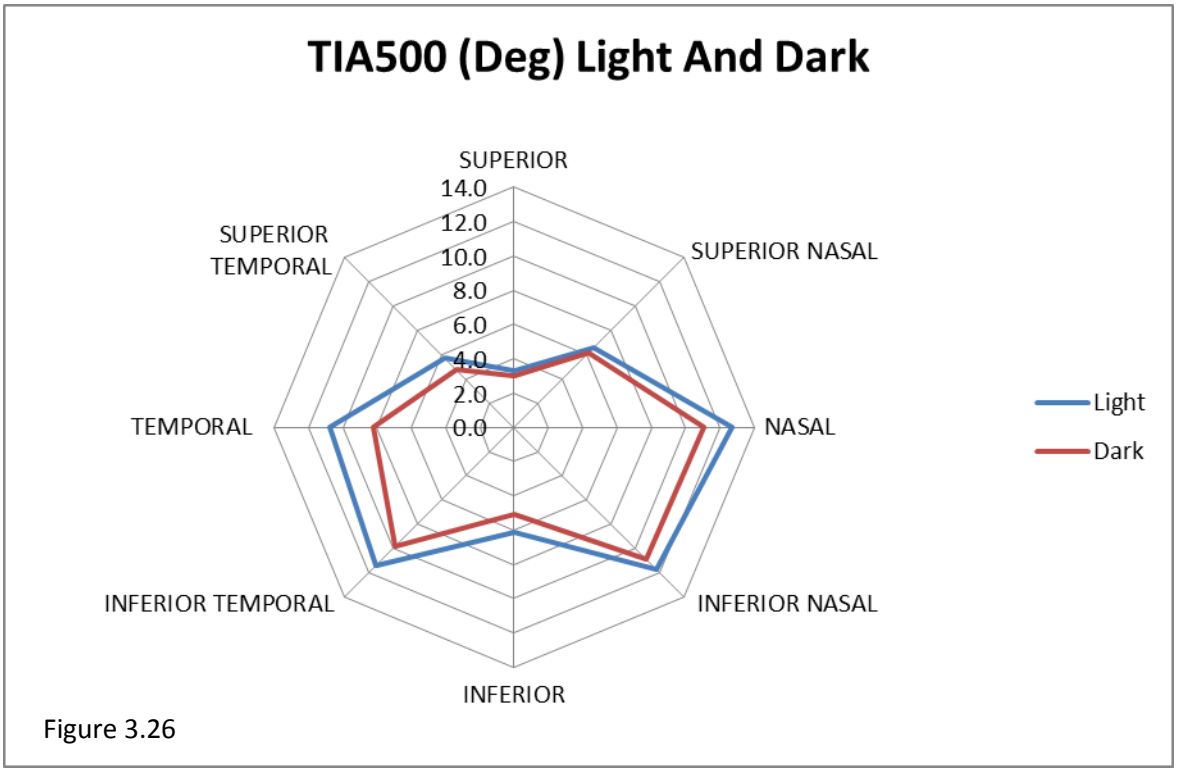

Figure 3.26

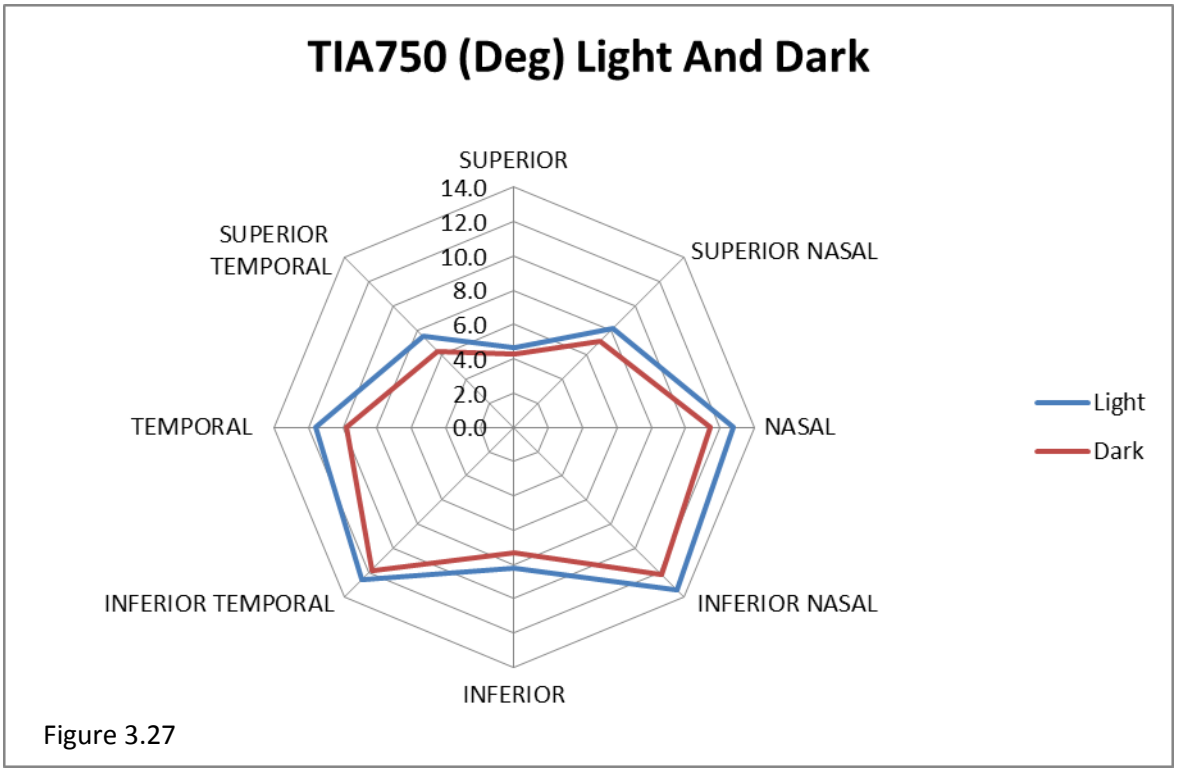

Figure 3.27

Figures 3.26 and 3.27. Mean value of TIA (Trabeculo-iris Angle) at 500 and 750µm for 70 participants under light and dark conditions for eight sections of the angle.

Investigation of a gonioscopically occludable angle using anterior segment ocular coherence tomography

When using the AS-OCT for diagnosis to verify the gonioscopic finding of an occludable angle (an angle in which the posterior pigmented trabecular meshwork could not be visualised in the primary position of gaze using applanation gonioscopy) taking into account the 4 main sections (Superior, Nasal, Inferior and Temporal), 62 eyes out of 70 were found to be occludable (2 or more sections appeared to be closed) and 8 non-occludable (3 or more sections appeared to be open) in light conditions. Using the OCT in dark conditions, 66 of the 70 eyes were found to be occludable and 4 non-occludable. If a decision on whether the angle was closed was made using 8 sections, fewer eyes were diagnosed with occludable angles in both dark and light conditions; 46 eyes were diagnosed as occludable (4 or more sections appeared to be closed) and 24 non-occludable (5 or more sections appear to be open) in light conditions. In darkness, 62 were found occludable and 8 non-occludable. A summary of this data can be found in Table 3.14. Sensitivity was determined using gonioscopy as the standard reference.

Specificity could not be calculated as no patients with gonioscopically open angles were recruited. Confidence limits were calculated by Wilson's method (as recommended by Agresti and Coull (1998)).

		Diagnosis using 4 sections		Diagnosis using 8 sections	
Occludable angle with gonioscopy		AS-OCT occludable	AS-OCT non-occludable	AS- OCT occludable	AS-OCT non-occludable
Gonioscopy found all the eyes were occludable n=70	LIGHT	n=62 Sensitivity of 88.6% (79.0%-94.0%)CI 95%	n=8	n=46 Sensitivity of 65.7% (54.0%-75.7%) CI 95%	n=24
	DARK	n=66 Sensitivity of 94.3% (86.2%-97.7%) CI 95%	n=4	n=62 Sensitivity of 88.6% (79.0%-94.0%) CI 95%	n=8

Table 3.14. Number of gonioscopical occludable angles detected with AS-OCT depending of number of sections taken in account and lighting conditions. Sensitivity values for the AS-OCT diagnosis are given only for those angles found to be occludable with both methods, gonioscopy and AS-OCT. CI= Confidence Interval

A more detailed comparison between gonioscopical and AS-OCT diagnosis of the sections was carried out for the 4 main sections (Superior, Nasal, Temporal and Inferior). As shown in Tables 3.15 and 3.16, it was found that in light and dark conditions, AS-OCT showed a higher number of occludable angles in the Superior section (45 eyes) while gonioscopy found higher numbers of occludable angles in the Inferior Section (28 eyes in light and 31 eyes in darkness).

The AS-OCT showed a high sensitivity for gonioscopically occludable angles in Superior and Inferior sections in light and dark, but this decreased for Temporal and Nasal for the same lighting conditions. Specificity was highest in the Nasal section in light (64.2%) and lowest for the Inferior section in dark.

The diagnosis of occludable sections, independently of position or lighting conditions, was always higher in number using the AS-OCT than using gonioscopy.

ANALYSIS OF 70 EYES	Superior		Inferior		Nasal		Temporal	
	AS-OCT LIGHT		AS-OCT LIGHT		AS-OCT LIGHT		AS-OCT LIGHT	
	Closed	Open	Closed	Open	Closed	Open	Closed	Open
Gonioscopy Closed	n=45	n=2	n=34	n=4	n=14	n=42	n=15	n=39
Gonioscopy Open	n=21	n=2	n=28	n=4	n=5	n=9	n=8	n=8
Total	n=66	n=4	n=62	n=8	n=19	n=51	n=23	n=47
Sensitivity AS-OCT in LIGHT	95.7% (85.7%-98.8%) CI 95%		89.7% (75.9%-95.8%) CI 95%		25.0% (15.5%-37.7%) CI 95%		27.7% (17.6%-40.9) CI 95%	
Specificity AS-OCT in LIGHT	8.7 % (2.4%-26.8%) CI 95%		12.5% (5.0%-28.1%) CI 95%		64.28% (38.8%-83.6%) CI 95%		50.0% (28.0%-72.0%) CI 95%	

Table 3.15. Number of gonioscopical occludable sections detected with AS-OCT and gonioscopy depending on position of the section in light condition. Sensitivity values for the AS-OCT diagnosis are given only for those sections found to be occludable with both methods, gonioscopy and AS-OCT. Specificity values are given only when both methods found the section non-occludable. CI= Confidence Interval

ANALYSIS OF 70 EYES	Superior		Inferior		Nasal		Temporal	
	AS-OCT DARK		AS-OCT DARK		AS-OCT DARK		AS-OCT DARK	
	Closed	Open	Closed	Open	Closed	Open	Closed	Open
Gonioscopy Closed	n=45	n=2	n=35	n=3	n=23	n=33	n=22	n=32
Gonioscopy Open	n=20	n=3	n=31	n=1	n=8	n=6	n=8	n=8
Total	n=65	n=5	n=66	n=4	n=31	n=6	n=30	n=40
Sensitivity AS-OCT in DARK	95.7% (85.7%-98.8%) CI 95%		92.1% (79.2%-97.3%) CI 95%		41.1% (29.2%-54.1%) CI 95%		40.7% (28.7%-54.0%) CI 95%	
Specificity AS-OCT in DARK	13.0% (4.5%-32.1%) CI 95%		3.1% (0.5%-15.7%) CI 95%		57.1% (21.4%-67.4%) CI 95%		50.0% (28.0%-72.0%) CI 95%	

Table 3.16. Number of gonioscopical occludable sections detected with AS-OCT and gonioscopy depending on position of the section in darkness. Sensitivity values for the AS-OCT diagnosis are given only for those sections found to be occludable with both methods, gonioscopy and AS-OCT. Specificity values are given only when both methods found the section non-occludable. CI= Confidence Interval.

Correlation between PAS and smaller dimensions of anterior chamber angle parameters

Correlation (Pearson's 2-tailed test) between the percentage/extend of PAS* found on gonioscopy and the values of the parameters found in the same sections with the CASIA OCT for light and dark conditions was analysed. 70 eyes were included in this analysis. Only the 4 gonioscopic quadrants/sections that would be described by gonioscopy were studied (Superior, Nasal, Inferior and Temporal). There was no statistically significant correlation ($p>0.05$) for any of the four studied angle sections with the exception of AOD and TIA 750 Temporal section in light conditions, which showed a weak association with presence of PAS in the same section with correlation coefficients of $r=0.309$ ($p=0.007$) and $r=0.304$ ($p=0.010$), respectively.

*All eyes were included in this analysis including those with no PAS (0% of PAS).

Relationship between IOP behaviour (DIOP fluctuation, DRPT and SIOP) and anterior chamber angle dimensions

Using both univariate and multivariate regression models the levels of fluctuation for the DIOP found earlier in this report were related to each angle section in both light and dark conditions. The higher contribution to the model was achieved by negative standardised coefficients showing an inverse relationship between magnitude of fluctuation and angle dimensions. The multivariate models were statistically significant ($p<0.05$) for AOD 750 (light), ARA 750 (light and dark), TISA 500 (light), TISA 750 (light), TIA 500 (light) and TIA 750 (light and dark). Detailed results are given in Tables 3.17 to 3.24 (Appendix 1).

The dark room provocation test result showed a statistically significant inverse relationship with four parameters measured in light conditions (AOD 750, ARA 500 and ARA and TIA 750). However, in the case of the supine IOP test, the same statistical models did not show any relationship between these IOP test results and any of the angle parameters independent of lighting conditions. Detailed results are given in Tables 3.25 to 3.32 for DRPT results, and in Tables 3.33 to 3.40 for the supine IOP test measurements. These tables can be found in Appendix 1.

3.2.4 Discussion

The dimensions of the anterior chamber angle of the Superior section were shown to be statistically different to the other sectors of the circumference of the angle, with the exception of the Superior-Temporal parameters and some parameters of the Inferior and Superior-Nasal sections. Additionally, there were significant differences in most angle parameters between the

Inferior section and the Nasal section. Similar results for the narrowest section were found by He, et al. (2007) in a study of Chinese subjects. Using ultrasound biomicroscopy (UBM), they described the Superior section parameters AOD 250 and 500 as narrowest when compared to the other 3 sections under study (Temporal, Nasal and Inferior) in a sample of PACS eyes. The widest was found to be the Temporal section, which differed from the present study results. Although, their data were not tested for statistical significance they were very similar to another study carried out by See and colleagues in eyes of Chinese and Eurasian ethnicity (See, et al., 2007). See, et al. (2007) found a statistically significant difference in the parameter dimensions among the three sections they studied with an AS-OCT in light conditions (Temporal, Nasal and Inferior sections) in an untreated sample of patients with diagnoses of PAC, PACS and PACG. They reported that the two parameters under study, AOD 500 and TISA 750, were significantly narrower in the Inferior section and wider in the Temporal section. These results were consistent with those found in the present study in the case of their narrowest section, but not in the widest. Although See and colleagues did not include the Superior section in their analysis, if in the present study only Temporal, Nasal and Inferior sections would have been the only sections to be considered, the Nasal section may have remained as the narrowest. These differences may be due to differences in ethnicity. Leung, et al. (2010) studied a group of 30 Chinese and 30 Caucasian subjects who presented with narrow angles. In their study AOD, TISA and TIA were measured in Nasal and Temporal using an AS-OCT in both Chinese and Caucasian eyes. They found that there were no differences between these parameters in the two ethnicities, but their data showed that the Nasal parameters were larger than the Temporal in the Caucasian group and similar for the Chinese. Another study in Caucasian participants diagnosed with PACS, PAC or PACG showed that TIA was widest in the Nasal section and narrowest in the Superior as measured with AS-OCT (Mansouri, Sommerhalder and Shaarawy, 2010). Although these differences were not statistically tested for the last two studies mentioned, it is possible that Chinese eyes present wider angles in the Temporal section while Caucasian present it in the Nasal.

Given that the present study involved testing for differences between angle sectors in an image set acquired over less than 5 seconds, potential bias that may occur due to differences in lighting conditions and different time points, is minimised. Additionally these measurements were made under physiological conditions without any intervention from pharmacologic agents. In order to relate the average of the dimensions found in the studied sectors for every parameter to other factors such as peripheral anterior synechiae (PAS) or changes in the IOP, prior tests to check the statistical homogeneity of the parameters dimensions should be performed. Additionally, by averaging the parameters found in different sections, the contribution of single sections on their

own to the correlation may be missed. Hence, in this study the 8 sections parameters (Superior, Superior-Nasal, Nasal, Inferior-Nasal, Inferior, Inferior-Temporal, Temporal and Superior-temporal) were included for statistical analysis. Several studies in the published literature, have taken an average of only 3 sections, for example, Su, et al., (2008) studied a sample of Chinese Singaporean eyes with PACS, PAC, PACG, primary open glaucoma and normal healthy eyes. They found a correlation between the mean value of AOD, ARA, TISA 500 and ARA and TISA 750 in 3 sections (Inferior, Nasal and Temporal) with AS-OCT and the PAS found on gonioscopy for the same sections. Although the correlation was weak in every case, it showed a statistically significant inverse association between the clock hours of PAS and the averaged dimension of the parameters. In this thesis, separate correlations between percentages of PAS and smaller dimensions of the parameters of the main 4 sections in light and dark conditions were not found for the majority of the parameters. With the aim of being able to compare the present study's result and those found by Su and colleagues, the average of the three sections together with the degree of presence of PAS was correlated (mirroring Su et al's methods). The Spearman's coefficients showed an extremely weak inverse association between averaged parameters and degree of PAS (-0.027, -0.096, -0.088, -0.048 and -0.041 for of AOD, ARA, TISA 500 and ARA and TISA 750 respectively). Additionally, none of these correlations were statistically significant. The differences between studies were therefore unlikely to be due to the different statistical methodology. It is still unclear whether these differences are due to different mechanisms of angle closure in Chinese and Caucasians. Aung, et al., (2005) found that while PAS increased as the anterior chamber depth (ACD) decreased in Singaporeans, in Mongolians there was a threshold where PAS were not commonly found (ACD of 2.4 mm or more). It is possible that the rate of PAS in Caucasians is not related to narrowing of the angle until a certain threshold is reached, akin to that observed in the Mongolian study. It would be for further studies comparing Chinese and Caucasian populations to determine this.

Relatively good concordance was found between AS-OCT and gonioscopy when diagnosing an occludable angle in dark conditions. It is not surprising that the highest sensitivity (of the OCT in predicting a gonioscopically occludable angle) was achieved when using OCT scans of the 4 principal sections and also when making the comparison using OCT in dark conditions rather than in the light. The higher sensitivity in dark conditions can be explained on account of the similarity in light intensity used for gonioscopy to that of the OCT measurement in darkness. The improved agreement when considering 4 sections rather than more than 4 sub-sections can be explained by the fact that the gonioscopy technique used in this study involved specific description of 4 quadrants, the technique most commonly employed in clinical practice. This gonioscopic technique involves the examiner observing the corneal wedge in low lighting, with the slit-lamp

beam aimed at the centre of the quadrant. It would have been interesting to perform gonioscopy in the diagonal sections and re-assessed sensitivity of the AS-OCT taking in account these 8 sections again. If the sensitivity would have been similar to that found using 4 sections, gonioscopy may have been overestimating the number of occludable angles in the clinical environment. This can be determined in the future.

Nolan, et al. (2007) reported that among 152 eyes gonioscopically diagnosed with angle closure, the AS-OCT was able to detect 143 in darkness (94.1% sensitivity) and that this number decreased when the diagnosis was performed using the scans taken in light conditions, where the AS-OCT detected only 127 occludable angles out of 149 diagnosed by gonioscopy (85.23% sensitivity). However, in their study the OCT occludable diagnosis criterion was based on the analysis of only 3 sections (Nasal, Inferior and Temporal). The authors diagnosed an occludable angle if one or more sections were occludable. This criterion may have resulted in their reporting higher rates of sensitivity for the AS-OCT on account of the increased likelihood of detecting 1 section closed of 3 possible sections than 2 sections closed of 4 sections, the latter being the criteria for the present study. The reason why this present study found similar results to that of Nolan et al. is probably because the present study found occludable angles more commonly in the Superior section. To explore this assertion, we used Nolan et al's criterion to re-analyse the data and this led to increased values for sensitivity to 97.1% (95% CI: 90.1%-99.2%) for darkness and to 92.85% (95% CI: 84.3%-96.9%) for light conditions.

Additionally, Nolan et al. reported values for sensitivity of the OCT in the Inferior section that were very similar to the ones found in the present study, but Nolan's Nasal and Temporal sections sensitivities were higher (81.5% and 66.1%, respectively). In Nolan's study there is no allusion to whether the sensitivity results related to these sections were calculated when comparing AS-OCT in light or AS-OCT in dark versus gonioscopy and it is therefore difficult to deduce a possible reason for these differences.

The low rates of specificity found with the AS-OCT instrument may be explained if one considers the differences in how the diagnosis is made with the OCT image compared to that with gonioscopy. As described in the methodology, a section was diagnosed as occludable if there was irido-corneal contact anterior to the scleral spur observed with AS-OCT. While, in the case of gonioscopy, an occludable angle was diagnosed when the posterior pigmented trabecular meshwork was not visible. On occasion there can be contact between iris and cornea anterior to the scleral spur noted on OCT ('occludable' by OCT), while on gonioscopy the area of contact is judged to be sufficiently posterior with adequate visibility of the posterior trabecular meshwork

to justify a diagnosis of a gonioscopically open angle (i.e. the OCT is calling a 'false positive'). The choice of this OCT criterion in this study is justified, given the absence of a more accurate method for judging the height or extent of the posterior pigmented trabecular meshwork on current OCT instruments.

The results found for diurnal IOP fluctuation suggested that an eye with smaller angle dimensions would exhibit a greater range of IOP (difference between peak and trough) during the day. Furthermore, the multiple predictor statistical models were able to predict this fluctuation from OCT measurements of anterior chamber angle parameters. This is a novel finding. Were this to be confirmed with a larger sample size, OCT angle parameter measurements could be used to predict IOP diurnal fluctuations in at-risk patients, allowing clinicians to selectively offer laser treatment to those where a higher diurnal IOP range would be judged as high-risk. This could be explored in a future study.

Wang, et al., (2010) reported a statistically significant relationship between numbers of closed sections in the angle of a given eye in dark conditions and a positive result in the dark room provocative test (DRPT). In their study, a positive DRPT result was considered when the IOP rose $\geq$ 8mmHg after the subject had remained in the prone position for 1.5 hours in darkness. The level of IOP after the test and not the difference pre and post-test was used in their statistical correlation with sectors of angle closure. Additionally a sector was considered closed if the scleral spur was obscured by the root of the iris in the AS-OCT scan. This definition of closure may overestimate the number of closed sections (physiologically the trabecular meshwork is placed anterior to the scleral spur and, therefore, sections of the eyes where only the scleral spur and posterior areas are obscured should still drain aqueous humour). The association they reported involved an association between a simple variable for angle closure, namely 'closed' or 'open', and the IOP level post-DRPT. They found a direct association between those two variables ($r=0.755$, R^2 of 0.074, $p<0.001$). Quantitative measurements of the anterior chamber angle such as angle opening distance were not used in their analyses. In the case of the present study, an inverse association between the change in IOP pre and post-DRPT and smaller dimensions for only three parameters in light was found. It was not possible to accurately replicate Wang's study, as the DRPT duration in the present study was 15 minutes. However, in an attempt, a regression model was fitted with the number of closed sections found with gonioscopy and the IOP found after the DRPT. A statistically significant association was found with an r-value of 0.272 and an R^2 of 0.074. When the same number of sections was fitted in another regression model with the DRPT result (IOP post DRPT minus IOP pre DRPT), no association was found ($r=0.068$, R^2 of 0.005, $p=0.585$). It was possible that the number of closed sections in the angle was associated with the

IOP independently to the time of measurement (before or after the DRPT). Another regression model was then fitted for finding a possible association between the number of closed sections and the IOP found pre-DRPT. This model gave a statistically significant association between the two variables (r=0.248, R^2 of 0.061, p=0.045). It is, therefore, possible that the number of closed angle sections found in an eye may be associated with the IOP level found for the same eye, but it seems to be unlikely to show a similar association with the IOP differential due to the DRPT.

No published studies have been found regarding a possible association between the angle dimensions and the SIOP. This study did not demonstrate any differences in IOP between seated and supine IOP in those eyes with smaller angle dimensions.

As shown in the results the Temporal section of the angle was the most affected by light changes. All the parameters of this section measured at 500μm from the scleral spur duplicated or nearly duplicated their dimension because of the light effect (rates from 1.7 to 2.2 times the dimension of the parameter in dark). In the case of the parameters found at 750 μm, light increased the dimension 1.2 to 1.4 times. These results differ slightly from those found by Ang and Wells (2010) in the Temporal section of Caucasian eyes diagnosed with PAC, PACS or PACG. Their parameters increased dimension by 1.49 to 1.6 times and this increase was similar in the group of parameters measured at 500 and 750μm. The Temporal section angle configuration in the present sample changes less at 750μm than at 500μm. Differences between this and the study by Ang and Wells (2010) may be due to different proportions of eyes with a plateau iris configuration in the two subject groups. One can hypothesize that eyes with a plateau iris configuration will differ from steep or regular iris configurations in terms of the angle opening at these two distances from the scleral spur in response to light.

The Van Herick and the flashlight technique have been described as less accurate in the detection of narrow angles when compared with gonioscopy (Thomas, George, Braganza and Muliyil, 1996). Thomas, George, Braganza and Muliyil, (1996) performed a comparative study using gonioscopy as the gold standard versus the flashlight test and Van Herick's test in the diagnosis of occludable angles. The specificity rates for the flashlight and Van Herick were 82.7% and 89.3% respectively. Their rates of sensitivity were lower, 45.5% and 61.9%, respectively. Both of these tests are performed by focusing light on the temporal section of the angle. The Van Herick's technique uses a lower amount of lighting (similar to that used in gonioscopy) than is used in the flashlight test. It is, therefore, unsurprising that higher rates of concordance were found for Van Herick's than for the flashlight test when compared to gonioscopy. In the present study it has been found that there is a statistically significant widening of the Temporal sector of the angle due to the effect of

light (Temporal, Superior-Temporal and Inferior-Temporal). Furthermore, the Temporal sector seemed to be the most affected by the ambient light compared to the other sections. Following on from these results, it would be interesting to assess the sensitivity of the Van Herick technique with the lights of the room on (achieving similar levels of lux as in lighting conditions in the present study) and while considering the Van Herick as the gold standard when comparing to gonioscopical results. It may happen that the majority of eyes detected as narrow with Van Herick in light conditions would be further detected with gonioscopy in darkness.

3.2.5 Conclusions

The superior section of the anterior chamber angle was found to be narrower than the inferior and horizontal sectors. The statistical analysis highlighted the importance of comparing OCT dimensions of different sections of the angle when using fewer than eight sections for multiple regression/and or correlation statistical analysis, a finding that has been overlooked in some studies in the current literature in this area.

Examiners who may attempt a diagnosis of occludable angle using the AS-OCT should be aware of the difference in the outcomes when using 4 or 8 sections for a diagnosis. To achieve better concordance between OCT and gonioscopy, a diagnosis of an occludable angle based on the 4 main sections in dark conditions is recommended.

No statistical association was found between smaller dimensions of the angle found with AS-OCT and the extent of PAS in dark or light conditions.

Professionals managing patients with narrow angles should be aware of the possible higher levels of IOP fluctuation that this study has found to be associated with narrower anterior chamber angles.

CHAPTER 4. Investigation of the effect of the Laser Peripheral Iridotomy (LPI) on the anterior chamber angle dimensions and on the diurnal intraocular pressure.

4.1 Relationship between the degree of anterior chamber angle opening following laser peripheral iridotomy and intraocular pressure

4.1.1 Introduction

An understanding of how the anatomical dimensions change with time following laser peripheral iridotomy is of clinical importance. Most studies that have examined anterior segment imaging of Caucasian subjects with narrow angles report on a post-LPI assessment at less than 3 months. These assessments did not explore the longer-term effect of the laser on the chamber angle. Additionally, this effect has always been measured on the treated eye. A comparison with an untreated fellow eye with an occludable angle has not been reported previously in the literature that involves anterior chamber imaging post-iridotomy (López-Caballero, et al., 2010; Mansouri, Burgener, Bagnoud and Shaarawy, 2009; Ang and Wells, 2010; Antoniazzi, et al., 2010). It is unknown what the effect of time is on the untreated eye's anterior chamber dimensions. Previous studies report that the anterior chamber angle widens post-LPI. It is possible to hypothesise that in subjects with bilateral occludable angles, those eyes that received treatment with LPI would show an increase of the angle parameters (widening) as observed with AS-OCT whereas the fellow untreated eyes would remain unchanged **(1st Hypothesis)**.

Additionally, the post-LPI IOP level in Caucasian treated eyes has been reported as either remaining unchanged from a baseline measurement 1 week and 3 months post-LPI (Moster, et al., 1986) or to decrease by 1 month post-LPI (López-Caballero, et al., 2010). One may also hypothesise that there exists a relationship between rate of opening and time of measurement post-LPI and that a reduction in IOP may be associated with the degree of opening **(2nd Hypothesis)**.

4.1.2 Methodology and Statistical Analysis plan

The CASIA OCT scans and IOP data collected in Visit 1 (Baseline; Mean time from Visit 2= 17.4 days, SD 16.5), Visit 4 (1 week post LPI; Mean time from Visit 2= 8.2 days, SD 2.0), Visit 5 (1 month

post LPI; Mean time from Visit 2= 43.6 days, SD 5.1), Visit 6 (3 moths post LPI; Mean time from Visit 2= 92.5 days, SD 8.4) and Visit 11 (6 months post LPI; Mean time from Visit 2= 178.4 days, SD 11.1) were used for the analysis in this section. Those scans taken in dark conditions were quantified (this would allow comparison with other reports using the UBM and Pentacam, commonly taken in darkness). The data of 39 participants, 78 eyes scans (treated and fellow untreated) and IOP were used in the statistical analysis until the second randomisation took place (Visit 6). From that time point onwards only the data obtained for those patients who only received LPI as a laser treatment was used (28 treated and their fellow 28 untreated eyes scans for Visit 11 data). The figure below (Figure 4.1) shows a visual of the participants flow before and after the second randomisation (Visit 6).

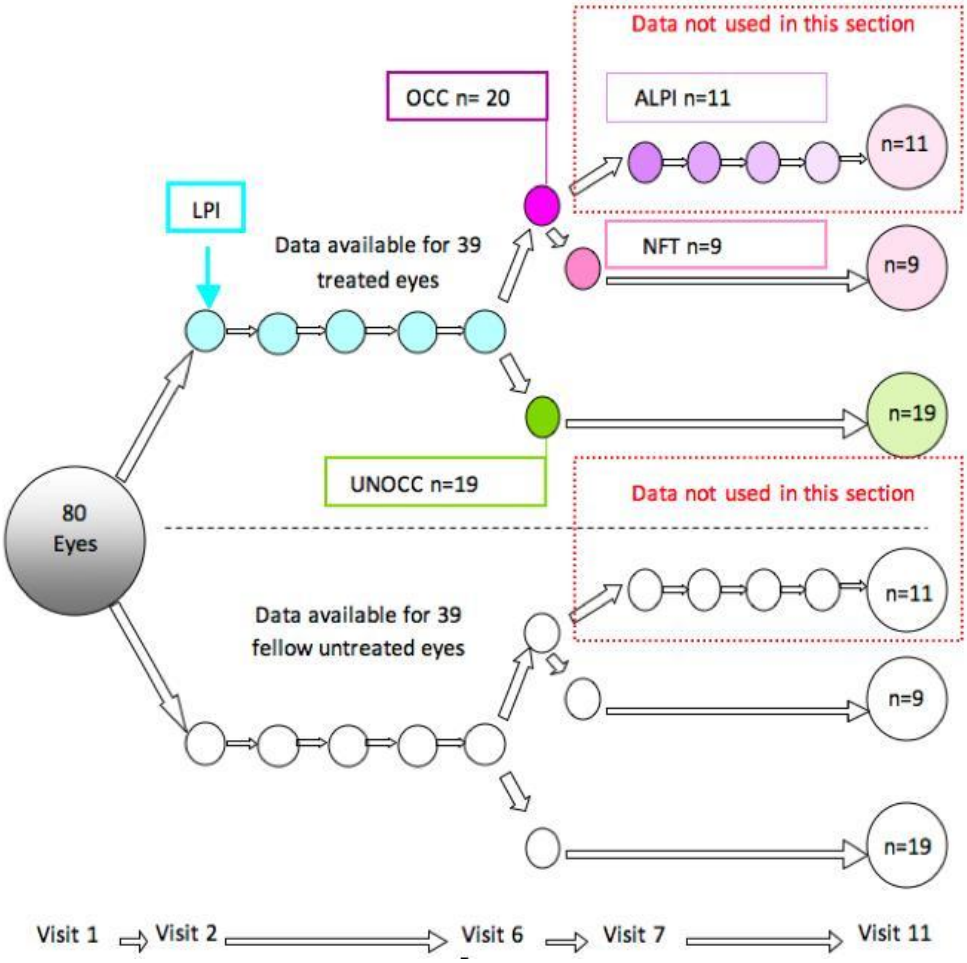

Figure 4.1. Participant pathway through the study. The upper half of the figure, as divided by the dashed line, shows the pathway of those eyes randomised to receive Laser Peripheral Iridotomy (LPI) and the lower half of the figure shows the pathway of the untreated fellow eyes. Abbreviations in this figure: n= number of eyes in each group. LPI= Laser Peripheral Iridotomy. OCC= Post-LPI eyes with occludable angles. UNOCC= Post-LPI eyes with unoccludable eyes. ALPI= Eyes with post-LPI occludable angles that were further randomised into receiving ALPI. NFT= Eyes with post-LPI occludable angles that were further randomised into not receiving further treatment. The data for the eyes in the red boxes was not used in the analysis for this section results.

Eight sectors (Superior, Superior-Nasal, Nasal, Inferior-Nasal, Inferior, Inferior-Temporal, Temporal and Superior-Temporal) for every eye with their corresponding 8 parameters (AOD, ARA, TISA and TIA at 500 and 750 microns) were assessed with the CASIA analysis software.

The IOP used for Visit 1 and Visit 11 was the diurnal IOP taken closest in time to the CASIA capture of images. However, it is important to be aware that the aim of this section was not to show changes of the IOP through time, but to show changes associated with differences in the parameter dimensions between groups (treated versus untreated eyes) and measured at different time points.

The mean total power used to perform the iridotomy was 16.11mJ (SD 10.879mJ) and the mean number of shots 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 with the retroillumination technique using the same slit lamp.

The statistical analysis was divided in two sub-sections depending on the hypothesis to be tested:

1st Hypothesis: "The treated eye angle parameters would experience a widening effect after the LPI while the untreated eyes parameters would remain unchanged. Furthermore, in the case of the treated eye, this widening would be directly associated with time elapsed since the procedure"

To statistically show the effect of the LPI on the angle parameters of treated and untreated eyes, two different statistical models were performed. The first statistical approach was to use paired samples t-test to compare Visit 4, Visit 5, Visit 6 and Visit 11 against Visit 1 (baseline) for the treated eye angle parameters and a separate analysis for the untreated ones. These analyses would show differences through time for both groups, but not differences between groups. A second analysis was designed to show differences through time between treated and untreated eyes adjusted for differences at baseline. Analysis of covariance was used with this aim. Both groups were compared against each other at Visits 4, 5, 6 and 11 while these differences were adjusted for the differences between the same groups at Visit 1.

The association with time was investigated with mixed effects regression between time elapsed since the LPI and the adjusted mean differences in the parameters found between the treated and untreated groups.

2nd Hypothesis: "There may be an association between, first, the widening effect on the angle and time elapsed since LPI (direct association) and, second, between this effect and a decrease in IOP levels (inverse association)"

These associations were investigated using mixed effects regression models. The adjusted mean differences between the parameters for the two groups (treated and untreated) were associated to adjusted differences in time elapsed (first regression model) and IOP (second regression model) for both groups.

4.1.3 Results

Forty eyes of forty patients received LPI. The eye receiving the LPI was randomly selected as previously described in this thesis. Three months after the LPI (Visit 6, Mean time 92.5 days, SD 8.4), 21 eyes remained occludable as observed with applanation gonioscopy. Eleven eyes of these 21 were further randomised to receive ALPI and were not included in the statistical analysis.

The mean values for every parameter in every visit together with their standard deviation can be found in Table 4.1 (Appendix 1). Both treated and untreated eyes dimensions were graphed for the 8 sections and for each of the eight parameters studied through time (Visit 1, 4, 5, 6 and 11). These graphs/figures can be found in Appendix 1.

Results 1st Hypothesis: "The treated eye parameters would experience a widening effect after the LPI while the untreated eyes parameters would remain unchanged".

The paired samples t-test showed a widening effect through time for the treated and untreated eye in the majority of the parameters for the sections under study. There were very few statistical significant differences between the follow-up visits angle parameters and those found at baseline.

The most marked widening effect of the angle was found for the Inferior-Temporal in the case of the treated eye. In this section the parameters tended to increase through time until Visit 11 were there was a slight regression in widening. The majority of the mean differences in this section were statistically significant. As an example of this trend of widening through visits and final slight regression, Inferior-Temporal ARA 750 presented a mean difference with Visit 1 of 0.0201mm^2 (0.035) p=0.002 at Visit 4, 0.0277mm^2 (0.046) p=0.001 at Visit 5, 0.0296mm^2 (0.041) p<0.001 at Visit 6 and 0.0242mm^2 (0.045) p=0.015 at Visit 11. Similar pattern was followed by TISA 750 in the same section, where the differences found at Visit 4 when compared to Visit 1 were 0.0157mm^2

(0.030) p=0.005; at Visit 5, 0.0206mm^2 (0.042) p=0.006; at Visit 6, 0.0235mm^2 (0.035) p<0.001 and at Visit 11, 0.0189mm^2 (0.038) p=0.024.

There was a statistically significant widening of the treated eye in ARA 500 found in the Superior-Nasal section between Visit 1 and Visits 4, 5 and 6. It increased by 0.090mm^2 (0.016) p=0.002 at Visit 4, by 0.062mm^2 (0.018) p=0.049 at Visit 5 and by 0.0067mm^2 (0.019) p=0.050 at Visit 6. There was an increase of 0.058mm^2 (0.020) at Visit 11, but this difference resulted non statistically significant (p=0.165).

Nasal and Temporal sections also showed some statistically significant widening effect of the parameters. In the case of these two sections, the significant widening effect was as commonly found in the treated eye as it was in the untreated. For example, a statistically significant increase in Temporal AOD 500 was found at Visit 4 and Visit 5 for the treated eye (0.0254mm (0.052) p=0.007 and 0.0212mm (0.054) p=0.030, respectively) and similar widening occurred in the untreated eye for the same parameter (0.0189 (0.036) p=0.005 at Visit 4 and 0.0214mm (0.044) p= 0.009 at Visit 5). Additionally some statistically significant widening was observed in the untreated Temporal ARA and TISA 750 at Visits 4, 5 and 6. The same effect was statistically non-significant in the case of the treated eye for the same parameters. Something similar happened at Visit 4 when assessing the mean differences for the untreated eye in the case of Nasal ARA and TISA 500 and ARA and TISA 750. These four parameters experienced a statistically significant widening in the untreated eye while the treated eye was non-statistically significant.

Superior-Temporal parameters widened in its majority at Visit 4 for both, treated and untreated eyes, although the effect was higher in the case of the treated group. For example, ARA 500 increased by 0.0105mm (0.027) p=0.033 in the treated eye and by 0.0081mm (0.022) p=0.044 in the untreated eye. Similar widening differences between treated and untreated eyes were found for TISA 500 and AOD, ARA and TISA 750 for this section at Visit 4. At Visit 5, the statistically significant widening of the parameters in this section was only found in the treated eyes.

The mean differences and p-values for every parameter under study can be found in Table 4.2 (next 4 pages). The statistically significant mean differences are highlighted in yellow colour.

Paired Samples t test		Visit 4- Visit 1				Visit 5- Visit 1				Visit 6- Visit 1				Visit 11- Visit 1			
		TREATED EYE		UNTREATED EYE		TREATED EYE		UNTREATED EYE		TREATED EYE		UNTREATED EYE		TREATED EYE		UNTREATED EYE	
		M. Diff	P value	M. Diff	P value	M. Diff	P value	M. Diff	P value	M. Diff	P value	M. Diff	P value	M. Diff	P value	M. Diff	P value
SUPERIOR	AOD500	-0.0021 (0.044)	0.777	0.0094 (0.037)	0.152	0.0003 (0.048)	0.967	0.0096 (0.034)	0.113	0.0051 (0.047)	0.529	0.0060 (0.040)	0.388	-0.000 (0.042)	0.969	0.0126 (0.038)	0.123
	ARA500	-0.0021 (0.016)	0.464	0.0018 (0.012)	0.389	-0.0009 (0.020)	0.777	-0.0017 (0.013)	0.467	0.0007 (0.016)	0.803	-0.0007 (0.012)	0.764	0.0033 (0.012)	0.198	0.0025 (0.010)	0.221
	TISA500	-0.0020 (0.015)	0.447	0.0016 (0.011)	0.398	-0.0005 (0.018)	0.873	-0.0014 (0.013)	0.542	0.0011 (0.015)	0.691	-0.0006 (0.012)	0.759	0.0040 (0.012)	0.124	0.0023 (0.009)	0.268
	TIA500	-0.0059 (4.018)	0.993	0.6333 (3.019)	0.237	0.0943 (3.886)	0.887	0.7147 (2.805)	0.147	0.2471 (3.365)	0.671	0.2765 (2.628)	0.544	-0.2375 (3.201)	0.720	1.0130 (3.110)	0.133
	AOD750	0.0170 (0.077)	0.207	0.0055 (0.059)	0.610	0.0169 (0.071)	0.168	0.0067 (0.052)	0.469	0.0299 (0.062)	0.009	0.0013 (0.075)	0.920	0.0240 (0.064)	0.087	0.0127 (0.054)	0.281
	ARA750	0.0013 (0.026)	0.772	0.0046 (0.021)	0.247	0.0009 (0.032)	0.861	0.0010 (0.023)	0.812	0.0046 (0.027)	0.338	0.0037 (0.026)	0.421	0.0054 (0.020)	0.209	0.0059 (0.018)	0.137
	TISA750	0.0016 (0.025)	0.719	0.0042 (0.021)	0.283	0.0014 (0.030)	0.791	0.0015 (0.023)	0.711	0.0051 (0.026)	0.267	0.0038 (0.026)	0.408	0.0054 (0.019)	0.193	0.0063 (0.017)	0.099
	TIA750	0.9853 (4.765)	0.237	0.2633 (3.067)	0.642	0.7457 (4.077)	0.287	0.4375 (2.492)	0.328	1.4206 (3.471)	0.023	0.1906 (3.557)	0.764	0.5739 2.791)	0.335	0.9591 (3.456)	0.207
INFERIOR	AOD500	-0.0022 (0.053)	0.809	-0.0085 (0.055)	0.376	0.0008 (0.062)	0.938	0.0020 (0.059)	0.845	-0.0016 (0.063)	0.880	-0.0110 (0.053)	0.224	-0.0157 (0.090)	0.401	0.0075 (0.066)	0.586
	ARA500	0.0027 (0.019)	0.415	-0.0024 (0.030)	0.650	0.0027 (0.021)	0.464	0.0039 (0.020)	0.257	-0.0005 (0.016)	0.869	-0.0011 (0.018)	0.718	-0.0055 (0.021)	0.213	0.0034 (0.025)	0.512
	TISA500	0.0022 (0.014)	0.360	-0.0020 (0.028)	0.673	0.0027 (0.020)	0.433	0.0043 (0.020)	0.225	-0.0003 (0.015)	0.912	-0.0013 (0.016)	0.645	-0.0049 (0.020)	0.260	0.0015 (0.022)	0.737
	TIA500	0.4559 (3.543)	0.458	-1.0618 (4.818)	0.208	0.4057 (4.040)	0.556	-0.3343 (4.565)	0.668	0.4971 (4.211)	0.490	-(1.0314 (3.691)	0.107	-0.6208 (4.082)	0.464	0.2833 (4.755)	0.773
	AOD750	0.0116 (0.061)	0.272	-0.0085 (0.064)	0.452	0.0098 (0.078)	0.464	0.0001 (0.050)	0.995	0.0297 (0.083)	0.042	-0.0091 (0.082)	0.520	-0.0012 (0.077)	0.941	-0.0165 (0.083)	0.343
	ARA750	0.0053 (0.023)	0.191	-0.0019 (0.039)	0.788	0.0042 (0.033)	0.459	0.0044 (0.027)	0.330	0.0033 (0.028)	0.490	-0.0017 (0.029)	0.727	-0.0068 (0.035)	0.350	0.0029 (0.040)	0.728
	TISA750	0.0049 (0.020)	0.167	-0.0019 (0.037)	0.767	0.0046 (0.033)	0.429	0.0045 (0.027)	0.327	0.0031 (0.028)	0.529	-0.0020 (0.027)	0.669	-0.0061 (0.034)	0.401	0.0011 (0.038)	0.889
	TIA750	0.5088 (3.484)	0.401	-0.7606 (3.315)	0.197	0.1057 (4.114)	0.880	-0.2543 (2.753)	0.588	1.4571 (4.826)	0.083	-0.6143 (4.213)	0.394	-0.3417 (3.584)	0.645	-0.8833 (4.172)	0.310

Table 4.2. Pair Samples t test comparing the dimensions of the angle parameters for treated and untreated eyes through time using Visit 1 as baseline. The eight angles sections were compared (Superior, Inferior, Superior-Nasal, Inferior-Temporal, Nasal, Temporal, Inferior-Nasal and Superior-Temporal). Statistically significant values have been highlighted in yellow colour. M Diff=Mean difference. SD=Standard Deviation

Paired Samples t test		Visit 4- Visit 1				Visit 5- Visit 1				Visit 6- Visit 1				Visit 11- Visit 1			
		TREATED EYE		UNTREATED EYE		TREATED EYE		UNTREATED EYE		TREATED EYE		UNTREATED EYE		TREATED EYE		UNTREATED EYE	
		M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value
SUPERIOR-NASAL	AOD500	0.0132 (0.040)	0.061	-0.0009 (0.030)	0.858	0.0135 (0.036)	0.034	0.0006 (0.042)	0.935	0.0109 (0.044)	0.151	0.0129 (0.037)	0.054	0.0143 (0.050)	0.176	0.0075 (0.050)	0.476
	ARA500	0.0090 (0.016)	0.002*	0.0006 (0.017)	0.837	0.0062 (0.018)	0.049*	-0.0020 (0.026)	0.661	0.0067 (0.019)	0.050*	0.0032 (0.016)	0.263	0.0058 (0.020)	0.165	-0.0010 (0.023)	0.846
	TISA500	0.0075 (0.013)	0.002*	0.0010 (0.015)	0.718	0.0055 (0.016)	0.053	-0.0019 (0.021)	0.600	0.0055 (0.017)	0.063	0.0037 (0.014)	0.148	0.0048 (0.018)	0.215	-0.0001 (0.021)	0.984
	TIA500	0.6794 (3.935)	0.321	-0.6500 2.836)	0.190	0.3514 (3.627)	0.570	-0.1559 (4.184)	0.829	-0.3657 (4.009)	0.593	0.4727 (4.503)	0.551	-0.0500 (4.424)	0.956	0.2000 (5.055)	0.851
	AOD750	0.0229 (0.049)	0.011*	0.0153 (0.051)	0.091	0.0127 (0.052)	0.155	0.0168 (0.053)	0.068	0.0206 (0.055)	0.040*	0.0185 (0.046)	0.021	0.0210 (0.073)	0.170	0.0067 (0.047)	0.492
	ARA750	0.0148 (0.024)	0.001*	0.0029 (0.023)	0.471	0.0110 (0.027)	0.020*	0.0009 (0.032)	0.875	0.0093 (0.026)	0.052	0.0058 (0.022)	0.132	0.0070 (0.030)	0.267	-0.0003 (0.029)	0.967
	TISA750	0.0130 (0.021)	0.001*	0.0039 (0.020)	0.288	0.0098 (0.025)	0.027*	0.0008 (0.026)	0.863	0.0079 (0.025)	0.074	0.0062 (0.020)	0.083	0.0058 (0.028)	0.323	0.0006 (0.026)	0.914
	TIA750	1.0882 (3.377	0.069	0.3794 (3.044)	0.472	0.1371 (3.444)	0.815	0.8571 (2.870)	0.086	0.0515 (3.968)	0.941	0.5771 (3.265)	0.303	0.2750 (4.555)	0.770	-0.0750 (3.281)	0.912
INFERIOR-TEMPORAL	AOD500	0.0297 (0.056)	0.004*	0.0047 (0.048)	0.579	0.0263 (0.074)	0.044	0.0132 (0.056)	0.181	0.0386 (0.056)	<0.001*	0.0085 (0.055)	0.369	0.0308 (0.068)	0.036*	0.0163 (0.043)	0.074
	ARA500	0.0071 (0.023)	0.078	-0.0009 (0.022)	0.828	0.0135 (0.029)	0.010*	0.0035 (0.024)	0.413	0.0139 (0.027)	0.004*	0.0032 (0.023)	0.426	0.0083 (0.024)	0.111	-0.0010 (0.019)	0.808
	TISA500	0.0049 (0.020)	0.165	-0.0018 (0.020)	0.612	0.0087 (0.025)	0.051	0.0029 (0.024)	0.481	0.0100 (0.024)	0.019*	0.0015 (0.021)	0.683	0.0064 (0.021)	0.150	-0.0021 (0.017)	0.563
	TIA500	1.2971 (5.933)	0.211	-0.6939 (4.204)	0.350	-0.5886 (5.748)	0.549	0.8471 (5.847)	0.404	1.0486 (6.049)	0.312	-0.7857 (4.174)	0.273	0.3500 (6.355)	0.790	0.6125 (3.669)	0.422
	AOD750	0.0663 (0.081	<0.001*	0.0024 (0.074)	0.851	0.0602 (0.092)	<0.001*	0.0169 (0.068)	0.148	0.0707 (0.071)	<0.001*	0.0202 (0.069)	0.102	0.0653 (0.110)	0.008*	0.0058 (0.050)	0.579
	ARA750	0.0201 (0.035)	0.002*	0.0014 (0.034)	0.811	0.0277 (0.046)	0.001*	0.0080 (0.037)	0.210	0.0296 (0.041)	<0.001*	0.0059 (0.035)	0.346	0.0242 (0.045)	0.015*	-0.0002 (0.024)	0.973
	TISA750	0.0157 (0.030)	0.005*	0.0003 (0.032)	0.957	0.0206 (0.042)	0.006*	0.0069 (0.037)	0.278	0.0235 (0.035)	<0.001*	0.0042 (0.034)	0.474	0.0189 (0.038)	0.024*	-0.0014 (0.023)	0.761
	TIA750	2.3176 (4.194	0.003*	-0.8588 (4.145)	0.236	0.6200 (4.507)	0.421	0.7229 (4.631)	0.362	1.7000 (3.893)	0.014*	-0.0606 (3.439)	0.920	1.4875 (5.632)	0.209*	-0.3208 (2.579)	0.548

Table 4.2. (CONTINUATION). Pair Samples t test comparing the dimensions of the angle parameters for treated and untreated eyes through time using Visit 1 as baseline. The eight angles sections were compared (Superior, Inferior, Superior-Nasal, Inferior-Temporal, Nasal, Temporal, Inferior-Nasal and Superior-Temporal). Statistically significant values have been highlighted in yellow colour. M Diff=Mean difference. SD=Standard Deviation.

Paired Samples t test		Visit 4- Visit 1				Visit 5- Visit 1				Visit 6- Visit 1				Visit 11- Visit 1			
		TREATED EYE		UNTREATED EYE		TREATED EYE		UNTREATED EYE		TREATED EYE		UNTREATED EYE		TREATED EYE		UNTREATED EYE	
		M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value
NASAL	AOD500	0.0120 (0.058)	0.234	0.0126 (0.054)	0.182	0.0098 (0.054)	0.288	0.0114 (0.045)	0.139	0.0133 (0.049)	0.117	0.0130 (0.044)	0.091	0.0217 (0.052)	0.054	0.0049 (0.060)	0.700
	ARA500	0.0021 (0.027)	0.654	0.0137 (0.032)	0.018*	0.0015 (0.025)	0.728	0.0076 (0.027)	0.112	0.0039 (0.030)	0.444	0.0104 (0.031)	0.061	-0.0002 (0.024)	0.967	0.0085 (0.039)	0.314
	TISA500	0.0018 (0.023)	0.660	0.0117 (0.026)	0.014*	0.0000 (0.025	0.995	0.0071 (0.021)	0.053	0.0020 (0.028)	0.670	0.0097 (0.027)	0.043*	-0.0013 (0.021)	0.765	0.0060 (0.030)	0.341
	TIA500	0.5706 (5.978)	0.582	0.6647 5.474)	0.484	-0.7486 (5.526)	0.428	0.3771 (4.717)	0.639	0.0314 (5.186)	0.972	0.2294 (3.799)	0.727	0.3667 (4.556)	0.697	-1.1565 (4.237)	0.204
	AOD750	0.0352 (0.058)	0.001*	0.0094 (0.052)	0.298	0.0149 (0.053)	0.102	0.0217 (0.069)	0.075	0.0349 (0.053)	<0.001	0.0182 (0.061)	0.089	0.0309 (0.071)	0.044*	0.0133 (0.085)	0.452
	ARA750	0.0100 (0.034)	0.098	0.0142 (0.040)	0.048*	0.0047 (0.031)	0.379	0.0087 (0.036)	0.170	0.0103 (0.037)	0.111	0.0116 (0.038)	0.080	0.0056 (0.029)	0.359	0.0090 (0.052)	0.404
	TISA750	0.0094 (0.031)	0.089	0.028 (0.036)	0.047*	0.0029 (0.032)	0.591	0.0083 (0.030)	0.113	0.0079 (0.034)	0.184	0.0110 (0.033)	0.057	0.0037 (0.026)	0.506	0.0070 (0.042)	0.423
	TIA750	1.6176 (4.528)	0.045*	0.1147 2.965)	0.823	-0.3057 (3.752)	0.633	0.6029 (3.388)	0.307	1.1857 (3.870)	0.079	0.3886 (3.201)	0.478	0.7500 (3.615)	0.320	-0.3875 (4.039)	0.643
TEMPORAL	AOD500	0.0254 (0.052)	0.007*	0.0189 (0.036)	0.005*	0.0212 (0.054)	0.030*	0.0214 (0.044)	0.009*	0.0167 (0.062)	0.121	0.0181 (0.036)	0.006*	0.0074 (0.050)	0.478	0.0215 (0.055)	0.069
	ARA500	0.0033 (0.021)	0.367	0.0059 (0.019)	0.075	0.0053 (0.022)	0.159	0.0045 (0.019)	0.171	0.0044 (0.022)	0.243	0.0078 (0.019)	0.024*	0.0002 (0.019)	0.966	0.0083 (0.025)	0.116
	TISA500	0.0024 (0.020)	0.489	0.0051 (0.015)	0.062	0.0024 (0.018)	0.431	0.0046 (0.015)	0.082	0.0029 (0.020)	0.405	0.0085 (0.015)	0.002*	-0.0020 (0.019)	0.612	0.0082 (0.022)	0.082
	TIA500	1.4853 (4.927)	0.088	1.1324 (3.764)	0.089	0.6559 (5.269)	0.473	1.1242 (4.262)	0.139	0.4286 (5.972)	0.674	(1.2412 (3.615)	0.054	-0.3292 (4.417)	0.718	1.3458 (5.446)	0.238
	AOD750	0.0227 (0.056)	0.024*	0.0149 (0.049)	0.087	0.0224 (0.062)	0.041*	0.0287 (0.038)	<0.001	0.0362 (0.057)	0.001*	0.0345 (0.055)	0.001*	0.0273 (0.067)	0.057	0.0202 (0.063)	0.132
	ARA750	0.0084 (0.030)	0.108	0.0121 (0.027)	0.014*	0.0065 (0.032)	0.232	0.0142 (0.028)	0.005*	0.0101 (0.030)	0.059	0.0166 (0.029)	0.002*	0.0033 (0.030)	0.590	0.0158 (0.037)	0.046*
	TISA750	0.0074 (0.028)	0.138	0.0114 (0.025)	0.013*	0.0036 (0.028)	0.459	0.0139 (0.025)	0.002*	0.0081 (0.029)	0.103	0.0174 (0.026)	0.000*	0.0010 (0.029)	0.863	0.0158 (0.035)	0.035*
	TIA750	0.7676 (3.596)	0.222	0.4529 (3.227	0.419	0.3743 (3.877)	0.572	1.0429 (2.584)	0.023*	1.2229 (3.449)	0.043*	(1.8543 (3.586)	0.004*	0.9708 (4.160)	0.265	0.6583 (4.176)	0.448

Table 4.2. (CONTINUATION). Pair Samples t test comparing the dimensions of the angle parameters for treated and untreated eyes through time using Visit 1 as baseline. The eight angles sections were compared (Superior, Inferior, Superior-Nasal, Inferior-Temporal, Nasal, Temporal, Inferior-Nasal and Superior-Temporal). Statistically significant values have been highlighted in yellow colour. M Diff=Mean difference. SD=Standard Deviation.

Paired Samples t test		Visit 4- Visit 1				Visit 5- Visit 1				Visit 6- Visit 1				Visit 11- Visit 1			
		TREATED EYE		UNTREATED EYE		TREATED EYE		UNTREATED EYE		TREATED EYE		UNTREATED EYE		TREATED EYE		UNTREATED EYE	
		M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value	M. Diff (SD)	P value
INFERIOR-NASAL	AOD500	0.0172 (0.061)	0.107	-0.0047 (0.064)	0.673	0.0027 (0.077)	0.835	0.0133 (0.058)	0.183	0.0245 (0.054)	0.012*	0.0029 (0.056)	0.765	0.0039 (0.064)	0.769	-0.0152 (0.069)	0.289
	ARA500	0.0019 (0.020)	0.582	0.0060 (0.029)	0.240	-0.0001 (0.037)	0.986	0.0088 (0.031)	0.102	0.0088 (0.035)	0.148	0.0039 (0.028)	0.414	-0.0068 (0.027)	0.237	-0.0043 (0.035)	0.557
	TISA500	0.0002 (0.017)	0.937	0.0042 (0.023)	0.310	-0.0033 (0.034)	0.562	0.0059 (0.023)	0.144	0.0038 (0.025)	0.377	0.0029 (0.023)	0.464	-0.0067 (0.024)	0.194	-0.0049 (0.030)	0.436
	TIA500	0.8168 (5.420)	0.386	-0.9353 (4.464)	0.230	-1.2266 (6.862)	0.298	0.1114 (5.629)	0.907	-0.0294 (4.731)	0.971	-0.4114 (5.371)	0.653	-1.4042 (5.378)	0.214	-1.9250 (5.956)	0.127
	AOD750	0.0149 (0.067)	0.205	0.0065 (0.065)	0.567	0.0090 (0.088)	0.546	0.0144 (0.070)	0.232	0.0413 (0.068)	0.001*	0.0105 (0.087)	0.483	0.0196 (0.075)	0.215	-0.0001 (0.108)	0.997
	ARA750	0.0054 (0.033)	0.343	0.0102 (0.039)	0.140	0.0002 (0.057)	0.986	0.0121 (0.043)	0.102	0.0150 (0.044)	0.053	0.0069 (0.044)	0.357	-0.0061 (0.040)	0.460	-0.0052 (0.055)	0.649
	TISA750	0.0044 (0.031)	0.410	0.0078 (0.034)	0.211	-0.0023 (0.053)	0.799	0.0089 (0.036)	0.151	0.0107 (0.036)	0.090	0.0057 (0.040)	0.404	-0.0062 (0.037)	0.424	-0.0060 (0.050)	0.568
	TIA750	0.1471 (3.704)	0.818	-0.1061 (3.599)	0.867	-1.0343 (5.438)	0.268	0.2914 (4.436)	0.700	0.5353 (4.211)	0.464	0.1829 (5.749)	0.852	-0.3750 (5.251)	0.730	-0.4750 (5.990)	0.701
SUPERIOR-TEMPORAL	AOD500	0.0275 (0.053)	0.005*	0.0146 (0.048)	0.086	0.0203 (0.052)	0.033*	0.0044 (0.045)	0.573	0.0074 (0.039)	0.274	0.0095 (0.040)	0.164	0.0027 (0.037)	0.720	0.0211 (0.062)	0.111
	ARA500	0.0105 (0.027)	0.033*	0.0081 (0.022)	0.044*	0.0080 (0.019)	0.024*	0.0035 (0.021)	0.339	0.0014 (0.019)	0.669	0.0011 (0.019)	0.722	0.0009 (0.017)	0.803	0.0088 (0.027)	0.126
	TISA500	0.0087 (0.023)	0.036*	0.0073 (0.019)	0.035*	0.0068 (0.018)	0.039*	0.0031 (0.019)	0.359	0.0008 (0.019)	0.806	0.0012 (0.017)	0.677	0.0004 (0.016)	0.899	0.0076 (0.025)	0.151
	TIA500	1.3853 (4.232)	0.065	0.6413 (4.244)	0.385	0.3303 (4.353)	0.666	0.3412 (4.693)	0.674	-0.4257 (3.758)	0.507	0.6914 (4.140)	0.330	-1.0417 (3.428)	0.150	0.9458 (5.479)	0.406
	AOD750	0.0390 (0.071)	0.003*	0.0232 (0.062)	0.037*	0.0285 (0.064)	0.015*	0.0061 (0.056)	0.525	0.0230 (0.069)	0.056	0.0094 (0.075)	0.467	0.0241 (0.061)	0.067	0.0014 (0.076)	0.931
	ARA750	0.0191 (0.039)	0.008*	0.0194 (0.038)	0.005*	0.0134 (0.030)	0.015*	0.0075 (0.031)	0.167	0.0044 (0.027)	0.348	0.0055 (0.030)	0.296	0.0045 (0.025)	0.381	0.0085 (0.041)	0.331
	TISA750	0.0171 (0.035)	0.007*	0.0160 (0.032)	0.007*	0.0120 (0.029)	0.020*	0.0070 (0.030)	0.175	0.0038 (0.027)	0.404	0.0056 (0.028)	0.261	0.0043 (0.024)	0.390	0.0081 (0.040)	0.339
	TIA750	1.4618 (4.133)	0.047*	0.7153 (4.017)	0.307	0.4265 (3.826)	0.520	0.3200 (3.700)	0.612	0.2514 (4.354)	0.735	0.3647 (4.663)	0.651	0.3917 (4.071)	0.642	-0.6435 (5.060)	0.548

Table 4.2 (CONTINUATION). Pair Samples t test comparing the dimensions of the angle parameters for treated and untreated eyes through time using Visit 1 as baseline. The eight angles sections were compared (Superior, Inferior, Superior-Nasal, Inferior-Temporal, Nasal, Temporal, Inferior-Nasal and Superior-Temporal). Statistically significant values have been highlighted in yellow colour. M Diff=Mean difference. SD=Standard Deviation.

At this point, it was necessary to test if the widening effect found in the parameters of the treated eye was due to the LPI or due to other uncontrolled factors (some widening effect has been found in the untreated eye using the paired samples t-test). The advantage of the analysis of covariance is that it compares the widening effect between the treated and untreated eyes at every visit while adjusting for their differences at Visit 1. When these adjustments were made in the statistical model, the angle parameters dimensions in the treated eye through the different visits were of a positive mean value in the majority of the cases. As the differences between treated and untreated eyes in the model were set as Treated minus Untreated, positive values meant wider parameters for the treated eye.

A visual representation of these parameter dimensions for treated and untreated eyes can be found in Figure 4.2 to 4.33 in Appendix 1.

Some of these positive values were statistically significant and commonly found in the Inferior-Temporal section. As an example of parameter differences in this section, the graph below (Figure 4.7) shows the dimensional change in the AOD 500 and 750 in the Inferior-Temporal section. In this graph, the treated eye experienced the most marked increase in dimension 1 week after the LPI (Visit 4) and, although in Visit 5 there was a slight decrease, at Visit 6 and 11 there was a tendency to increase again. In the case of the untreated eye the dimensional changes through time were minimal and constant. The dimensional widening in the treated eye while adjusted for the untreated eye in the case of AOD 750 was statistically significant for every visit. In the case of AOD 500, Visit 4 and 6 were the ones presenting the statistically significant widening.

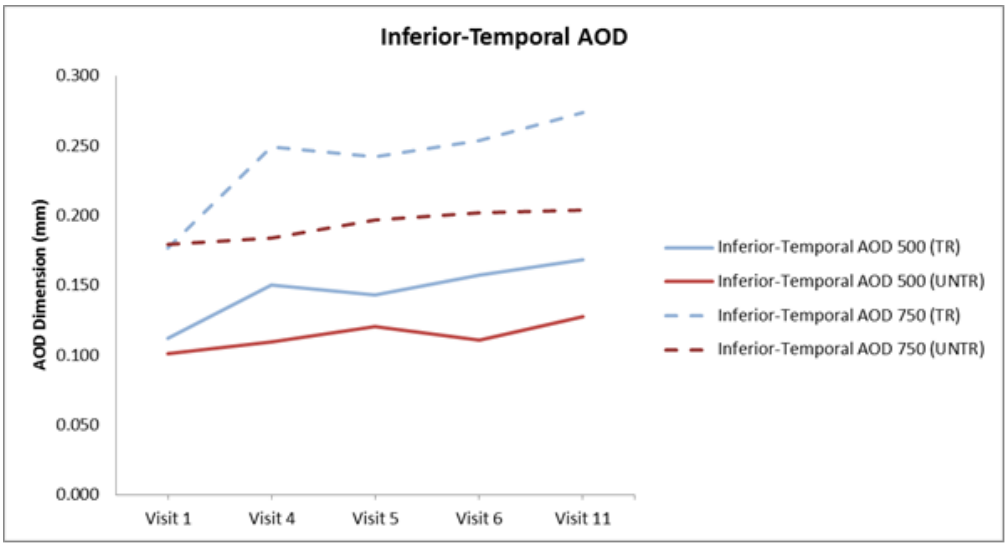

Figure 4.7. Mean values for the parameters AOD 500 and 750 in the Inferior-Temporal section for treated (TR) and untreated (UNTR) eyes at Visits 1, 4, 5, 6 and 11.

Another example of this pattern can be found in the Inferior-Temporal section as well. Figure 4.15 (below), shows the dimensional changes of ARA 500 and 750 for this section. It is clear in this graph the tendency of the treated eye to increase in dimension through time while the untreated eye remains within a minimal change range. The changes in the treated eye where found statistically significant for all the time points in the case of ARA 750 when adjusted for the untreated eye. Visits 4 and 6 showed as well statistically significant changes of the same nature for the parameter ARA 500, while the ones found at Visits 5 and 11 were not.

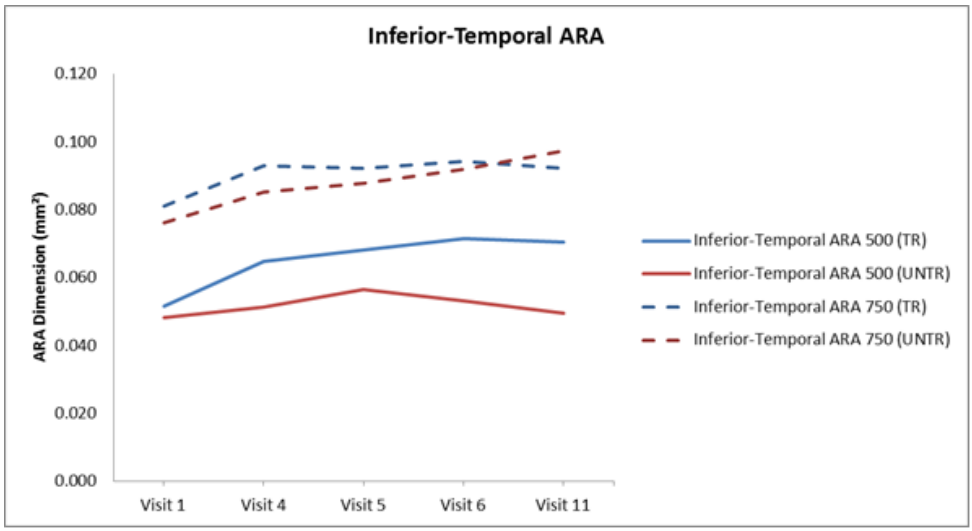

Figure 4.15 Mean values for the parameters ARA 500 and 750 in the Inferior-Temporal section for treated (TR) and untreated (UNTR) eyes at Visits 1, 4, 5, 6 and 11.

The two other parameters measured in the Inferior-Temporal section (TISA and TIA at 500 and 750) presented similar behaviours to ARA and AOD, although not all the changes were statistically significant (changes found at Visits 5 and 11 resulted non-statistically significant). Regarding the rest of the parameters found in the rest of the sections, the most of them showed an increase when compared to the untreated eye. The exceptional cases, when this did not happen, the change was found non-statistically significant.

For more information about the adjusted mean differences in the treated eye and their p-values for all the parameters, see Table 4.3 in the next page (it continues for the next 3 pages). The statistically significant differences have been highlighted in yellow colour.

	VISIT 4			VISIT 5			VISIT 6			VISIT 11		
	Mean Diff	St Error	P Value	Mean Diff	St Error	P Value	Mean Diff	St Error	P Value	Mean Diff	St Error	P Value
SUPERIOR AOD500	-0.010	(0.010)	0.335	-0.006	(0.010)	0.556	0.003	(0.010)	0.747	-0.011	(0.012)	0.348
SUPERIOR ARA500	-0.003	(0.003)	0.322	0.002	(0.004)	0.596	0.002	(0.003)	0.549	0.001	(0.003)	0.765
SUPERIOR TISA500	-0.003	(0.003)	0.323	0.002	(0.003)	0.583	0.002	(0.003)	0.485	0.002	(0.003)	0.572
SUPERIOR TIA500	-0.511	(0.881)	0.564	-0.420	(0.818)	0.609	0.249	(0.717)	0.729	-1.016	(0.924)	0.277
SUPERIOR AOD750	0.012	(0.017)	0.466	0.012	(0.014)	0.407	0.032	(0.015)	0.032*	0.010	(0.017)	0.551
SUPERIOR ARA750	-0.003	(0.006)	0.670	0.003	(0.006)	0.611	0.003	(0.006)	0.617	-0.000	(0.006)	0.937
SUPERIOR TISA750	-0.002	(0.006)	0.759	0.003	(0.006)	0.645	0.004	(0.006)	0.564	-0.001	(0.006)	0.870
SUPERIOR TIA750	0.848	(0.997)	0.398	0.496	(0.793)	0.534	1.539	(0.783)	0.054	-0.366	(0.914)	0.691
INFERIOR AOD500	0.012	(0.012)	0.326	0.004	(0.013)	0.767	0.014	(0.013)	0.274	-0.014	(0.020)	0.482
INFERIOR ARA500	0.007	(0.006)	0.227	-0.001	(0.005)	0.914	0.001	(0.004)	0.717	-0.007	(0.006)	0.246
INFERIOR TISA500	0.006	(0.005)	0.221	-0.001	(0.005)	0.835	0.002	(0.004)	0.652	-0.004	(0.005)	0.431
INFERIOR TIA500	1.704	(0.861)	0.052	0.924	(0.890)	0.303	1.648	(0.889)	0.068	-0.729	(1.128)	0.521
INFERIOR AOD750	0.022	(0.014)	0.110	0.011	(0.015)	0.470	0.041	(0.018)	0.030*	0.016	(0.022)	0.474
INFERIOR ARA750	0.010	(0.007)	0.196	0.001	(0.007)	0.919	0.006	(0.007)	0.348	-0.007	(0.010)	0.471
INFERIOR TISA750	0.009	(0.007)	0.177	0.001	(0.007)	0.853	0.006	(0.007)	0.341	-0.004	(0.010)	0.669
INFERIOR TIA750	1.476	(0.708)	0.041*	0.524	(0.769)	0.498	2.276	(1.002)	0.026*	0.609	(1.046)	0.563
SUPERIOR-NASAL AOD500	0.014	(0.009)	0.120	0.011	(0.009)	0.230	-0.003	(0.010)	0.737	0.005	(0.015)	0.749
SUPERIOR-NASAL ARA500	0.008	(0.004)	0.057	0.007	(0.005)	0.200	0.003	(0.004)	0.508	0.005	(0.006)	0.418
SUPERIOR-NASAL TISA500	0.006	(0.003)	0.088	0.006	(0.004)	0.150	0.001	(0.004)	0.709	0.004	(0.006)	0.492
SUPERIOR-NASAL TIA500	1.173	(0.806)	0.150	0.286	(0.893)	0.750	-1.243	(0.924)	0.183	-0.442	(1.271)	0.729
SUPERIOR-NASAL AOD750	0.007	(0.012)	0.528	-0.004	(0.012)	0.753	0.003	(0.012)	0.813	0.018	(0.017)	0.306
SUPERIOR-NASAL ARA750	0.011	(0.006)	0.057	0.009	(0.007)	0.205	0.003	(0.006)	0.595	0.007	(0.009)	0.441

Table 4.3. Analysis of covariance comparing LPI treated eyes angle parameters versus untreated eyes parameters at Visits 4, 5, 6 and 11 and adjusting for baseline visit (Visit 1). Mean Diff=Mean differences; St= Standard. Statistically significant differences have been highlighted in yellow colour.

	VISIT 4			VISIT 5			VISIT 6			VISIT 11		
	Mean Diff	St Error	P Value	Mean Diff	St Error	P Value	Mean Diff	St Error	P Value	Mean Diff	St Error	P Value
SUPERIOR-NASAL TISA750	0.008	(0.005)	0.105	0.008	(0.006)	0.190	0.002	(0.006)	0.778	0.005	(0.008)	0.543
SUPERIOR-NASAL TIA750	0.760	(0.704)	0.284	-0.655	(0.713)	0.362	-0.267	(0.740)	0.719	0.831	(0.988)	0.405
INFERIOR TEMPORAL AOD500	0.027	(0.012)	0.025*	0.015	(0.016)	0.356	0.033	(0.012)	0.010*	0.016	(0.017)	0.328
INFERIOR TEMPORAL ARA500	0.008	(0.005)	0.125	0.010	(0.006)	0.110	0.011	(0.006)	0.062	0.009	(0.006)	0.190
INFERIOR TEMPORAL TISA500	0.007	(0.005)	0.129	0.006	(0.006)	0.279	0.009	(0.005)	0.078	0.009	(0.006)	0.143
INFERIOR TEMPORAL TIA500	2.591	(1.116)	0.023*	-0.932	(1.298)	0.475	2.634	(1.003)	0.011*	0.756	(1.457)	0.606
INFERIOR TEMPORAL AOD750	0.063	(0.018)	0.001*	0.043	(0.019)	0.028*	0.048	(0.016)	0.004*	0.061	(0.025)	0.018*
INFERIOR TEMPORAL ARA750	0.019	(0.008)	0.023*	0.020	(0.010)	0.050*	0.024	(0.009)	0.011*	0.022	(0.010)	0.040*
INFERIOR TEMPORAL TISA750	0.017	(0.007)	0.029*	0.015	(0.009)	0.126	0.020	(0.008)	0.017*	0.019	(0.009)	0.051
INFERIOR TEMPORAL TIA750	3.476	(0.965)	0.001*	0.105	(1.083)	0.923	2.039	(0.807)	0.014*	1.941	(1.308)	0.145
NASAL AOD500	-0.000	(0.013)	0.993	-0.001	(0.011)	0.955	0.001	(0.011)	0.956	0.015	(0.016)	0.348
NASAL ARA500	-0.011	(0.007)	0.127	-0.005	(0.006)	0.394	-0.006	(0.007)	0.427	-0.009	(0.009)	0.344
NASAL TISA500	-0.009	(0.006)	0.134	-0.006	(0.005)	0.270	-0.007	(0.006)	0.295	-0.007	(0.007)	0.362
NASAL TIA500	0.135	(1.313)	0.919	-0.776	(1.137)	0.497	0.030	(1.017)	0.977	1.556	(1.208)	0.205
NASAL AOD750	0.029	(0.013)	0.028*	-0.006	(0.014)	0.696	0.018	(0.014)	0.188	0.019	(0.022)	0.381
NASAL ARA750	-0.003	(0.009)	0.709	-0.003	(0.008)	0.670	-0.001	(0.009)	0.948	-0.003	(0.012)	0.785
NASAL TISA750	-0.003	(0.008)	0.749	-0.005	(0.007)	0.526	-0.002	(0.008)	0.781	-0.003	(0.010)	0.793
NASAL TIA750	1.792	(0.885)	0.047*	-0.771	(0.846)	0.365	0.973	(0.832)	0.247	1.313	(1.071)	0.227
TEMPORAL AOD500	0.007	(0.011)	0.505	-0.001	(0.011)	0.938	-0.001	(0.012)	0.908	-0.011	(0.015)	0.445
TEMPORAL ARA500	-0.002	(0.005)	0.630	0.001	(0.005)	0.895	-0.003	(0.005)	0.482	-0.007	(0.006)	0.236
TEMPORAL TISA500	-0.002	(0.004)	0.583	-0.002	(0.004)	0.583	-0.005	(0.004)	0.211	-0.009	(0.006)	0.125
TEMPORAL TIA500	0.470	(0.985)	0.635	-0.524	(1.012)	0.606	-0.777	(1.088)	0.478	-1.262	(1.345)	0.353

Table 4.3. (CONTINUATION). Analysis of covariance comparing LPI treated eyes angle parameters versus untreated eyes parameters at Visits 4, 5, 6 and 11 and adjusting for baseline visit (Visit 1). Mean Diff=Mean differences; St= Standard. Statistically significant differences have been highlighted in yellow colour.

	VISIT 4			VISIT 5			VISIT 6			VISIT 11		
	Mean Diff	St Error	P Value	Mean Diff	St Error	P Value	Mean Diff	St Error	P Value	Mean Diff	St Error	P Value
TEMPORAL AOD750	0.010	(0.012)	0.418	-0.005	(0.012)	0.643	0.002	(0.013)	0.873	0.009	(0.018)	0.638
TEMPORAL ARA750	-0.003	(0.007)	0.694	-0.006	(0.007)	0.343	-0.006	(0.007)	0.402	-0.010	(0.009)	0.276
TEMPORAL TISA750	-0.003	(0.006)	0.669	-0.009	(0.006)	0.147	-0.009	(0.007)	0.186	-0.012	(0.009)	0.189
TEMPORAL TIA750	0.503	(0.746)	0.503	-0.552	(0.709)	0.439	-0.554	(0.814)	0.498	0.518	(1.152)	0.655
INFERIOR-NASAL AOD500	0.022	(0.015)	0.134	-0.010	(0.016)	0.523	0.022	(0.013)	0.092	0.025	(0.018)	0.155
INFERIOR-NASAL ARA500	-0.004	(0.006)	0.555	-0.009	(0.008)	0.290	0.005	(0.008)	0.484	0.000	(0.009)	0.998
INFERIOR-NASAL TISA500	-0.003	(0.005)	0.483	-0.009	(0.007)	0.220	0.002	(0.006)	0.796	0.001	(0.008)	0.892
INFERIOR-NASAL TIA500	1.937	(1.141)	0.094	-1.089	(1.417)	0.445	0.614	(1.115)	0.583	1.420	(1.430)	0.326
INFERIOR-NASAL AOD750	0.010	(0.016)	0.527	-0.002	(0.018)	0.896	0.034	(0.018)	0.063	0.032	(0.025)	0.205
INFERIOR-NASAL ARA750	-0.004	(0.009)	0.664	-0.011	(0.012)	0.348	0.009	(0.011)	0.376	0.005	(0.013)	0.726
INFERIOR-NASAL TISA750	-0.003	(0.008)	0.740	-0.010	(0.011)	0.355	0.007	(0.009)	0.471	0.006	(0.012)	0.644
INFERIOR-NASAL TIA750	0.474	(0.859)	0.582	-0.839	(1.092)	0.445	0.920	(1.138)	0.421	1.297	(1.455)	0.377
SUPERIOR-TEMPORAL AOD500	0.014	(0.012)	0.267	0.020	(0.012)	0.099	0.001	(0.009)	0.947	-0.014	(0.015)	0.357
SUPERIOR-TEMPORAL ARA500	0.003	(0.006)	0.672	0.005	(0.005)	0.336	0.001	(0.004)	0.825	-0.006	(0.006)	0.322
SUPERIOR-TEMPORAL TISA500	0.002	(0.005)	0.757	0.004	(0.005)	0.371	-0.000	(0.004)	0.908	-0.005	(0.006)	0.364
SUPERIOR-TEMPORAL TIA500	1.094	(1.002)	0.279	0.695	(1.036)	0.505	-0.625	(0.894)	0.487	-0.919	(1.215)	0.453
SUPERIOR-TEMPORAL AOD750	0.016	(0.016)	0.321	0.025	(0.014)	0.079	0.016	(0.016)	0.324	0.022	(0.020)	0.260
SUPERIOR-TEMPORAL ARA750	-0.000	(0.009)	0.999	0.007	(0.007)	0.352	0.001	(0.007)	0.879	-0.003	(0.010)	0.754
SUPERIOR-TEMPORAL TISA750	0.001	(0.008)	0.872	0.006	(0.007)	0.379	0.001	(0.006)	0.931	-0.003	(0.009)	0.768
SUPERIOR-TEMPORAL TIA750	0.900	(0.974)	0.359	0.511	(0.829)	0.540	0.304	(0.956)	0.752	1.257	(1.197)	0.299

Table 4.3. (CONTINUATION). Analysis of covariance comparing LPI treated eyes angle parameters versus untreated eyes parameters at Visits 4, 5, 6 and 11 and adjusting for baseline visit (Visit 1). Mean Diff=Mean differences; St= Standard. Statistically significant differences have been highlighted in yellow colour.

2nd Hypothesis: "There may be an association between, first, the widening effect on the angle and time elapsed since LPI (direct association) and, second, between this effect and a decrease in IOP (inverse association)"

The analysis was undertaken using the computer program 'R '(Douglas Bates, Martin Maechler and Ben Bolker, 2012; R Core Team, 2013). In this case, the slopes indicate the direction and magnitude of the relationship between the parameters under study (similar to the unstandardised coefficients produced by regression models in SPSS).

Table 4.4 shows the two regression models performed with 'R'. First, showing the relationship between the widening or change in the parameters dimensions and the time since the LPI and, second, the relationship between widening and IOP levels. The first model showed the relationship was not statistically significant in the majority of the parameters, but, when it was, the relationship was direct (i.e. Superior, Inferior-Nasal and Temporal AOD 750). Additionally nearly all the sectional parameters found in the Inferior-Temporal section showed a widening effect statistically significant directly associated with time since LPI. However, the values of the slopes (relationship indicator) were very small (maximum slope of 0.00027 in Inferior-Temporal AOD 750), indicating the minimal effect that time since LPI may have had on the widening factor during the first 6 months after LPI.

When looking at the second model assessing the relationship between widening of the angle and levels of IOP, the most of the slopes (indicator of relationship) resulted non-statistically significant. When these were, they were indicating a direct association (against the hypothesis). The statistically significant relationships were small (Slopes <0.0014) and found for Superior-Nasal ARA 500, ARA 750 and TISA 750 and for Inferior-Nasal ARA 500. The rest of the relationships given by the slopes magnitude were also small and they were not consistent, some being of a direct nature (majority of the parameters found in Superior, Superior-Temporal, Temporal, Inferior-Temporal and Superior-Nasal) and some of an inverse nature (Nasal and Inferior sections).

PARAMETER (dimension)	Time slope	P value	IOP slope	P Value
DARK SUPERIOR AOD500	0.00004839	0.2012	0.0004773	0.5796
DARK SUPERIOR ARA500	0.00002061	0.3253	-0.0001287	0.6987
DARK SUPERIOR TISA500	0.00002235	0.2482	-0.0000782	0.7858
DARK SUPERIOR TIA500	0.00140970	0.2703	0.0648794	0.2913
DARK SUPERIOR AOD750	0.00016189	0.0370*	0.0017097	0.1922

DARK SUPERIOR ARA750	0.00004910	0.1431	0.0003512	0.5115
DARK SUPERIOR TISA750	0.00004941	0.0981	0.0003992	0.4304
DARK SUPERIOR TIA750	0.00482129	0.2202	0.1293918	0.0531
DARK INFERIOR AOD500	-0.00004757	0.5696	-0.0015232	0.1281
DARK INFERIOR ARA500	-0.00003379	0.1281	-0.0005428	0.1992
DARK INFERIOR TISA500	-0.00002671	0.2482	-0.0003953	0.2743
DARK INFERIOR TIA500	-0.00224742	0.6206	-0.0653873	0.3403
DARK INFERIOR AOD750	0.00008367	0.3844	-0.0011322	0.3874
DARK INFERIOR ARA750	-0.00002845	0.4354	-0.0006523	0.2913
DARK INFERIOR TISA750	-0.00002059	0.6466	-0.0004669	0.4304
DARK INFERIOR TIA750	0.00355190	0.6106	-0.0619405	0.3604
DARK SUP NASAL AOD500	0.00003653	0.5335	0.0013604	0.0931
DARK SUP NASAL ARA500	0.00000337	0.9530	0.0008162	0.0380*
DARK SUP NASAL TISA500	0.00000686	0.9109	0.0006316	0.0831
DARK SUP NASAL TIA500	-0.00179296	0.8759	0.0277948	0.6987
DARK SUP NASAL AOD750	0.00008971	0.2282	0.0019353	0.0641
DARK SUP NASAL ARA750	0.00001233	0.8589	0.0013311	0.0230*
DARK SUP NASAL TISA750	0.00001221	0.8729	0.0011044	0.0370*
DARK SUP NASAL TIA750	0.00150454	0.7197	0.0324475	0.6216
DARK INF TEMPORAL AOD500	0.00018528	0.0020*	0.0008329	0.4515
DARK INF TEMPORAL ARA500	0.00006310	0.0420*	0.0002916	0.5646
DARK INF TEMPORAL TISA500	0.00005115	0.0420*	0.0002402	0.5996
DARK INF TEMPORAL TIA500	0.00839855	0.2302	-0.0484288	0.6196
DARK INF TEMPORAL AOD750	0.00027701	< 0.0001*	0.0013640	0.3514
DARK INF TEMPORAL ARA750	0.00012817	0.0040*	0.0005024	0.5265
DARK INF TEMPORAL TISA750	0.00010889	0.0070*	0.0004004	0.5846
DARK INF TEMPORAL TIA750	0.00851575	0.1451	-0.0214800	0.7998
DARK NASAL AOD500	0.00006795	0.2462	0.0000896	0.8929
DARK NASAL ARA500	-0.00000873	0.4014	-0.0000910	0.8498
DARK NASAL TISA500	-0.00001768	0.3884	0.0000520	0.8889
DARK NASAL TIA500	-0.00199655	0.8739	-0.0138678	0.8859
DARK NASAL AOD750	0.00011046	0.1882	-0.0000706	0.8909
DARK NASAL ARA750	0.00000737	0.6096	-0.0002121	0.7938
DARK NASAL TISA750	-0.00000449	0.6997	-0.0000478	0.8949
DARK NASAL TIA750	0.00088970	0.9520	-0.0369770	0.6657
DARK TEMPORAL AOD500	0.00005738	0.1251	0.0006025	0.5516
DARK TEMPORAL ARA500	0.00001144	0.2863	0.0002842	0.5666
DARK TEMPORAL TISA500	0.00000828	0.1782	0.0001617	0.7267
DARK TEMPORAL TIA500	0.00266782	0.1792	-0.0265432	0.7788
DARK TEMPORAL AOD750	0.00009929	0.0320*	0.0006131	0.6176
DARK TEMPORAL ARA750	0.00002495	0.0821	0.0005342	0.4354
DARK TEMPORAL TISA750	0.00001821	0.0601	0.0003869	0.5576
DARK TEMPORAL TIA750	0.00412774	0.0551	-0.0413306	0.6046
DARK INF NASAL AOD500	0.00011147	0.1502	0.0020448	0.1041
DARK INF NASAL ARA500	0.00001229	0.7758	0.0012402	0.0420*
DARK INF NASAL TISA500	0.00000215	0.8849	0.0009188	0.0671
DARK INF NASAL TIA500	0.00145104	0.7888	0.0541778	0.5876
DARK INF NASAL AOD750	0.00020544	0.0400*	0.0020035	0.1902
DARK INF NASAL ARA750	0.00004116	0.5526	0.0017909	0.0501
DARK INF NASAL TISA750	0.00003278	0.5475	0.0014544	0.0781
DARK INF NASAL TIA750	0.00520786	0.5125	0.0347990	0.7197
DARK SUP TEMPORAL AOD500	-0.00002348	0.6166	0.0004176	0.6967
DARK SUP TEMPORAL ARA500	-0.00001404	0.8188	0.0004983	0.2503

DARK SUP TEMPORAL TISA500	-0.00001270	0.8078	0.0004644	0.2492
DARK SUP TEMPORAL TIA500	-0.00541715	0.4184	-0.0068469	0.8819
DARK SUP TEMPORAL AOD750	0.00002948	0.8869	0.0010845	0.4164
DARK SUP TEMPORAL ARA750	-0.00002175	0.8038	0.0004776	0.4284
DARK SUP TEMPORAL TISA750	-0.00001411	0.8769	0.0005587	0.3914
DARK SUP TEMPORAL TIA750	-0.00177548	0.8929	0.0282718	0.6967

Table 4.4. Slopes (similar to the unstandardised coefficients, is presented as an indicator of relationship between widening of the parameters and time and between the same widening and IOP); P values indicating statistical significant relationship among parameters, time and IOP and between the treated and untreated eye groups.

4.1.4 Discussion

There is considerable evidence in the published literature that reports 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. When such effect has been quantified with anterior segment imaging technologies, it has commonly been measured solely in the vertical and horizontal meridians (Nasal and Temporal section) and often at one time point after the LPI. Caronia, et al. (1996) found an increase in AOD at 250μm, anterior chamber angle and Iris-lens contact distance in the Temporal section measured with UBM at a single time point after the LPI in aphakic patients (1 week). Lei, Wang, Wang and Wang (2009) found a statistically significant increase in anterior chamber volume and depth measured with AS-OCT in addition to a decrease in IOP (from 17.8 mean, 3.3 SD, to 15.9 mean, 3.1 SD) in 15 PAC patients, 20.2 mean (12.7 SD) days after this laser treatment. Memarzadeh, et al. (2007), found a statistically significant increase in AOD, ARA and TIA at 500μm and 750μm in Temporal and Nasal sections when comparing pre and 1 week post-LPI; however the description of the sample involved did not specify if these patients had glaucoma. He, et al. (2007) studied 72 PACS subjects using UBM scans taken before and 2 weeks after LPI. They quantified AOD at 250 and 500 μm for the four main sections and found a statistically significant increase for the same parameters and for all the sections after LPI. They also measured the parameter ARA for the same four sections and found it increased statistically significantly through the same amount of time.

It could be argued that all the studies mentioned in the paragraph above were based on mixed or Asian ethnicities; however, more recently, new evidence showing the effect of the LPI in Caucasian populations with narrow angles has been reported. López-Caballero ,et al., (2010) showed widening effect on the treated angle based in the four main sections (Superior, Inferior, Nasal and Temporal); the effect of the LPI was quantified in angle degrees of opening and assessed with Pentacam. They reported a significant increase in the anterior chamber angle, depth and volume in comparison with the measurements taken pre-laser. Mansouri, Burgener,

Bagnoud and Shaarawy (2009) studied PAC and PACG patients using the UBM to show post-LPI widening of TIA in the four main sections and AOD 500 in Superior and Inferior sections in light and dark conditions. Another study carried out by Ang and Wells (2010) in eyes diagnosed with PAC/PACS showed AOD, TISA and TIA (500 and 750) were statistically significantly wider after the LPI when compared to baseline measurements. Antoniazzi, et al., (2010) found a statistically significant increase in anterior chamber volume and anterior chamber angle measured with Pentacam in a PAC/PACS sample of 14 subjects 4 weeks after LPI. They reported a statistically significant increase in the peripheral anterior chamber angle of the 4 main sections at the same time point. All the above studies have studied the effect of the LPI uniquely in the treated eye and the results of this study for the same group are consistent with this published literature. However, when the fellow untreated eye was used as a control (analysis of covariance), the widening effect was shown to be of a lower magnitude than when assessing the treated eye on its own (t-tests). AOD 750 in the Inferior-Temporal section is an example of this assertion. For this parameter, the t-test comparing the treated eye between baseline and Visit 4 result was 0.066mm (SD 0.081mm; $p<0.001$*), between baseline and Visit 5 was 0.060mm (SD 0.092mm; $p<0.001$*) and between baseline and Visit 6 and 11 was 0.071mm (SD 0.071mm; $p<0.001$*) and 0.065mm (SD 0.110mm; $p=0.008$*) respectively. However, when analysis of covariance was fitted and adjusted to the untreated eye differences, the differences with baseline decreased to 0.063mm (SD 0.018mm;$p=0.001$*) for Visit 4, 0.043mm (SD 0.019mm;$p=0.028$*) for Visit 5, 0.048mm (SD 0.016mm; $p=0.004$*) for Visit 6 and 0.061mm (SD 0.025mm; $p=0.018$*) for Visit 11. It can be argued that this is one of the statistically significant comparisons given by both models, but when comparing the results given by the t-test and the analysis of covariance in the majority of the parameters the t-test gave wider mean differences than the analysis of variance. It is possible that previous reports in the literature may have overestimated the widening effect of the LPI.

The fact that some angle sections in the untreated eye increased slightly in dimension through time is not contradictory to the progression rate described by Wilensky, et al., (1993) in Caucasian untreated eyes with narrow angles as the first assessment for narrow angle was carried out after one year since recruitment and followed for a maximum of 6 years. They found that after the first year of follow up, only 7 eyes out of 111 showed appositional or synechial closure in at least 180 degrees as assessed with gonioscopy; in the second year 8 additional eyes out of 90 showed the same features and in the third, fourth, fifth and sixth year of follow up, the number of eyes with gonioscopically occludable angles increased and they were reported as 7 of 67 eyes, 2 of 38 eyes, 3 of 21 eyes and 0 of 3 eyes, respectively. Therefore, it is possible that further follow up of the

present sample using the CASIA AS-OCT would show similar results to that of the study by Wilensky.

The present study results have demonstrated that in only one angle section of the model there was a statistically significant association between parameter adjusted dimension differences and time. This was found in the Inferior-Temporal section and the relationship, although direct, was extremely small. There is some similarity in these results with a longer period LPI follow-up study performed by Kumar, Baskaran, Ronnie and Vijaya (2009) in PACS patients where no statistically significant differences were found between base line data and that found at 1 week, 6 months, 1 year, 1.5 years and 2 years after the procedure. They used UBM to study AOD 500 and ACA (Anterior Chamber Angle) in the four main angle sections in treated eyes only.

Additionally, these very few and direct statistically significant associations between IOP and difference in parameters dimensions between treated and untreated eyes may be explained on account of the relatively low levels of IOP measured at recruitment (the mean diurnal IOP peak was found to be 18.5 mmHg, SD 4.27 mmHg; Range: 12.0- 30.5; in Section 3.1). These baseline IOPs are similar to the pre-Nd:YAG laser treated eyes in a study by Moster, et al., (1986) where the mean IOP was found to be 17.1 mmHg (SD 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 afterwards. In the present research study, such assessment was not attempted as not all the follow up visits took place at the same time of the day and therefore a possible fluctuation in the diurnal IOP would have biased the results. It is not possible to compare results between the IOP changes in both studies, but the assessment of the effect of LPI on the IOP diurnal fluctuation may show some light on this subject. Additionally, López-Caballero, et al., (2010) reported a correlation between angle widening due to the LPI effect and reduction in IOP in a group of patients with angle closure, some with glaucoma. They found a statistically significant correlation between a decrease in IOP levels and an increase in the anterior chamber depth. It needs to be pointed out that the graph showed in their study actually showed a direct association (higher IOP with deeper anterior chamber depth), but this must have been an editing error. In the case of the present study this relationship was either non-existent or direct (the wider the angle the higher the IOP) which was unexpected. It was not possible to compare results between studies as in López-Caballero's; the widening assessment was only performed for the treated eye. However, in order to investigate this possible relationship a linear regression model was fitted using the present study treated eye data. This model attempted to simulate López-Caballero's and therefore only TIA 500 and 750 in

Superior, Nasal, Inferior and Temporal sections were related to a change in the angle. The results for the model resulted non-statistically significant and the relationship was again direct (Univariate regression; Standardised Coefficient 0.250; Adjusted R^2 0.063; p value=0.167).
More recently, a retrospective study of 469 Caucasian eyes with an initial diagnosis of PAC (due only to PAS) or PACS reported a post-LPI IOP raise to more than 21 mmHg in 38.7% participants 10 years after treatment with LPI (Blondeau, Jaworski and Turcotte, 2011). The IOP was found to be more than 21 mmHg at a mean follow up time of 3.2 years (SD 3.6) despite the fact all eyes had pre-LPI IOP levels lower than 21 mmHg. They also found that gonioscopic results following LPI predicted those eyes that would have an IOP increase, although these gonioscopical findings were not specified in their publication. The authors suggested that this increase might have been caused by the natural growth of the lens, which would have narrowed the angle. Nevertheless, their study confirmed that even when LPI has been performed, more than a third of their sample later developed high IOPs (Blondeau, Jaworski and Turcotte, 2011). It would be interesting to know how the patients in the present study would perform on a longer follow up period to confirm Blondeau's findings. Advantages of the CASIA AS-OCT technology for quantifying angle parameters have already been explained in this thesis and its application over a longer period of follow up may confirm an association between higher IOP and gradual narrowing of the parameters post-LPI.

In summary, the statistical modelling fit allows a prediction of change in parameters dimensions (widening of the angle) in the case of the Inferior-Temporal section 6 months after LPI for the present research sample. It is known that the crystalline lens continues to thicken throughout life and that this increase in lens thickness may further narrow the anterior chamber angle. If this is the case, it is possible that the LPI has no longstanding widening effect on the angle in phakic patients.

To date there are no published studies showing a predictive model for changes in the angle related to time and IOP in treated eyes versus untreated.

In future studies it would be helpful to quantify the change in OCT-measured angle dimensions that equates to a gonioscopic finding of an open angle. This would mean the development of possible cut-off standards to determine the opening or closure of a given section.

4.1.5 Conclusions

The widening effect due uniquely to the effect of the LPI over the iridotrabecular angle remains unclear. The use of a control eye has demonstrated that this widening post-LPI, so commonly reported in the literature, may be due to additional uncontrolled factors.

It has been statistically significantly shown that, for this sample of eyes, at least one section of the angle parameters (Inferior-Temporal) increased in the treated eye in comparison to the untreated eye and that these differences in dimensions were weakly directly associated with time for the first 6 months after LPI. There was no statistical significant association between these differences and IOP for the majority of the measured angle parameters.

4.2 Effect of the laser peripheral iridotomy on the diurnal intraocular pressure (DIOP) fluctuation 6 months after the procedure

4.2.1 Introduction

DIOP fluctuation was reported in Section 3.1 to reach a range of up to 14.50 mmHg for the untreated eye (Mean DIOP fluctuation was 5.99 mmHg; 2.70 SD); however, little is known about the effect of laser peripheral iridotomy (LPI) on this fluctuation. Baskaran, et al. (2009) studied DIOP fluctuation in treated PAC and PACS in comparison with PACG and normals (non-glaucomatous eyes), finding that this fluctuation was lower for PACS and normals than for PAC and PACG. The effect of the LPI on IOP fluctuation in their sample could not be studied 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 the effect of LPI on diurnal IOP fluctuation.

One can hypothesise that the fluctuation of IOP would be lower in those eyes treated with LPI than in the untreated fellow eyes and that this effect may be dependent on the treatment outcome: treated eyes, which are found to be gonioscopically open after the LPI, would exhibit lower levels of fluctuation than the pre-laser state of the same eye and the fellow untreated eye, while those found to be occludable post-laser are predicted to show similar levels of fluctuation to their pre-laser state and the fellow untreated eye.

A second hypothesis was that those eyes which have occludable anterior chamber angles (established using gonioscopy) would show a higher diurnal IOP fluctuation than those with open anterior chamber angles after the LPI treatment.

4.2.2 Methodology and Statistical Analysis plan

Diurnal IOP fluctuation data of 29 participants who only received LPI (no subsequent ALPI treatment) during the study were analysed. The study design involved random selection of one eye of each participant for LPI treatment and the fellow eye was left untreated. Three months after the LPI was performed in these 29 randomly selected eyes, 19 eyes were considered to be open and 10 to be occludable using gonioscopy. Figure 4.34 gives more information about the participant's pathway throughout the study.

Prior to plan and perform the statistical analysis it was needed to test variability in the DIOP fluctuation, peaks and troughs due uniquely to time. This was tested through comparing the levels found in the untreated eyes between Visit 1 (baseline) and Visit 11 (the mean time from Visit 1 was 6.44 months, SD 0.56 months). Three comparisons were carried out using the paired samples t-test:

- 1st Comparison: comparing the fellow untreated eyes of those eyes treated with LPI (n=29 eyes). This comparison was not differentiating between occludable or unoccludable post-LPI fellows.

- 2nd Comparison: comparing the fellow eyes of those eyes observed to be gonioscopically unoccludable 3 months post-LPI (n=19 eyes).

- 3rd Comparison: comparing the fellow eyes of those eyes that having been treated with LPI were observed to be gonioscopically occludable 3 months after the procedure (n=10 eyes).

These results showed a lack of variability in any of the three comparisons and (these results can be found in the results section for this objective), therefore, there was a justification for comparisons between pre and post-LPI DIOP fluctuation data or for comparisons between post-LPI data adjusting for pre-LPI data.

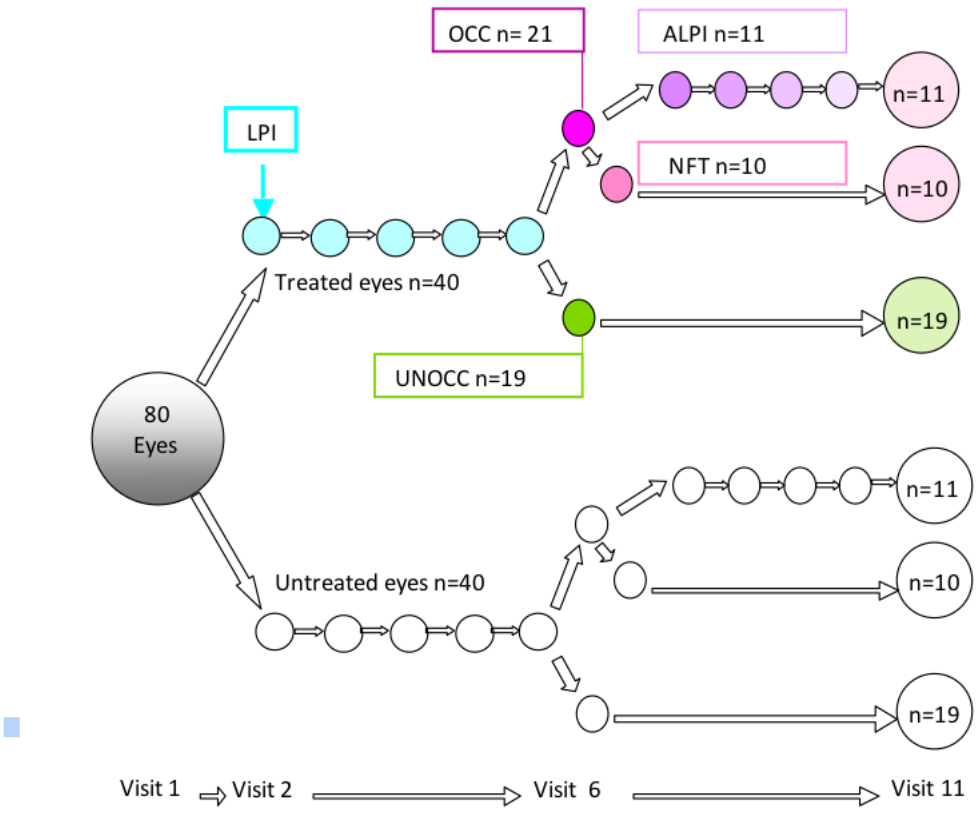

Figure 4.34. Participant pathway throughout the study. The upper half of the figure shows the pathway of those eyes randomised to receive Laser Peripheral Iridotomy (LPI) and the lower half of the figure shows the pathway of the untreated fellow eyes. Abbreviations in this figure: n= number of eyes in each group. LPI= Laser Peripheral Iridotomy. OCC= Post-LPI eyes with occludable angles. UNOCC= Post-LPI eyes with unoccludable eyes. ALPI= Eyes with post-LPI occludable angles that were further randomised into receiving ALPI. NFT= Eyes with post-LPI occludable angles that were further randomised into not receiving further treatment.

1st Hypothesis Methodology

To test this objective's first hypothesis of a reduction in DIOP fluctuation in those eyes treated with LPI, DIOP fluctuation 6 months (Mean 5.85 months; SD 0.37 months) after the LPI treatment was compared with their fellow untreated eyes. Analysis of covariance was used as this gave the advantage to adjust the model to the differences found at Visit 1 between the treated and their fellow untreated eyes. Three statistical models were carried out:

- 1st statistical model: Aimed to test if LPI reduced the DIOP fluctuation 6 months after the LPI independently of the outcome of the treatment (gonioscopically occludable or unoccludable eyes as diagnosed 3 months post-LPI, n=29). This was achieved by comparing the DIOP fluctuation of those treated eyes with their fellows at Visit 11 and adjusted for the data found at Visit 1.

- 2nd statistical model: To test if there was a reduction of DIOP fluctuation in those eyes with post-LPI unoccludable angles (n=19) when compared with their fellow eyes (n=19). This was achieved by comparing those treated eyes with gonioscopically open post-laser angles with their fellow eyes at Visit 11 (6 months after LPI) and adjusted for baseline data (Visit 1).

- 3rd statistical model: Comparing treated eyes that remained with occludable angles (n=10) with their fellow eyes (n=10) at Visit 11 and adjusted for baseline data (Visit 1).

2nd Hypothesis Methodology

To test the second hypothesis, which is that those eyes with occludable anterior chamber angles (established using gonioscopy, n=10), would show a higher diurnal IOP fluctuation than those with open anterior chamber angles after the LPI treatment (n=19), analysis of covariance was used. DIOP fluctuation, peaks and troughs were compared between those eyes with gonioscopically occludable angle (3 months post-laser) and those with an open angle (3 months post-laser). Only the data for the treated eyes was used and the statistical model was adjusted for Visit 1 differences (baseline, pre-LPI).

4.2.3 Results

Investigation of variability of the data found for DIOP fluctuation due to time:

1st Comparison:

Using the paired samples t-test the data for DIOP fluctuation found at Visit 1 and Visit 11 for all the fellow untreated eyes of those eyes treated with LPI was compared. There were no statistically significant differences for the DIOP fluctuation values between Visits 1 and 11. To further test that the DIOP fluctuation was within the same levels in both visits, a further two paired samples t-tests were carried out for the peaks and the troughs. None of these two later tests showed statistically significant differences. Additionally, the differences in IOP for these three parameters (fluctuation, peaks and troughs) were lower than 1 mmHg. The table below presents more information about the values of DIOP fluctuation, peaks and troughs in Visit 1 and V11, their means difference and the paired samples t-tests p values.

DIOP	Untreated eyes Visit 1 data Mean (SD)	Untreated eyes Visit 11 data Mean (SD)	Mean difference (SD)	T test P value
Fluctuation (mmHg)	6.02 (2.61)	6.02 (2.61)	0.14 (2.96)	0.800
Peak (mmHg)	20.03 (4.47)	20.17 (3.91)	0.16 (1.80)	0.640
Trough (mmHg)	14.02 (3.06)	14.17 (2.99)	0.02 (3.03)	0.975

Table 4.5 Paired Samples t test comparing DIOP fluctuation, peaks and troughs between Visit 1 and Visit 11 of the untreated eyes. SD= Standard Deviation.

2nd Comparison:

Paired samples t-test was used to analyse the differences between the DIOP fluctuation of the fellow untreated eyes of those observed to be gonioscopically unoccludable 3 months post-LPI found at Visit 1 and Visit 11. The test showed no statistically significant differences between the DIOP fluctuation found for this group of eyes at Visit 1 and their correspondent found at Visit 11. Two further paired samples t-tests showed that there were no statistically significant differences between the peaks or between the troughs when comparing both visits.

For more information about the mean values for DIOP fluctuation, peaks and troughs for this group of eyes at Visit 1 and 11 together with the results for the paired samples t-test please see table 4.6.

DIOP	Fellow untreated eyes of post-LPI gonioscopically unoccludable eyes Visit 1 data Mean (SD)	Fellow untreated eyes of post-LPI gonioscopically unoccludable Visit 11 data Mean (SD)	Mean difference (SD)	T test P value
Fluctuation (mmHg)	5.87 (2.53)	5.84 (2.09)	0.03 (2.76)	0.967
Peak (mmHg)	19.76 (4.42)	20.05 (4.31)	0.29 (1.53)	0.662
Trough (mmHg)	13.89 (2.90)	14.21 (3.35)	0.31 (3.58)	0.380

Table 4.6. Paired Samples t test comparing DIOP fluctuation, peaks and troughs between Visit 1 and Visit 11 of the fellow untreated eyes of post-LPI gonioscopically unoccludable eyes. SD= Standard Deviation.

3rd Comparison:

In order to test the differences in DIOP fluctuation between Visit 1 and Visit 11 of the fellow eyes of those that, having been treated with LPI, were observed to be gonioscopically occludable, a paired samples t-test was used. This statistical test showed no statistically significant differences in DIOP fluctuation, peaks or troughs for this group of eyes and between this two time points (Visit 1 and Visit 11). The differences for the three parameters tested (DIOP fluctuation, peaks and troughs) were lower than 1 mmHg. For more information about the mean values for DIOP fluctuation, peaks and troughs for this group of eyes at Visit 1 and 11 together with the results for the paired samples t-test please see table below.

DIOP	Fellow untreated eyes of post-LPI gonioscopically occludable eyes Visit 1 data Mean (SD)	Fellow untreated eyes of post-LPI gonioscopically occludable Visit 11 data Mean (SD)	Mean difference (SD)	T test P value
Fluctuation (mmHg)	6.33 (2.93)	6.33 (2.83)	0.00 (3.72)	1.000
Peak (mmHg)	20.61 (4.81)	20.44 (3.12)	0.17 (3.34)	0.885
Trough (mmHg)	14.28 (3.54)	14.11 (2.20)	0.40 (2.72)	0.837

Table 4.7. Paired Samples t test comparing DIOP fluctuation, peaks and troughs between Visit 1 and Visit 11 of the fellow untreated eyes of post-LPI gonioscopically occludable eyes. SD= Standard Deviation.

4.2.3.1 Results for 1st Hypothesis- "DIOP fluctuation would be lower in LPI treated eyes when compared with their fellow untreated eyes 6 months after the procedure"

1st Comparison: Differences between DIOP fluctuation between LPI-treated eyes and their untreated fellows at Visit 11:

Analysis of covariance showed no statistically significant result between the DIOP fluctuation of the post-LPI gonioscopically occludable eyes and their untreated fellows at Visit 11. The model was adjusted for differences in DIOP fluctuation found for these two groups at Visit 1. Two further analysis of covariance was performed to investigate differences in DIOP peaks and troughs

between these two groups of eyes at Visit 11 adjusted for the data found at Visit 1 for the same parameters (DIOP peaks and troughs). None of the models showed statistically significant differences for DIOP peaks or troughs. For information about the DIOP fluctuation, peaks and troughs mean values for the LPI treated eyes and their fellows at Visits 1 and 11, please see table below. Additionally, this table shows the mean differences in DIOP fluctuation, peaks and troughs between the LPI treated eyes and their fellows at Visit 11 and adjusted for Visit 1.

DIOP	Treated eyes Mean (SD)		Fellow untreated eyes Mean (SD)		Mean difference (SE)	ANCOVA P value
	Visit 1	Visit 11	Visit 1	Visit 11		
Fluctuation (mmHg)	6.46 (3.02)	6.43 (2.02)	5.95 (2.60)	6.00 (2.31)	0.32 (0.57)	0.576
Peak (mmHg)	20.57 (4.67)	21.12 (4.06)	20.03 (4.39)	20.18 (3.90)	0.55 (0.71)	0.442
Trough (mmHg)	14.10 (2.72)	14.70 (2.95)	14.09 (3.03)	14.18 (2.99)	0.45 (0.49)	0.365

Table 4.8. Analysis of covariance (ANCOVA) comparing DIOP fluctuation, peaks and troughs between LPI treated eyes and their untreated fellows at Visit 11 adjusted for Visit 1 data. SD= Standard deviation. SE= Standard error.

2nd Comparison: Differences in DIOP fluctuation between LPI-treated eyes that were gonioscopically unoccludable 3 months after the procedure and their untreated fellows at Visit 11:

It was not possible to find statistically significant differences in the DIOP fluctuation, peaks and troughs between LPI-treated eyes that were gonioscopically unoccludable 3 months after the procedure and their untreated fellows. Furthermore the differences found at Visit 11 (as adjusted for Visit 1) were in every case lower than 1 mmHg.

The analysis of covariance was adjusted for the differences found for these three parameters and between these two groups of eyes at Visit 1.

For more information about the mean values for DIOP fluctuation, peaks and troughs for these groups of eyes at Visit 1 and 11 together with their mean difference at Visit 11 (adjusted for the difference at Visit 1) please see table 4.9.

DIOP	Post-LPI gonioscopically unoccludable eyes Mean (SD)		Fellow eyes of Post-LPI gonioscopically unoccludable eyes Mean (SD)		Mean difference (SE)	ANCOVA P value
	Visit 1	Visit 11	Visit 1	Visit 11		
Fluctuation (mmHg)	6.39 (3.12)	6.34 (2.21)	5.87 (2.53)	5.84 (2.09)	0.35 (0.66)	0.602
Peak (mmHg)	19.95 (4.84)	20.92 (4.67)	19.76 (4.41)	20.05 (4.31)	0.73 (0.88)	0.414
Trough (mmHg)	13.55 (2.94)	14.58 (3.38)	13.89 (2.90)	14.58 (3.38)	0.71 (0.56)	0.214

Table 4.9. Analysis of covariance (ANCOVA) comparing DIOP fluctuation, peaks and troughs between post-LPI gonioscopically unoccludable eyes and their untreated fellows at Visit 11 adjusted for Visit 1 data. SD= Standard deviation. SE= Standard error.

3rd Comparison: Differences between DIOP fluctuation between LPI-treated eyes that were gonioscopically occludable 3 months after the procedure and their untreated fellows at Visit 11 and adjusted for baseline data (Visit 1):

Analysis of covariance adjusted for the data found at Visit 1 found no statistically significant differences between the DIOP fluctuation of those eyes found gonioscopically occludable after LPI and their fellows at Visit 11. Furthermore, there was no statistically significant difference between the peaks and troughs of these two groups at Visit 11. For more information about the mean value for the DIOP fluctuation, peaks and troughs of these two groups at Visits 1 and 11, see table below (Table 4.10). The mean difference for these three values and the p-values of the analysis of covariance can be additionally found in this table.

DIOP	Post-LPI gonioscopically occludable eyes Mean (SD)		Fellow eyes of Post-LPI gonioscopically occludable eyes Mean (SD)		Mean difference (SE)	ANCOVA P value
	Visit 1	Visit 11	Visit 1	Visit 11		
Fluctuation (mmHg)	6.60 (2.99)	6.61 (1.63)	6.10 (2.85)	6.33 (2.83)	0.48 (1.46)	0.748
Peak (mmHg)	21.75 (4.30)	21.55 (2.52)	20.55 (4.54)	20.44 (3.12)	0.37 (1.79)	0.838
Trough (mmHg)	15.15 (1.96)	14.94 (1.88)	14.45 (3.39)	14.11 (2.20)	0.23 (1.09)	0.833

Table 4.10. Analysis of covariance (ANCOVA) comparing DIOP fluctuation, peaks and troughs between post-LPI gonioscopically occludable eyes and their untreated fellows at Visit 11 adjusted for Visit 1 data. SD= Standard deviation. SE= Standard error.

4.2.1.1 Results for 2nd Hypothesis- "DIOP fluctuation measured 6 months post LPI would be lower in LPI-treated eyes that were found to be gonioscopically unoccludable when compared with those found to be gonioscopically occludable"

Using analysis of covariance, the data for DIOP fluctuation found at Visit 11 for those LPI treated eyes that were gonioscopically occludable was compared to that found for those considered

unoccludable after LPI. There were no statistically significant differences for the DIOP fluctuation values at Visit 11 as adjusted for the differences found at Visit 1. To further test that the DIOP fluctuation was within the same levels at Visit 11, two more analyses of covariance were carried out for the peaks and the troughs. None of these two last models showed statistically significant differences. Additionally, the differences in DIOP fluctuation, peaks and troughs were lower than 1 mmHg. Please, see table below for more information about the values of DIOP fluctuation, peaks and troughs in Visit 1 and V11, their means difference at Visit 11 (adjusted for Visit 1) and the analysis of covariance p-values.

DIOP	Post-LPI gonioscopically unoccludable eyes Mean (SD)		Post-LPI gonioscopically occludable eyes Mean (SD)		Mean difference (SE)	ANCOVA P value
	Visit 1	Visit 11	Visit 1	Visit 11		
Fluctuation (mmHg)	6.39 (3.12)	6.34 (2.21)	6.60 (2.99)	6.61 (1.64)	0.18 (0.81)	0.827
Peak (mmHg)	19.95 (4.84)	20.92 (4.67)	21.75 (4.30)	21.55 (2.52)	0.78 (1.16)	0.506
Trough (mmHg)	13.55 (2.94)	14.58 (3.38)	15.15 (1.96)	14.94 (1.88)	1.13 (0.81)	0.177

Table 4.11. Analysis of covariance (ANCOVA) comparing DIOP fluctuation, peaks and troughs between post-LPI gonioscopically occludable eyes and their untreated fellows at Visit 11 adjusted for Visit 1 data. SD= Standard deviation. SE= Standard error.

4.2.3 Discussion

One previous study reported on repeatability of IOP measurements between eyes of bilateral glaucomatous and normal (no ocular pathology) subjects in consecutive visits (Realini, Barber, and Burton, 2002). A change of more than 3 mmHg was observed in 24 of the 38 glaucomatous (3.7±1.2 mmHg) and in 21 of the 42 normals (4.0±1.2 mmHg) as measured with Goldmann applanation tonometry. The number of visits for both groups was approximately 9 and the total number of observations (measurement of IOP between visits) was 284 for normals and 283 for glaucomatous. From the total number of observations, 39 showed a variation of more than 3 mmHg in the normal group and 46 in the glaucomatous group. Only 31 observations in normals and 41 observations in glaucomatous had time of day recorded. Additionally, only 14 out of these 31 observations for normals and 30 of these 41 for glaucomatous were performed within 90 minutes of the same time of day. In the case of the glaucomatous group, although the same examiner measured the IOP, the authors acknowledged this result as expected as the mechanism of an elevated IOP in glaucoma is secondary to outflow obstruction and this may have been different in fellow glaucomatous eyes. In the case of the normal group, two different examiners measured the IOP throughout the study and no interobserver agreement was described. It was,

therefore, possible that the differences found between visits and between fellow normal eyes were due to a lack of good interobserver agreement.

Based on the lack of consistent evidence that the IOP changes differently between eyes at different time points and that in the case of this study the fellow untreated eyes (control eyes) had similar DIOP fluctuation between Visits 1 and 11 (period of time= 6.44 months, SD 0.56 months), comparisons between these two time points were justified for the treated eyes. Therefore, if a change in DIOP fluctuation was noticed in the treated group of eyes, this would have been due to the treatment with LPI and not to the time elapsed between Visits 1 and 11.

The results for this section showed that LPI treatment did not reduce DIOP fluctuation on this sample of treated eyes when compared to the fellow untreated group of eyes. The means for DIOP fluctuation for laser treated eyes that remained unoccludable and occludable post-laser compared with their respective fellows were very similar giving a non-statistically significant difference. However, the treated eyes that remained with an occludable angle showed a higher DIOP fluctuation than those that were open post laser treatment. From a clinical standpoint, such a small difference in fluctuation (of less than 1 mmHg) is unlikely to have any clinical significance. Furthermore, the DIOP for the different groups seemed to fluctuate within similar ranges.

It is not possible to compare these results to previous published literature on the same topic due to the novel nature of these results. The only research performed in DIOP fluctuation on narrow angle eyes has been that carried out by Baskaran in Asian subjects (89.1% were Chinese) on laser-treated eyes (Baskaran, et al., 2009). In Baskaran's study the eyes were divided in 4 groups (Normals, treated PACS, treated PAC, and treated PACG) and their DIOP fluctuation was studied separately. For normals the fluctuation was found to be 3.75 mmHg (SD 1.09), for PACS 3.75 mmHg (SD 1.24), for PAC 4.53 mmHg (SD 2.33) and for the PACG group 5.44 mmHg (SD 2.4). The mean time from LPI was 31.3 weeks (SD 41.9). The highest DIOP fluctuation was found in the PACG group. All the groups of eyes studied in the present study, even those treated eyes that opened after laser, showed higher DIOP fluctuations than those reported by Baskaran in the PAC/PACS groups and even higher than that reported for the PACG group. There may be a reason for this dissimilarity in DIOP fluctuation between studies. The most obvious different factor is ethnicity and, consequently, ocular biometry, but no current literature has studied differences in DIOP fluctuation in individuals of different ethnicity. One study in healthy young adults of diverse ethnicity (52% Caucasian, 36% Asian, 9.3% Hispanic and 12.6% Black) found an inverse correlation between axial ocular length and higher levels of 24 hours IOP fluctuation (Loewen, Liu and Weinreb, 2010) and another study has suggested that Caucasian's eyes have a deeper anterior

chamber when compared to Chinese eyes (Wang, et al., 2011). Therefore, ethnicity may not have been responsible for these differences.

The second possible reason was regarding the instrumentation used for measuring the DIOP. Baskaran and colleagues used a non-contact tonometer (Topcon CT-80), which was compared to Goldmann tonometry finding a mean difference of 0.2 mmHg (SD 1.5) and limits of agreement (95%) of -3.14 and +2.74 mmHg. It was unlikely that the differences in fluctuation were caused by the different instrumentation.

The third difference was the mean age of the groups. In Baskaran's study the groups diagnosed with PACS and PAC were 68 (SD 7.5) and 66.7 (SD 5.7) years old, respectively. In the present study, the sample presented an age of 59.6 (SD 11.3) years old at the time of recruitment. To assess if age had an inverse effect on fluctuation, a linear regression model was fitted between these two variables using the data of the present study (DIOP fluctuation at baseline for the 80 eyes ~ Age of the participant at recruitment). The model showed a statistically significant association (Standardized Coefficient -0.246; R^2 0.060; p=0.028). This association was weak and could not fully explain the differences.

4.2.4 Conclusions

No statistical significant difference in DIOP fluctuation between LPI treated eyes and their untreated fellow eyes was found. There were no significant differences in DIOP fluctuation between those eyes that remained closed after laser treatment and those eyes whose angles opened following laser.

4.3 Assessment of variability of the effect of the laser peripheral iridotomy depending on the angle section when using Ocular Coherence Tomography Technology

4.3.1 Introduction

As reported previously in this thesis, variability in the angle parameters exists depending on the angle sector/section being studied (i.e. Superior section was found to be the narrowest section). However, such variability is rarely mentioned in the published literature when the effects of the LPI are being considered involving anterior segment imaging. A recent study by Ang and Wells (2010) in a Caucasian population only the Nasal and Temporal sections were studied to assess the angle widening effect of the LPI using a 2 dimensional AS-OCT; the same sections were studied by Memarzadeh, et al., 2007, in a sample of mixed ethnicity. A similar study in Asian eyes using UBM assessed the data from Nasal, Temporal and Inferior sections (Gazzard, et al., 2003); the same 3 sections were evaluated in a study of the effect of LPI using 2 dimensional AS-OCT (See, et al., 2007).

It is possible that the widening effect of the LPI is not homogeneous and that some sections may be more affected than others. Mansouri, Burgener, Bagnoud and Shaarawy (2009) found greater change in the Superior and Nasal sections than in the opposite sections when assessing TIA with UBM in light before and after LPI; however, this difference was not statistically tested.

The aim of this section is to investigate the homogeneity of the effect of the LPI and to assess the relevance of quantifying at least the 4 main angle sections (Superior, Nasal, Inferior and Temporal) when analysed with anterior segment imaging technology.

As the iridotomy is commonly placed in the Superior Sector, one could hypothesise that the widening effect of this laser would be higher in this sector when compared to the Horizontal or Inferior and that this effect might be related to proximity of a given sector to the iridotomy site.

4.3.2 Methodology and Statistical Analysis plan

Data from 24 eyes of 24 participants who only received LPI in the randomised eye were used in this analysis. Ten angle sections of the scans (light and dark conditions) of each of these eyes were analysed. These 10 sections account for the ones already described (Superior, Superior-Temporal,

Nasal, Inferior-Nasal, Inferior, Inferior-Temporal, Temporal and Superior-Temporal) plus 2 new sections which are the sections on both sides of the angle in the meridian of the iridotomy, one on the side that incorporates the iridotomy and the other on the opposing side. Please see following pictures for visual information (Figures 4.35 to 4.40).

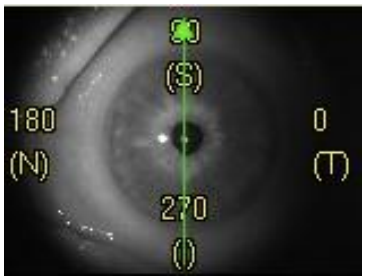

Figure 4.35

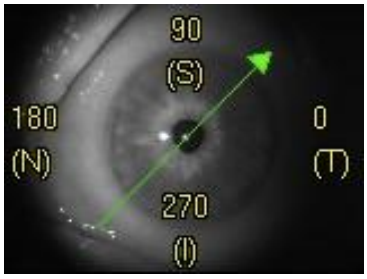

Figure 4.36

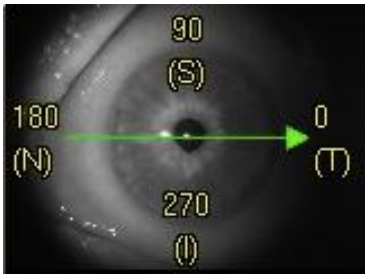

Figure 4.37

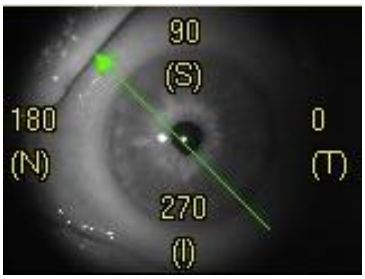

Figure 4.38

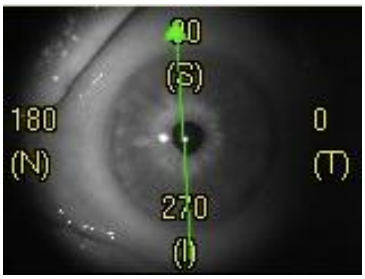

Figure 4.39

Figures 4.35, 4.36, 4.37, 4.38, and 4.39. Show a visual representation of the analysis cuts used that were later quantified with the CASIA OCT (please, note that these are corresponding to a Left Eye). The green arrow indicates the direction of the cut and the two sections involved. Figures 4.35, 4.36, 4.37 and 4.38 are those corresponding to Superior and Inferior, Superior-Temporal and Inferior-Nasal, Nasal and Temporal and Inferior-Temporal and Superior-Nasal, respectively. Figure 4.39 shows the cut located where the iridotomy was placed.

The CASIA OCT has the advantage of being able to quantify every sectional degree of the angle circumference. The manner the examiner selects the degree (angle section) that needs quantifying is using a rotating arrow tool (green arrow showed in Figures 4.35, 4.36, 4.37, 4.38, and 4.39. At the same time the examiner rotates this arrow over the eye picture, the CASIA gives a perpendicular cut of the angle corresponding with the head and nock of the arrow. This is how the iridotomy site was located. (Figure 4.40)

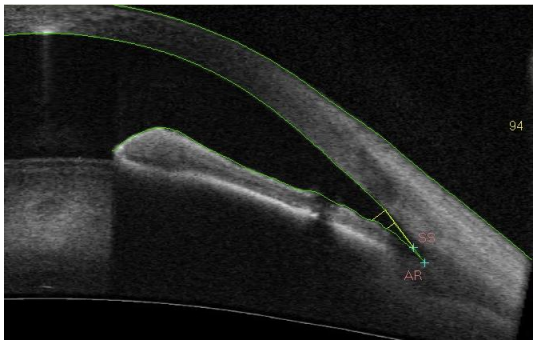

Figure 4.40. This is a section of the angle were the iridotomy was located using the CASIA software (94 degrees in the case of this participant's treated eye).

Only two time points Visit 1 and Visit 11 were compared. This decision was based on the results of Section 4.1 of this thesis, which showed a maximum increase for all the parameters between these two visits with very few exceptions.

The difference in dimension for the parameters found in each sector between Visits 1 and 11, and one-way analysis of variance was used for statistical analysis.

4.3.3 Results

Analysis of variance followed by Tukey HSD multiple comparisons showed no statistically significant differences among the 10 different sections parameters dimensions included in the analysis. This analysis was performed first for the parameters found in light conditions and secondfor the same in darkness. (Tukey HSD results for this analysis can be found in the attached compact disc).

The only exceptions to the paragraph above were found in light conditions and when comparing ARA 500 and 750 between Inferior and Nasal sections, TIA 500 between Superior and Nasal section and TISA 500 between Inferior section and the section opposite to the iridotomy. For more information about these statistically significant differences, see Table 4.12.

Parameter	Sections	Mean Difference (SD)	P values
ARA 500 (Light)	Inferior versus Nasal	0.029 (0.008)	0.022*
ARA 750 (Light)	Inferior versus Nasal	0.043 (0.013)	0.043*
TISA 500 (Light)	Inferior versus Opposite Iridotomy	0.031 (0.008)	0.012*
TIA 500 (Light)	Superior versus Nasal	-4.904 (1.444)	0.027*

Table 4.12 Parameters that were statistically significant different and details about which sections they were located

The differences in dimension between Visits 1 and 11 for the 8 parameters and for the 10 sections studied can be found in this section in Table 4.13 for light conditions and Table 4.14 for dark conditions. Negative values corresponded to a decrease in dimension and positive values to an increase. These differences were not found using the paired samples t test, but transforming these two dimensions into their difference.

The minimum effect of the LPI for the parameters measured in light condition was more frequently found in the Horizontal sector (Nasal section) whereas the maximum values for the same lighting were more frequent in the Inferior sector (Inferior and Opposite Iridotomy sections). In darkness, the maximum values were found, similar to light conditions, in the Inferior sector (Inferior-Temporal and Opposite Iridotomy sections); however, the minimum values were found in Superior (Iridotomy section) and Inferior sector with similar frequency (Inferior and Inferior-Nasal). As mentioned earlier, these values (maximums and minimums) were not statistically different from the rest.

LIGHT MEAN VALUES OF LPI EFFECT	AOD 500	ARA 500	TISA 500	TIA 500	AOD 750	ARA 750	TISA 750	TIA 750
IRIDOTOMY POSITION	0.0451 (0.060)	0.0045 (0.0188)	-0.0033 (0.0409)	2,9304 (5,8298)	0.0708 (0.0856)	0.0193 (0.0345)	0.0193 (0.0337)	3,3826 (5,5270)
SUPERIOR	0.0598 (0.0703)	0.0168 (0.0221)	0.0163 (0.0218)	5,0913 (5,6500)	0.0953 (0.0805)	0.0370 (0.0376)	0.0357 (0.0375)	6,0609 (4,8869)
SUPERIOR-NASAL	0.0562 (0.0811)	0.0145 (0.0338)	0.0147 (0.0306)	3,6478 (5,4316)	0.0840 (0.0855)	0.0352 (0.0535)	0.0033 (0.1729)	4,3174 (4,0966)
NASAL	0.0258 (0.0583)	0.0006 (0.0268)	0.0040 (0.0300)	-0.3652 (4,9076)	0.0486 (0.0674)	0.0123 (0.0389)	0.0179 (0.0474)	1,1565 (4,9375)
INFERIOR-NASAL	0.0634 (0.0773)	0.0131 (0.0283)	0.0136 (0.0272)	4,3609 (7,3844)	0.0808 (0.0831)	0.0309 (0.0444)	0.0316 (0.0434)	3,5174 (5,5343)
OPPOSITE IRIDOTOMY	0.0398 (0.0713)	0.0099 (0.0289)	0.0083 (0.0267)	0.9739 (5,7831)	0.4874 (1,8940)	0.0290 (0.0466)	0.0280 (0.0446)	3,5043 (5,3669)
INFERIOR	0.0739 (0.1032)	0.0293 (0.0374)	0.0276 (0.0354)	4,1696 (6,1377)	0.1100 (0.1231)	0.0557 (0.0658)	0.0537 (0.0645)	4,8739 (5,6209)
INFERIOR-TEMPORAL	0.0643 (0.0838)	0.0140 (0.0352)	0.0122 (0.0277)	2,6435 (6,2866)	0.0884 (0.0858)	0.0349 (0.0545)	0.0330 (0.0481)	3,3696 (4,9603)
TEMPORAL	0.0300 (0.0613)	0.0048 (0.0147)	0.0051 (0.0140)	1,1435 (6,0385)	0.0907 (0.0611)	0.0198 (0.0260)	0.0203 (0.0259)	4,4609 (3,7251)
SUPERIOR-TEMPORAL	0.0536	0.0077	0.0081	3,8217	0.0702	0.0222	0.0226	3,5261

	(0.0687)	(0.0271)	(0.0255)	(5,7863)	(0.0606)	(0.0374)	(0.0363)	(3,8438)

Table 4.13 Mean value of the LPI effect in the parameters in the 10 different sections measured in light conditions. The values in the table are mean values of the change between V1 (pre-laser) and V11 (post-laser). The standard deviation is the value within brackets. Minimum parameter mean value dimension for every section is boxed in blue and maximum value in red.

DARK MEAN VALUES OF LPI EFFECT	AOD 500	ARA 500	TISA 500	TIA 500	AOD 750	ARA 750	TISA 750	TIA 750
IRIDOTOMY POSITION	-0,0065 (0,0578)	-0,0066 (0,0237)	-0,0065 (0,0227)	-1,7174 (5,0368)	0,0115 (0,0655)	-0,0072 (0,0359)	-0,0073 (0,0352)	-0,375 (3,8136)
SUPERIOR	-0,0003 (0,0421)	0,0033 (0,0122)	0,004 (0,0117)	-0,2375 (3,2013)	0,0240 (0,0644)	0,0054 (0,0199)	0,0054 (0,0194)	0,5739 (2,7909)
SUPERIOR-NASAL	0,0143 (0,0502)	0,0058 (0,0196)	0,0048 (0,0180)	-0,0500 (4,4243)	0,021 (0,0728)	0,007 (0,0303)	0,0058 (0,0283)	0,275 (4,5546)
NASAL	0,0217 (0,0523)	-0,0002 (0,0243)	-0,0013 (0,0213)	0,3667 (4,5558)	0,0309 (0,0710)	0,0056 (0,0294)	0,0037 (0,0262)	0,7500 (3,6147)
INFERIOR-NASAL	0,0039 (0,0640)	-0,0067 (0,0272)	-0,0067 (0,0244)	-1,4042 (5,3785)	0,0196 (0,0755)	-0,0061 (0,0397)	-0,0062 (0,0371)	-0,375 (5,2507)
OPPOSITE IRIDOTOMY	0,0368 (0,0736)	0,0086 (0,0433)	0,0068 (0,0360)	1,6333 (6,2483)	0,0583 (0,1189)	0,0193 (0,0653)	0,0175 (0,0590)	2,1625 (7,0162)
INFERIOR	-0,0157 (0,0899)	-0,0055 (0,0209)	-0,0049 (0,0202)	-0,6208 (4,0824)	-0,0012 (0,0766)	-0,0068 (0,0349)	-0,0061 (0,0341)	-0,3417 (3,5835)
INFERIOR-TEMPORAL	0,0308 (0,0676)	0,0083 (0,0244)	0,0064 (0,0210)	0,3500 (6,3552)	0,0653 (0,1104)	0,0242 (0,0450)	0,0189 (0,0384)	1,4875 (5,6320)
TEMPORAL	0,0074 (0,0504)	0,0002 (0,0192)	-0,0020 (0,0187)	-0,3292 (4,4170)	0,0273 (0,0667)	0,0033 (0,0299)	0,0010 (0,0292)	0,9708 (4,1596)
SUPERIOR-TEMPORAL	0,0027 (0,0366)	0,0009 (0,0170)	0,0004 (0,0159)	-1,0417 (3,4279)	0,0241 (0,0615)	0,0045 (0,0249)	0,0043 (0,0238)	0,3917 (4,0714)

Table 4.14. Mean value of the LPI effect in the parameters in the 10 different sections measured in dark conditions. The values in the table are mean values of the change between V1 (pre-laser) and V11 (post-laser). The standard deviation is the value within brackets. Minimum parameter mean value dimension for every section is boxed in blue and maximum value in red.

4.3.4 Discussion

The results found in this thesis objective are partially consistent with those found by Ang and Wells (2010) when comparing the effect of the LPI between Temporal and Nasal sections approximately 6 weeks post-LPI. In their study the effect was greater in the Temporal section for both lighting conditions, light and dark; this difference was not statistically significantly different apart from TIA 500 in dark. In the present study, the effect of the LPI observed in the Temporal section were wider than in the Nasal section in light conditions, but not in dark.

He, et al. (2007) found that the opening effect quantified with UBM 2 weeks after LPI was greater in the Superior section for AOD 250 and 500 than for the other three sectors under study (Nasal, Temporal and Inferior). A statistical comparison of widening effect among the 4 sections was not performed.

One other study on a group of PACG patients found that, 4 weeks after LPI, on the iridotomy quadrant AOD 500 as measured with UBM increased from 110.2μm (SD 80.9) to 170.6μm (SD

83.4) p<0.001, and in the opposite quadrant from 117.2μm (SD 65.5) to 172.2μm (SD 81.7) p<0.001. The widening effect was, therefore very similar, although differences between quadrants were not statistically compared (Kaushik, et al., 2007).

The differences with these previous studies and the results of the present study might be explained using the results explained earlier in this thesis. It has been shown that every parameter in the treated eye group seemed to vary following a slightly different trend post LPI treatment. Although this variation resulted to be non-statistically significant in the majority of the cases, a further possible next step for this objective would have been to repeat this analysis for the rest of the follow up visits (Visit 4, 5 and 6).

It is important for future research to be aware that at least in the case of dark conditions there were some parameters sections that actually decreased, as was noted with TISA and TIA 500 which decreased in the majority of the sections and the majority of the parameters found in the Iridotomy section and Inferior-Nasal and Inferior sections, while the rest of the parameters for the rest of the sections commonly increased. This finding is understandable given the corrugated nature of the peripheral iris both radially and circumferentially. As previously discussed in this thesis, it is not uncommon to quantify the effect of the LPI in dark conditions and it is therefore surprising the absence of literature regarding a decrease in the parameters dimensions in darkness after the LPI has been performed.

There are no published studies showing the effect of the LPI in more than 6 sections. There is also a lack of publications comparing this effect between a particular section and the rest of the sections under study.

There are few limitations to this specific section. While analysing the CASIA images, the iridotomy seemed to be found at different locations between visits. There was a variability of several degrees. (i.e. the iridotomy could be found to be located at 94 degrees at Visit 4 and at 96 and 92 at Visits 6 and 11 respectively). This may have been caused by a natural rotational/fixation effect of the eye between visits or a possible head tilted. There are no studies addressing this issue and this was another novel finding that needs to be explored in future research. Visit 6 was chosen as the time to mark this iridotomy section, as it was the middle time point of the duration of the research project.

4.3.5 Conclusions

The present study was unable to demonstrate a statistically significant difference in the dimensional change in the angle parameters in the 10 different sections under study 6 months post-LPI.

CHAPTER 5. Effect of Argon Laser Peripheral Iridoplasty (ALPI) on anterior chamber angle dimensions and intraocular pressure

5.1 Relationship between degree of angle opening post ALPI treatment and intraocular pressure

5.1.1 Introduction

ALPI has been found to be effective in widening the anterior chamber angles of eyes presenting with iris plateau syndrome where the angle remains occludable after LPI (review by Ritch, Tham and Lam, 2007). Using OCT, Leung, et al. (2005) described a PACG case where ALPI succeeded in changing the angle configuration to a non-occludable configuration.

When treating acute angle closure cases, ALPI has shown to be more effective in lowering IOP than systemic medications in the early post-attack phase (Lam, et al., 2002) and an equivalent effect in the mid-term (Lai, et al., 2006). In a study of 11 eyes with chronic angle glaucoma, ALPI initially lowered the IOP in all the 11 eyes treated with 7 remaining controlled after 6 months (Chew and Yeo, 1995).

Published literature suggests that ALPI may cause further opening of a gonioscopically occludable angle previously treated by LPI, however, the mechanism of how the IOP is lowered is unclear. One may hypothesise that there may exist a relationship between the opening rate and lower levels of IOP and, that this effect is dependent on time. If the hypothesis is proven, it would be possible to predict how much an angle may open 3 months after ALPI and what would be the IOP lowering effect.

5.1.2 Methodology and Statistical Analysis plan

The statistical analysis was split into two statistical sub-analyses.

The first analysis was aiming to assess the difference through time in the angle dimensions when assessing solely the eye that was treated with ALPI. This analysis used the paired samples t test to compare the parameter dimensions assessed at baseline (Visit 6, 12.55 days, SD 5.24 days, prior to ALPI) with the same data collected at Visit 8 (1 day after ALPI, SD 0.00 days), Visit 9 (7 days after ALPI, SD 0.89 days), Visit 10 (1.43 months after ALPI, SD 0.18 moths) and Visit 11 (2.39 months after ALPI, SD 0.30 months). Second, it was of interest to assess the differences in angle

parameter dimensions between those participants whose angle remained gonioscopically occludable 3 months after LPI but did not receive further treatment (NFT group; n=10 eyes) compared to those whose angles were treated with ALPI (n=11 eyes). The comparison was carried out at two time points, Visit 6 (12.55 days, SD 5.24 days, before ALPI) and Visit 11 (2.09 months, SD 0.30, months after ALPI). Only those scans taken in dark conditions were quantified. The statistical analysis was performed using analysis of covariance to assess the differences in angle parameter dimensions depending on the group at Visit 11 while being adjusted for differences at Visit 6 (ALPI or NFT). For more schematic information please see Figure 5.1.

The second analysis aimed to assess how the angle dimensions (parameters) change through time and if a relationship between this change and the IOP exists. The data of those eyes whose angles were treated with ALPI (n=11 eyes) were used. To assess the relationship between IOP and time was not possible as the IOP for these participants were measured at different times of the day. IOP and parameters dimensions data (scans in darkness) collected in Visit 6 (12.55 days, SD 5.241 days, before laser), Visit 8 (1 day, SD 0.00, after ALPI), Visit 9 (7 days, SD 0.894, after ALPI), Visit 10 (5.91 weeks, SD 0.944, after ALPI) and Visit 11 (3 months after ALPI) for those eyes treated with ALPI and NFT (when applicable) was statistically studied using analysis of covariance*.

*Five patients were instilling pilocarpine 2% on Visit 8 and one of them remained using the drug on Visit 9. Their data was, therefore, not included in the model at those time points.

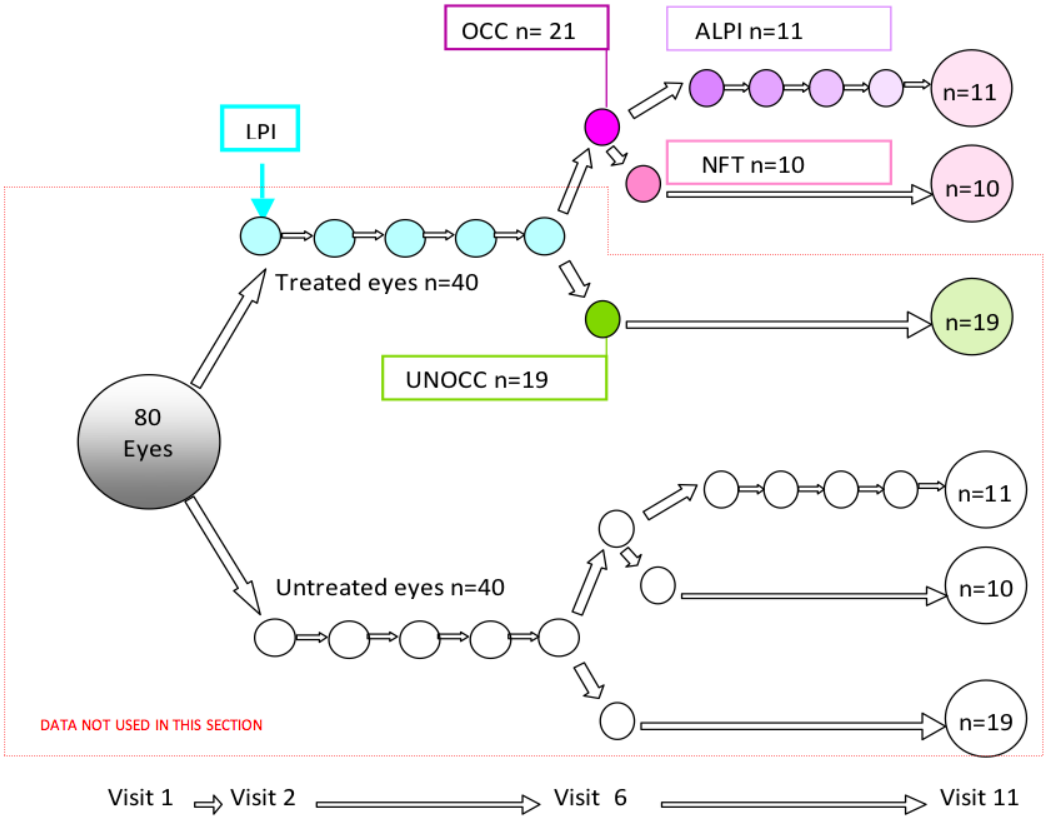

Figure 5.1. Participant pathway throughout the study. The upper half of the figure shows the pathway of those eyes randomised to receive Laser Peripheral Iridotomy (LPI) and the lower half of the figure shows the pathway of the untreated fellow eyes. Abbreviations in this figure: n= number of eyes in each group. LPI= Laser Peripheral Iridotomy. OCC= Post-LPI eyes with occludable angles. UNOCC= Post-LPI eyes with unoccludable eyes. ALPI= Eyes with post-LPI occludable angles that were further randomised into receiving ALPI. NFT= Eyes with post-LPI occludable angles that were further randomised into not receiving further treatment. The data within the dashed red box has not been used in the present section.

5.1.3 Results

The first analysis aimed to assess differences through time in the parameters dimensions in eyes which had received the ALPI. The paired samples t test found that there was a widening effect in all the sections and in all the parameters under study. There were only four exceptions out of 256 comparisons, these were found in the Inferior section (AOD 500 at Visits 9 and 10) and in the Superior-Nasal section (TISA and TIA 750 at Visit 8). The detailed analysis can be found in the following table (Table 5.1)

T-Test Comparisons with Baseline		Visit 8 - Visit 6 Diff Mean (SD); P Value	Visit 9 - Visit 6 Mean Diff (SD); P Value	Visit 10 - Visit 6 Mean Diff (SD); P Value	Visit 11 - Visit 6 Mean Diff (SD); P Value
	IOP	-3.227 (2.284); P=0.001*	-0.750 (2.072); P=0.282	0.091 (2.256); P=0.896	-2.500 (3.209); P=0.027*
SUPERIOR	AOD 500	0.038 (0.058); P=0.217	0.051 (0.082); P=0.101	0.038 (0.046); P=0.027*	0.028 (0.030); P=0.015*
	ARA 500	0.015 (0.022); P=0.208	0.017 (0.033); P=0.151	0.022 (0.035); P=0.074	0.012 (0.023); P=0.128
	TISA 500	0.014 (0.021); P=0.197	0.015 (0.035); P=0.222	0.020 (0.033); P=0.085	0.012 (0.021); P=0.112
	TIA 500	3.800 (5.105); P=0.171	4.756 (8.877); P=0.147	3.270 (3.321); P=0.012*	2.550 (2.658); P=0.014*
	AOD 750	0.055 (0.088); P=0.235	0.061 (0.124); P=0.180	0.032 (0.053); P=0.087	0.046 (0.077); P=0.110
	ARA 750	0.028 (0.041); P=0.205	0.033 (0.059); P=0.132	0.032 (0.042); P=0.040*	0.025 (0.032); P=0.044*
	TISA 750	0.028 (0.039); P=0.190	0.031 (0.061); P=0.164	0.030 (0.040); P=0.045*	0.025 (0.030); P=0.037*
	TIA 750	3.680 (5.710); P=0.223	4.078 (9.007); P=0.211	2.180 (3.169); P=0.058	2.922 (4.751); P=0.102
INFERIOR	AOD 500	0.039 (0.068); P=0.217	-0.098 (0.121); P=0.031*	-0.074 (0.089); P=0.027*	0.030 (0.068); P=0.169
	ARA 500	0.011 (0.031); P=0.414	0.036 (0.044); P=0.029*	0.028 (0.039); P=0.049*	0.001 (0.023); P=0.849
	TISA 500	0.012 (0.029); P=0.350	0.034 (0.041); P=0.028*	0.026 (0.037); P=0.052	0.002 (0.022); P=0.773
	TIA 500	4.950 (6.770); P=0.133	6.960 (6.839); P=0.011*	6.110 (7.084); P=0.023*	2.200 (5.359); P=0.203
	AOD 750	0.108 (0.149); P=0.136	0.146 (0.164); P=0.020*	0.090 (0.094); P=0.010*	0.030 (0.087); P=0.277
	ARA 750	0.032 (0.058); P=0.236	0.068 (0.077); P=0.021*	0.048 (0.059); P=0.021*	0.010 (0.043); P=0.482
	TISA 750	0.033 (0.056); P=0.212	0.065 (0.075); P=0.022*	0.046 (0.057); P=0.023*	0.010 (0.043); P=0.458
	TIA 750	7.900 (9.914); P=0.108	7.200 (7.145); P=0.011*	5.355 (5.902); P=0.013*	1.636 (5.413); P=0.340
SUPERIOR-NASAL	AOD 500	0.057 (0.055); P=0.052	0.066 (0.107); P=0.081	0.022 (0.040); P=0.099	0.029 (0.045); P=0.057
	ARA 500	0.008 (0.022); P=0.441	0.008 (0.031); P=0.451	0.010 (0.025); P=0.213	0.015 (0.027); P=0.103
	TISA 500	0.007 (0.022); P=0.455	0.007 (0.031); P=0.494	0.008 (0.022); P=0.227	0.012 (0.023); P=0.102
	TIA 500	4.467 (4.881); P=0.075	2.760 (7.525); P=0.276	1.400 (3.175); P=0.174	2.164 (3.640); P=0.077
	AOD 750	0.068 (0.107); P=0.296	0.074 (0.117); P=0.119	0.067 (0.065); P=0.015*	0.042 (0.086); P=0.181
	ARA 750	0.027 (0.036); P=0.225	0.024 (0.053); P=0.237	0.027 (0.032); P=0.035*	0.022 (0.037); P=0.106
	TISA 750	-0.026 (0.036); P=0.245	0.025 (0.054); P=0.239	0.027 (0.028); P=0.023*	0.020 (0.033); P=0.108
	TIA 750	-3.875 (6.761); P=0.335	5.050 (8.659); P=0.143	3.489 (3.621); P=0.020*	2.244 (5.338); P=0.243
INFERIOR-TEMPORAL	AOD 500	0.075 (0.066); P=0.040	0.051 (0.097); P=0.129	0.070 (0.072); P=0.009*	0.043 (0.072); P=0.075
	ARA 500	0.015 (0.023); P=0.166	0.007 (0.033); P=0.531	0.027 (0.042); P=0.056	0.023 (0.022); P=0.006*
	TISA 500	0.018 (0.022); P=0.109	0.009 (0.031); P=0.356	0.023 (0.030); P=0.031*	0.020 (0.018); P=0.003*
	TIA 500	6.650 (3.651); P=0.007*	4.020 (9.562); P=0.216	4.582 (5.270); P=0.016*	3.100 (6.612); P=0.151
	AOD 750	0.043 (0.065); P=0.164	0.045 (0.084); P=0.124	0.038 (0.069); P=0.096	0.044 (0.065); P=0.049*
	ARA 750	0.030 (0.036); P=0.097	0.019 (0.051); P=0.266	0.038 (0.054); P=0.044*	0.032 (0.031); P=0.007*
	TISA 750	0.033 (0.036); P=0.073	0.021 (0.049); P=0.199	0.033 (0.042); P=0.026*	0.030 (0.028); P=0.005*
	TIA 750	3.000 (2.860); P=0.050	3.240 (6.978); P=0.176	2.082 (3.514); P=0.078	2.755 (4.477); P=0.069
NASAL	AOD 500	0.085 (0.075); P=0.040	0.067 (0.070); P=0.014*	0.050 (0.055); P=0.013*	0.030 (0.049); P=0.068
	ARA 500	0.025 (0.032); P=0.123	0.017 (0.033); P=0.129	0.013 (0.028); P=0.173	0.015 (0.028); P=0.117
	TISA 500	0.022 (0.026); P=0.092	0.014 (0.025); P=0.108	0.010 (0.024); P=0.179	0.013 (0.024); P=0.111
	TIA 500	7.000 (6.320); P=0.042*	5.920 (7.391); P=0.032*	3.736 (4.709); P=0.025*	2.573 (4.497); P=0.087
	AOD 750	0.070 (0.085); P=0.100	0.066 (0.097); P=0.058	0.040 (0.073); P=0.102	0.056 (0.071); P=0.034*
	ARA 750	0.047 (0.049); P=0.065	0.034 (0.045); P=0.040*	0.024 (0.039); P=0.068	0.026 (0.048); P=0.118
	TISA 750	0.045 (0.044); P=0.054	0.031 (0.039); P=0.030*	0.022 (0.037); P=0.072	0.024 (0.045); P=0.122
	TIA 750	4.133 (5.906); P=0.147	4.220 (7.143); P=0.095	2.091 (4.652); P=0.167	3.370 (5.036); P=0.063
TEMPORAL	AOD 500	0.062 (0.077); P=0.106	0.049 (0.079); P=0.082	0.060 (0.057); P=0.006*	0.056 (0.064); P=0.016*
	ARA 500	0.014 (0.033); P=0.335	0.017 (0.032); P=0.126	0.024 (0.020); P=0.003*	0.029 (0.035); P=0.019*
	TISA 500	0.011 (0.035); P=0.509	0.017 (0.035); P=0.178	0.022 (0.023); P=0.014*	0.026 (0.032); P=0.028*
	TIA 500	5.617 (7.372); P=0.121	5.120 (9.198); P=0.112	5.391 (5.677); P=0.010*	3.773 (6.445); P=0.081
	AOD 750	0.059 (0.082); P=0.141	0.066 (0.121); P=0.117	0.070 (0.055); P=0.002*	0.039 (0.060); P=0.056
	ARA 750	0.032 (0.044); P=0.142	0.030 (0.052); P=0.108	0.040 (0.031); P=0.002*	0.040 (0.044); P=0.013*
	TISA 750	0.032 (0.044); P=0.139	0.030 (0.054); P=0.108	0.039 (0.033); P=0.003*	0.036 (0.039); P=0.013*
	TIA 750	4.100 (5.430); P=0.124	4.960 (9.025); P=0.116	4.727 (3.834); P=0.002*	1.900 (4.050); P=0.151
INFERIOR-NASAL	AOD 500	0.091 (0.069); P=0.024*	0.082 (0.093); P=0.021*	0.055 (0.050); P=0.004*	0.057 (0.041); P=0.001*
	ARA 500	0.013 (0.021); P=0.186	0.025 (0.051); P=0.162	0.025 (0.036); P=0.045*	0.019 (0.034); P=0.104
	TISA 500	0.016 (0.019); P=0.087	0.021 (0.049); P=0.205	0.021 (0.030); P=0.040*	0.017 (0.028); P=0.066
	TIA 500	7.383 (7.834); P=0.069	6.930 (10.711); P=0.071	3.364 (6.023); P=0.094	5.309 (4.647); P=0.004*
	AOD 750	0.109 (0.079); P=0.037*	0.075 (0.110); P=0.075	0.054 (0.092); P=0.094	0.035 (0.063); P=0.116
	ARA 750	0.045 (0.037); P=0.054	0.049 (0.069); P=0.065	0.041 (0.044); P=0.016*	0.029 (0.042); P=0.057
	TISA 750	0.047 (0.038); P=0.048*	0.046 (0.069); P=0.081	0.037 (0.041); P=0.019*	0.028 (0.035); P=0.034*
	TIA 750	6.320 (5.690); P=0.068	4.500 (9.132); P=0.178	2.160 (5.824); P=0.271	2.450 (4.315); P=0.106
SUPERIOR-TEMPORAL	AOD 500	0.035 (0.086); P=0.360	0.049 (0.079); P=0.082	0.035 (0.082); P=0.187	0.031 (0.029); P=0.006*
	ARA 500	0.011 (0.020); P=0.251	0.012 (0.016); P=0.053	0.005 (0.028); P=0.558	0.006 (0.010); P=0.082
	TISA 500	0.009 (0.022); P=0.372	0.011 (0.017); P=0.064	0.004 (0.027); P=0.650	0.005 (0.010); P=0.114
	TIA 500	2.450 (7.208); P=0.443	4.300 (7.591); P=0.107	2.091 (7.271); P=0.363	2.418 (2.354); P=0.007*
	AOD 750	0.090 (0.125); P=0.138	0.069 (0.090); P=0.038*	0.074 (0.086); P=0.018	0.055 (0.046); P=0.003*

	ARA 750	0.027 (0.044); P=0.192	0.026 (0.035); P=0.043*	0.018 (0.042); P=0.176	0.018 (0.016); P=0.003*
	TISA 750	0.026 (0.046); P=0.224	0.027 (0.036); P=0.044*	0.018 (0.042); P=0.188	0.018 (0.016); P=0.004*
	TIA 750	5.267 (7.810); P=0.159	4.450 (6.086); P=0.046*	3.709 (4.975); P=0.033	3.373 (3.086); P=0.005*

Table 5.1 Paired t test comparing the angle parameters in the different eight sections for ALPI treated eyes through visits 8, 9, 10 and 11 using visit 6 as baseline. Statistically significant values have been flagged with an asterisk, additionally they have been highlighted in yellow colour.

When assessing the effect of the ALPI on the angle parameters at Visit 11 and adjusting for the untreated occludable, all of the 8 sections parameters under study showed an increase in dimension. Furthermore, the increase in dimension found in the Superior, Inferior-Temporal and Superior-Temporal were statistically significant (P<0.05). The amount of opening found at Visit 11 for every parameter and their p-value for this analysis can be found in Table 5.2.

Difference in Parameters at Visit 11 adjusted for Visit 6 data

	Mean (SD)	P values
SUPERIOR AOD500	0.034 (0.032)	0.014*
SUPERIOR ARA500	0.016 (0.000)	0.039*
SUPERIOR TISA500	0.015 (0.000)	0.047*
SUPERIOR TIA500	3.136 (2.402)	0.014*
SUPERIOR AOD750	0.062 (0.032)	0.053
SUPERIOR ARA750	0.034 (0.032)	0.010*
SUPERIOR TISA750	0.033 (0.000)	0.008*
SUPERIOR TIA750	4.101 (3.584)	0.037*
INFERIOR AOD500	0.049 (0.063)	0.082
INFERIOR ARA500	0.012 (0.000)	0.086
INFERIOR TISA500	0.012 (0.000)	0.091
INFERIOR TIA500	4.220 (4.186)	0.039*
INFERIOR AOD750	0.022 (0.084)	0.574
INFERIOR ARA750	0.019 (0.032)	0.178
INFERIOR TISA750	0.016 (0.032)	0.293
INFERIOR TIA750	1.557 (4.520)	0.458
SUPERIOR NASAL AOD500	0.040 (0.045)	0.063
SUPERIOR NASAL ARA500	0.021 (0.000)	0.051
SUPERIOR NASAL TISA500	0.013 (0.000)	0.156
SUPERIOR NASAL TIA500	2.914 (3.230)	0.061
SUPERIOR NASAL AOD750	0.013 (0.071)	0.710
SUPERIOR NASAL ARA750	0.027 (0.032)	0.064
SUPERIOR NASAL TISA750	0.021 (0.032)	0.100
SUPERIOR NASAL TIA750	0.212 (3.931)	0.910
INFERIOR TEMPORAL AOD500	0.066 (0.063)	0.033*
INFERIOR TEMPORAL ARA500	0.038 (0.032)	0.002*
INFERIOR TEMPORAL TISA500	0.031 (0.000)	0.002*
INFERIOR TEMPORAL TIA500	5.192 (5.202)	0.040*
INFERIOR TEMPORAL AOD750	0.068 (0.071)	0.048*

INFERIOR TEMPORAL ARA750	0.054	(0.032)	0.003*
INFERIOR TEMPORAL TISA750	0.046	(0.032)	0.003*
INFERIOR TEMPORAL TIA750	4.616	(4.110)	0.023*
NASAL AOD500	0.034	(0.045)	0.132
NASAL ARA500	0.017	(0.032)	0.186
NASAL TISA500	0.015	(0.032)	0.153
NASAL TIA500	3.314	(4.151)	0.094
NASAL AOD750	0.064	(0.063)	0.041*
NASAL ARA750	0.034	(0.045)	0.105
NASAL TISA750	0.032	(0.032)	0.097
NASAL TIA750	3.848	(3.999)	0.053
TEMPORAL AOD500	0.047	(0.055)	0.064
TEMPORAL ARA500	0.026	(0.032)	0.067
TEMPORAL TISA500	0.024	(0.000)	0.039*
TEMPORAL TIA500	2.777	(4.857)	0.236
TEMPORAL AOD750	0.041	(0.055)	0.117
TEMPORAL ARA750	0.037	(0.032)	0.033*
TEMPORAL TISA750	0.033	(0.032)	0.029*
TEMPORAL TIA750	1.879	(3.803)	0.287
INFERIOR NASAL AOD500	0.052	(0.045)	0.028*
INFERIOR NASAL ARA500	0.014	(0.032)	0.294
INFERIOR NASAL TISA500	0.015	(0.000)	0.143
INFERIOR NASAL TIA500	4.596	(4.553)	0.041
INFERIOR NASAL AOD750	0.039	(0.071)	0.244
INFERIOR NASAL ARA750	0.024	(0.032)	0.185
INFERIOR NASAL TISA750	0.026	(0.032)	0.092
INFERIOR NASAL TIA750	2.482	(4.503)	0.256
SUPERIOR TEMPORAL AOD500	0.044	(0.032)	0.003*
SUPERIOR TEMPORAL ARA500	0.013	(0.071)	0.011*
SUPERIOR TEMPORAL TISA500	0.011	(0.071)	0.020*
SUPERIOR TEMPORAL TIA500	3.754	(2.307)	0.003*
SUPERIOR TEMPORAL AOD750	0.062	(0.055)	0.020*
SUPERIOR TEMPORAL ARA750	0.029	(0.000)	0.002*
SUPERIOR TEMPORAL TISA750	0.028	(0.000)	0.003*
SUPERIOR TEMPORAL TIA750	3.871	(3.575)	0.028*

Table 5.2 Analysis of covariance for the angle parameters found in dark conditions. The response variable (parameters change in dimensions) has been adjusted for the untreated occludable eye using the Visit 6 data. Those p values statistically significant ($p<0.05$) have been flagged with an asterisk and highlighted in yellow colour.

On exploring whether a relationship exists between the opening of the parameters and time, analysis of covariance showed a positive slope for every one of the parameters (Table 5.3; with this being strongest for the parameter TIA in every case. These results, although not statistically significant, showed a trend of opening of the parameters through time.

For most of the parameters, the slope defined by the relationship between IOP and the rate of opening of the parameters was positive but weak (slope<0.03). The only two cases when this relationship was statistically significant (both in the Nasal section) showed an inverse relationship;

one of them being relatively strong (Slope=-0.022298; p=0.0020) compared to the rest of the values.

For more information about the magnitude of these relationships and their p-values please see Table 5.3 as follows:

Univariate regression where the change in parameters has been adjusted for time and IOP (two separate models)

	Time slope	Time P-value	IOP slope	IOP P-value
DARK SUPERIOR AOD500	0.121	0.5245	0.000123	0.3493
DARK SUPERIOR ARA500	0.004	0.1772	0.000152	0.4725
DARK SUPERIOR TISA500	0.012	0.1862	0.000139	0.6366
DARK SUPERIOR TIA500	12.988	0.6757	0.007920	0.2122
DARK SUPERIOR AOD750	0.252	0.6647	0.000132	0.0971
DARK SUPERIOR ARA750	0.055	0.2172	0.000207	0.8218
DARK SUPERIOR TISA750	0.062	0.2583	0.000192	0.8008
DARK SUPERIOR TIA750	16.162	0.7447	0.007145	0.1201
DARK INFERIOR AOD500	0.050	0.7618	0.000120	0.5926
DARK INFERIOR ARA500	0.008	0.7788	-0.000033	0.4114
DARK INFERIOR TISA500	0.011	0.7798	-0.000030	0.4264
DARK INFERIOR TIA500	5.563	0.7888	0.005719	0.7137
DARK INFERIOR AOD750	0.153	0.7688	-0.000135	0.7508
DARK INFERIOR ARA750	0.043	0.7738	-0.000043	0.6096
DARK INFERIOR TISA750	0.045	0.8378	-0.000042	0.6076
DARK INFERIOR TIA750	10.728	0.7197	-0.008707	0.8138
DARK SUP NASAL AOD500	0.211	0.8378	-0.000047	0.1231
DARK SUP NASAL ARA500	0.055	0.1852	0.000125	0.5295
DARK SUP NASAL TISA500	0.052	0.2543	0.000101	0.5105
DARK SUP NASAL TIA500	14.644	0.8198	0.002696	0.1622
DARK SUP NASAL AOD750	0.225	0.8268	-0.000005	0.2342
DARK SUP NASAL ARA750	0.087	0.2342	0.000198	0.6256
DARK SUP NASAL TISA750	0.084	0.2913	0.000172	0.5986
DARK SUP NASAL TIA750	14.467	0.7658	-0.005607	0.1902
DARK INF TEMPORAL AOD500	0.169	0.2372	0.000316	0.6587
DARK INF TEMPORAL ARA500	0.092	0.0300*	0.000236	0.3824
DARK INF TEMPORAL TISA500	0.095	0.0290*	0.000177	0.1622
DARK INF TEMPORAL TIA500	15.215	0.4474	0.016566	0.5485
DARK INF TEMPORAL AOD750	0.264	0.4204	0.000233	0.6697
DARK INF TEMPORAL ARA750	0.155	0.0681	0.000273	0.3504
DARK INF TEMPORAL TISA750	0.156	0.0931	0.000214	0.2392
DARK INF TEMPORAL TIA750	15.844	0.4785	0.012840	0.6517
DARK NASAL AOD500	0.278	0.7838	-0.000049	0.1491
DARK NASAL ARA500	0.117	0.7508	0.000026	0.2392
DARK NASAL TISA500	0.105	0.7578	0.000022	0.2082
DARK NASAL TIA500	22.830	0.7538	-0.006954	0.1662
DARK NASAL AOD750	0.367	0.4585	0.000213	0.1061

DARK NASAL ARA750	0.203	0.7487	0.000044	0.1502
DARK NASAL TISA750	0.192	0.7658	0.000038	0.1101
DARK NASAL TIA750	21.640	0.5686	0.010927	0.1081
DARK TEMPORAL AOD500	0.157	0.0661	0.000429	0.5836
DARK TEMPORAL ARA500	0.058	0.0060*	0.000288	0.8168
DARK TEMPORAL TISA500	0.055	0.0160*	0.000226	0.8278
DARK TEMPORAL TIA500	10.819	0.2232	0.028208	0.8208
DARK TEMPORAL AOD750	0.163	0.3614	0.000284	0.7497
DARK TEMPORAL ARA750	0.099	0.0310*	0.000366	0.8358
DARK TEMPORAL TISA750	0.097	0.0330*	0.000312	0.8268
DARK TEMPORAL TIA750	8.914	0.5566	0.012461	0.6066
DARK INF NASAL AOD500	0.251	0.5335	0.000168	0.1902
DARK INF NASAL ARA500	0.082	0.3524	0.000126	0.6747
DARK INF NASAL TISA500	0.091	0.3934	0.000092	0.3213
DARK INF NASAL TIA500	23.073	0.6737	0.011795	0.1682
DARK INF NASAL AOD750	0.483	0.4024	-0.000301	0.0140*
DARK INF NASAL ARA750	0.173	0.6476	0.000098	0.3273
DARK INF NASAL TISA750	0.184	0.7708	0.000060	0.1702
DARK INF NASAL TIA750	32.816	0.3053	-0.022298	0.0020*
DARK SUP TEMPORAL AOD500	0.143	0.6346	0.000114	0.3754
DARK SUP TEMPORAL ARA500	0.039	0.7778	0.000022	0.7638
DARK SUP TEMPORAL TISA500	0.039	0.8188	0.000010	0.7377
DARK SUP TEMPORAL TIA500	14.101	0.8138	0.003502	0.2563
DARK SUP TEMPORAL AOD750	0.240	0.3433	0.000299	0.2062
DARK SUP TEMPORAL ARA750	0.085	0.3814	0.000107	0.5656
DARK SUP TEMPORAL TISA750	0.086	0.5646	0.000071	0.5475
DARK SUP TEMPORAL TIA750	16.150	0.4805	0.013428	0.1171

Table 5.3. Slopes (similar to the ustandardised coefficients, is presented as an indicator of relationship between widening of the parameters and time and between the same widening and IOP); P values indicating statistical significant relationship among parameters, time and IOP and between the treated and untreated eye groups.

The mean values for every parameter (treated eyes with ALPI and occludable eyes left untreated) in dark for visits 6, 8, 9, 10 and 11 together with their standard deviation within brackets can be found in Table 5.4 (Appendix 1).

The changes in the parameters through time and in the different sections for ALPI treated and pot-LPI occludable untreated have been visually represented in graphs 5.2 to 5.7

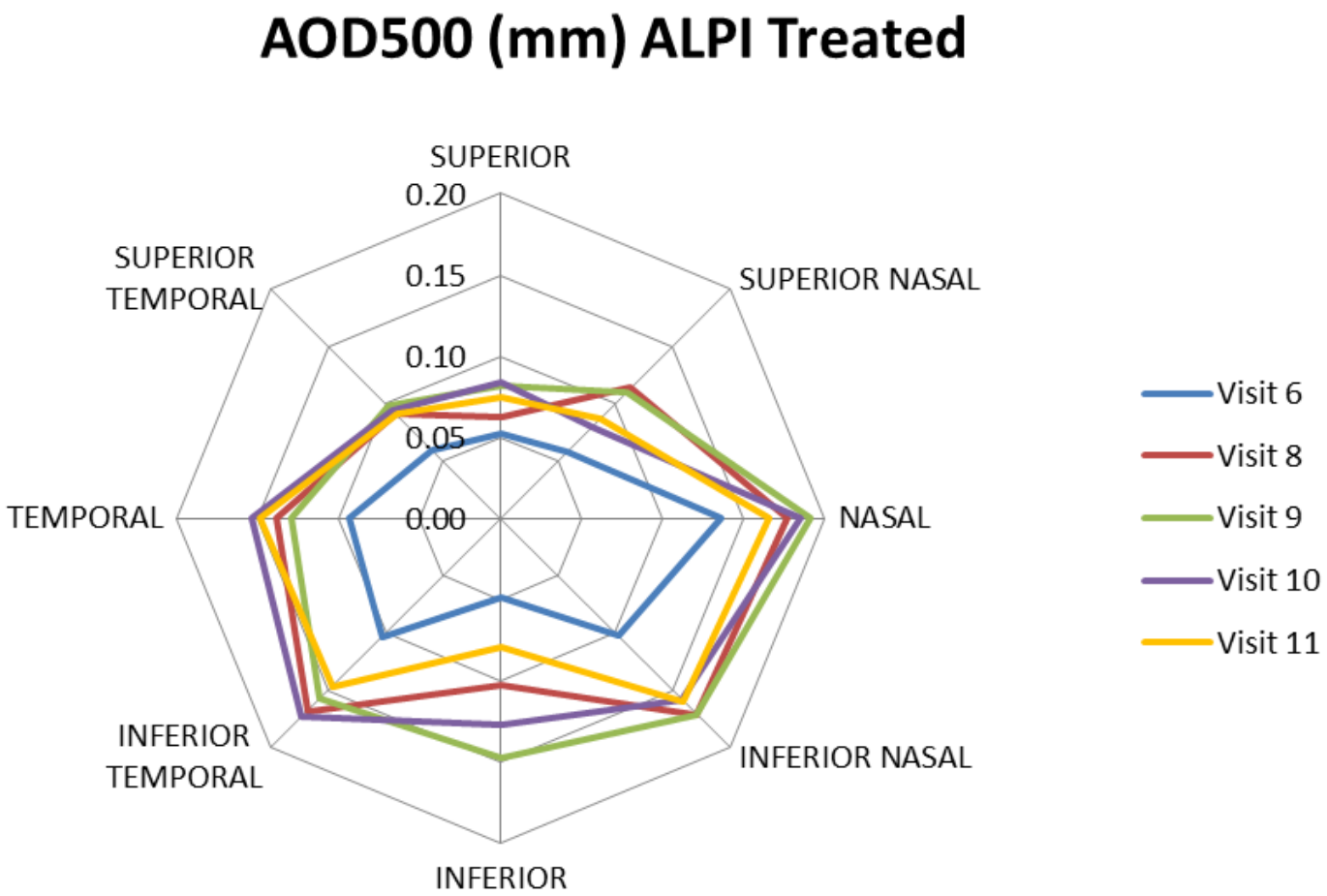

Figure 5.2 Dimensions for the parameter AOD 500 for all of the eight different sections in ALPI treated eye at visits 6, 8, 9, 10 and 11.

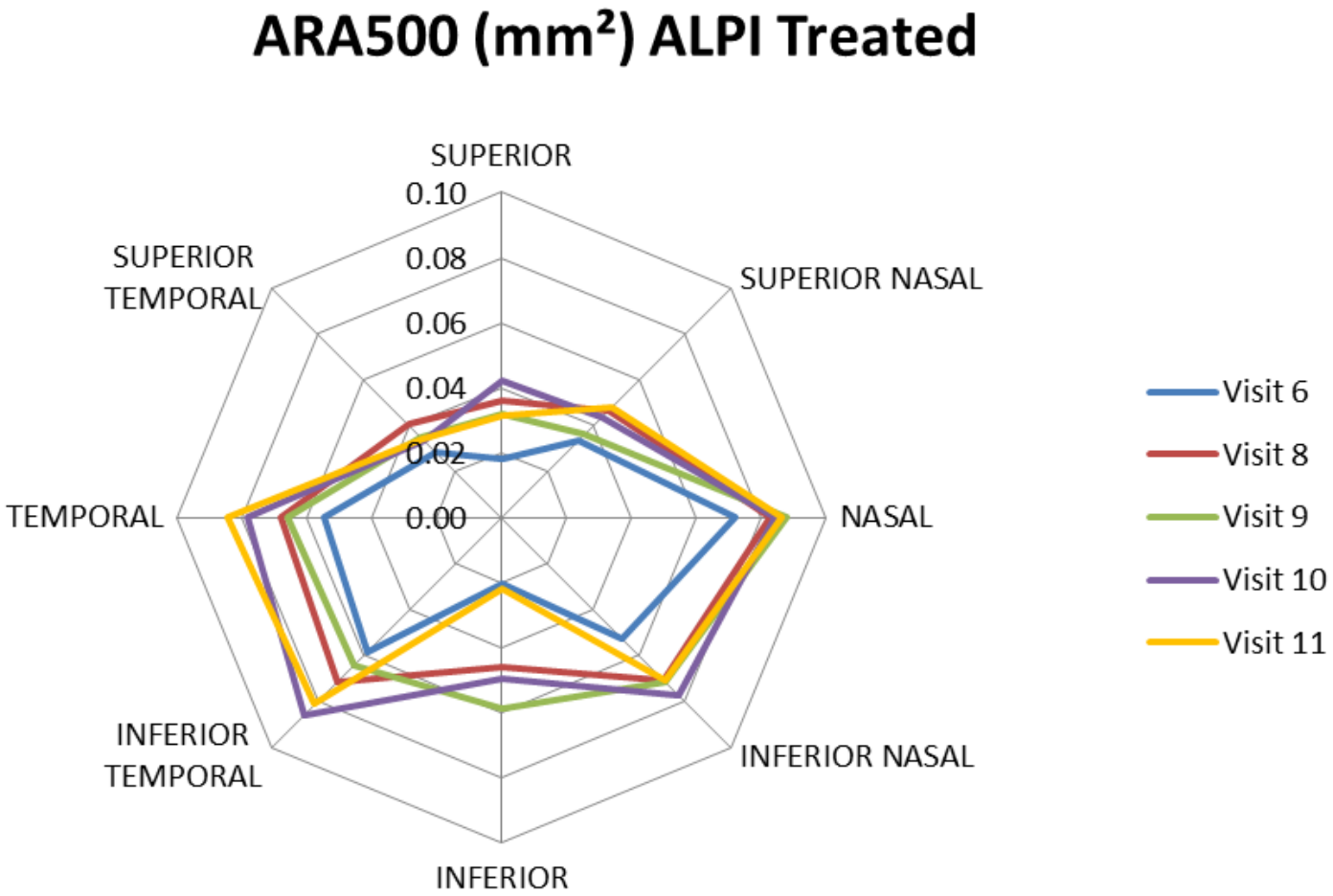

Figure 5.3 Dimensions for the parameter ARA 500 for all of the eight different sections in ALPI treated eye at visits 6, 8, 9, 10 and 11.

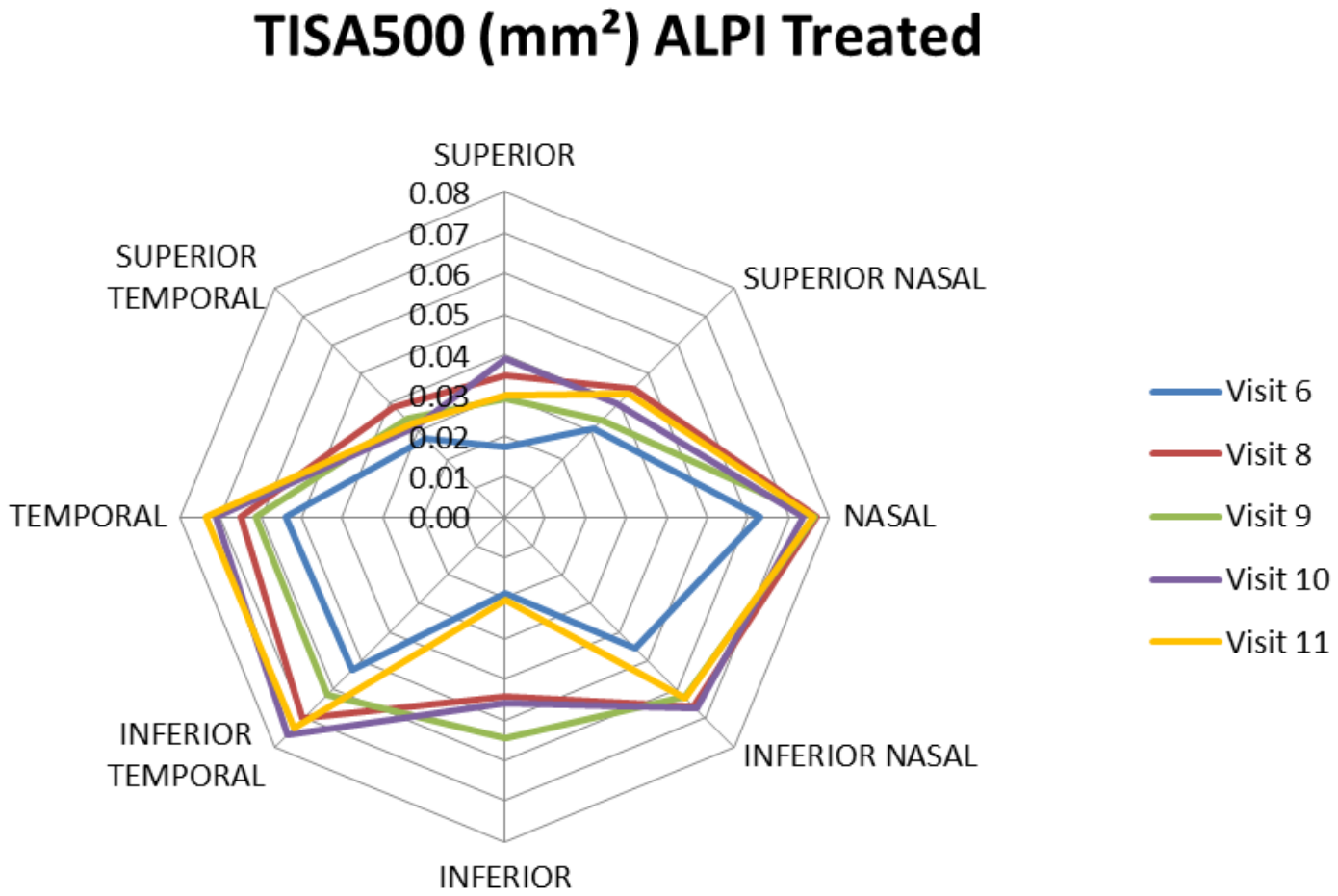

Figure 5.4 Dimensions for the parameter TISA 500 for all of the eight different sections in ALPI treated eye at visits 6, 8, 9, 10 and 11.

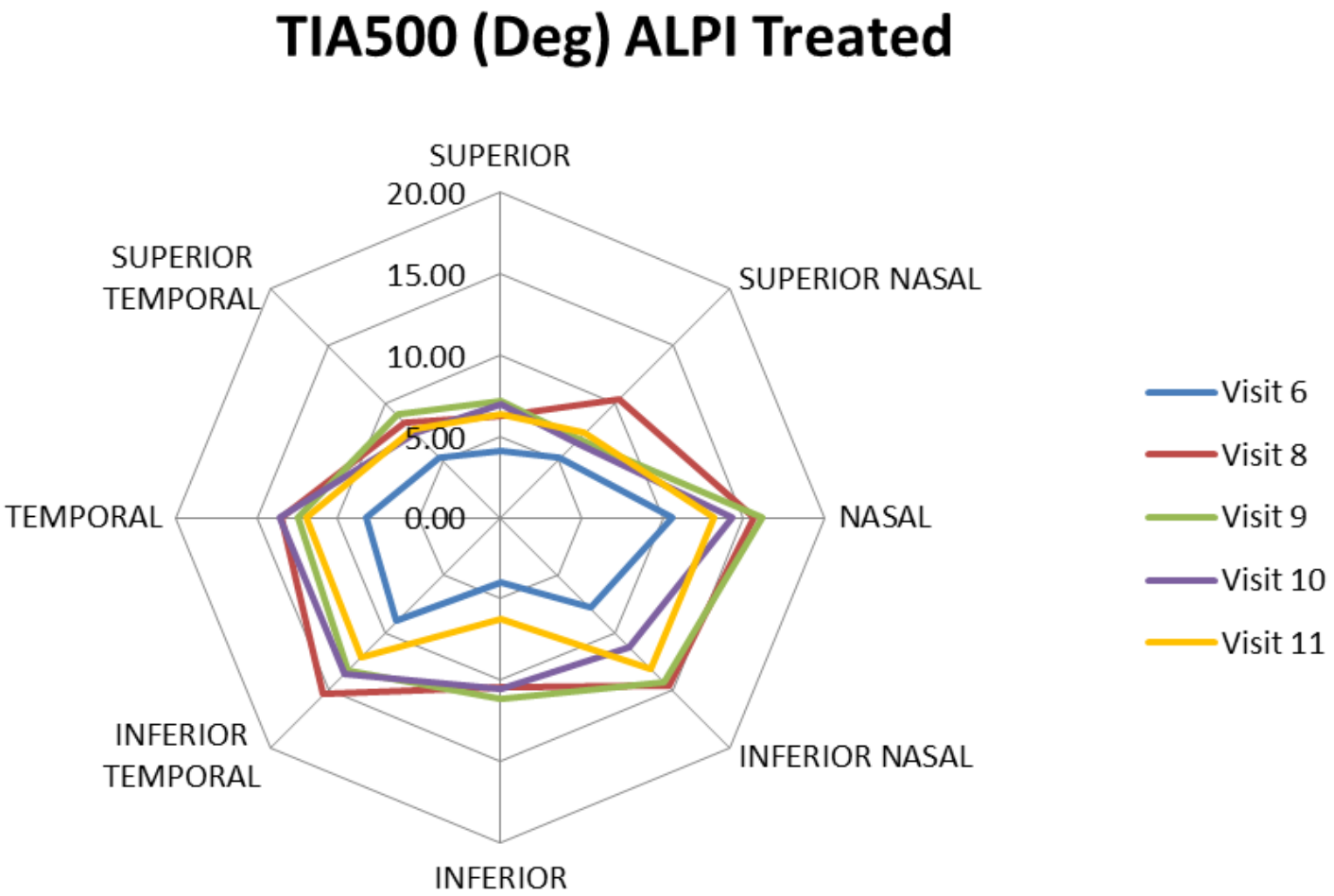

Figure 5.5 Dimensions for the parameter TIA 500 for all of the eight different sections in ALPI treated eye at visits 6, 8, 9, 10 and 11.

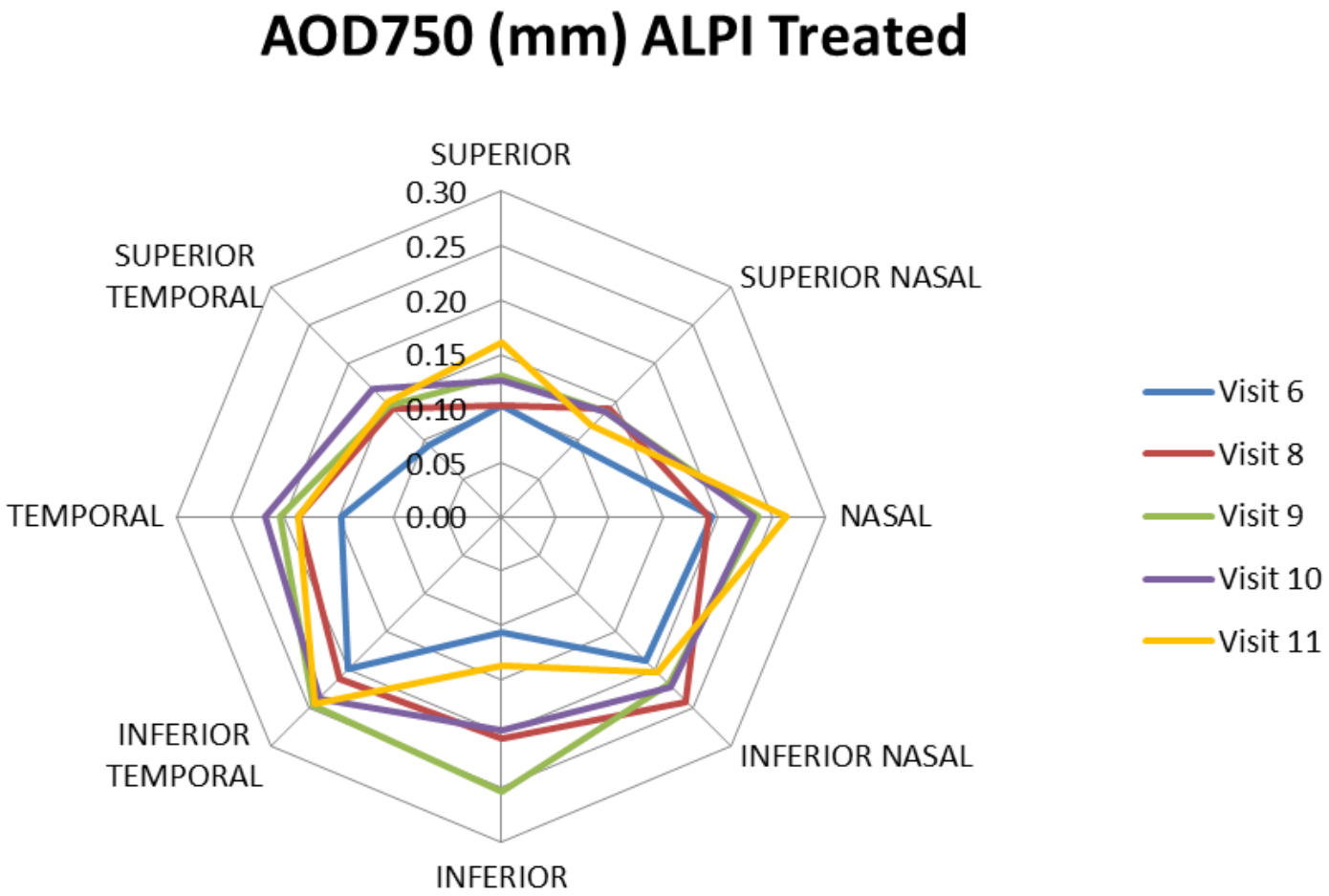

Figure 5.6 Dimensions for the parameter AOD 750 for all of the eight different sections in ALPI treated eye at visits 6, 8, 9, 10 and 11.

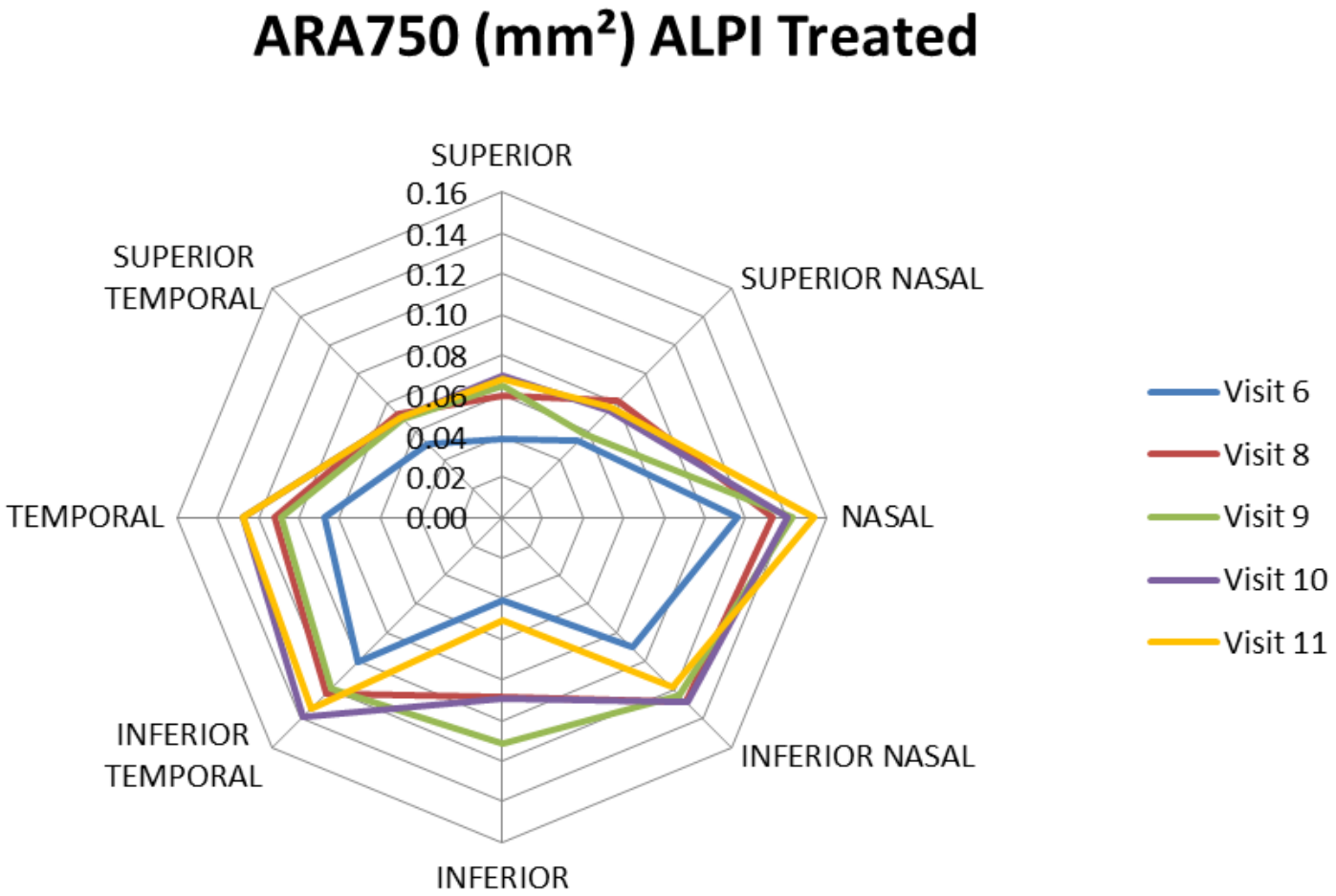

Figure 5.7 Dimensions for the parameter ARA 750 for all of the eight different sections in ALPI treated eye at visits 6, 8, 9, 10 and 11.

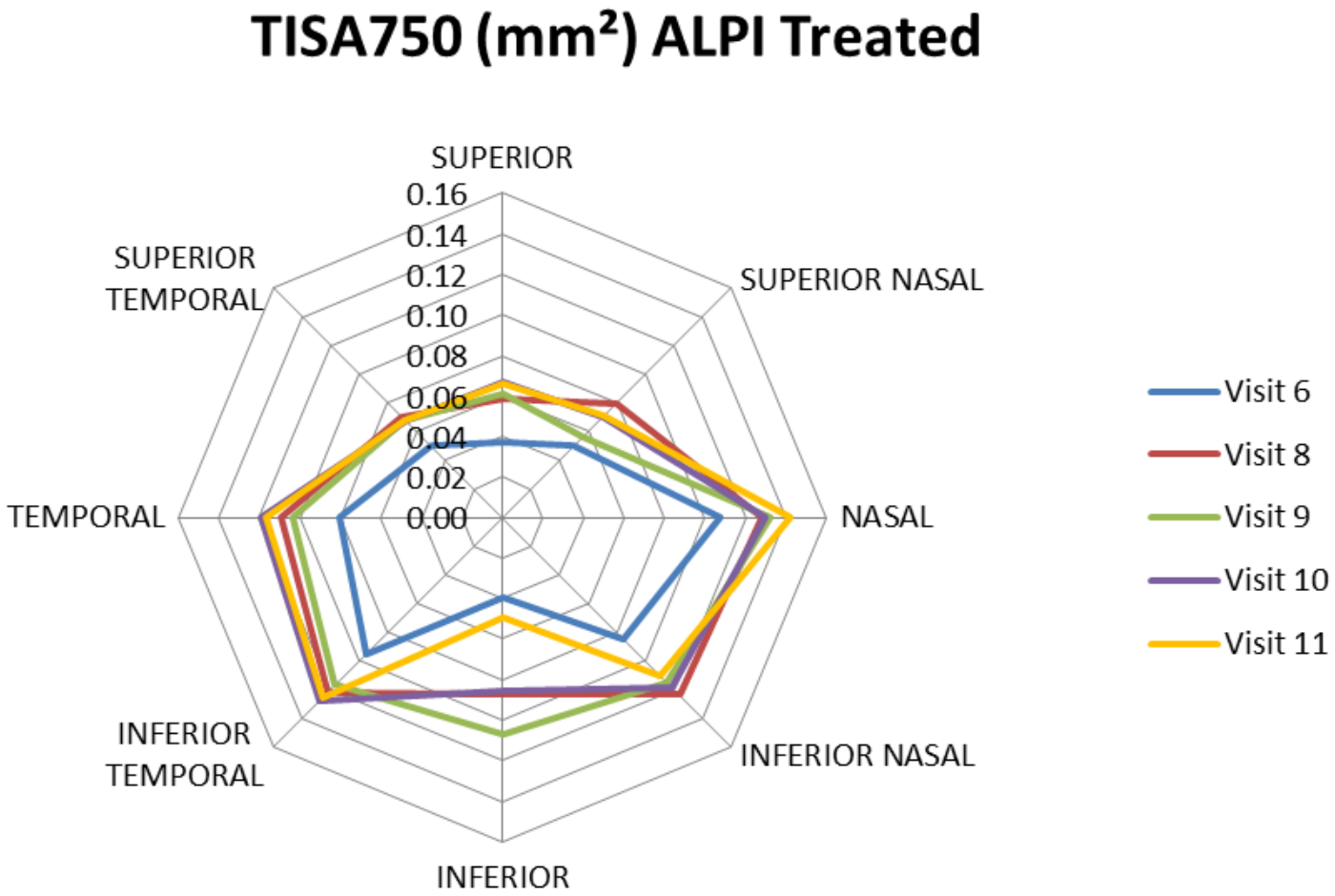

Figure 5.8 Dimensions for the parameter TISA 750 for all of the eight different sections in ALPI treated eye at visits 6, 8, 9, 10 and 11.

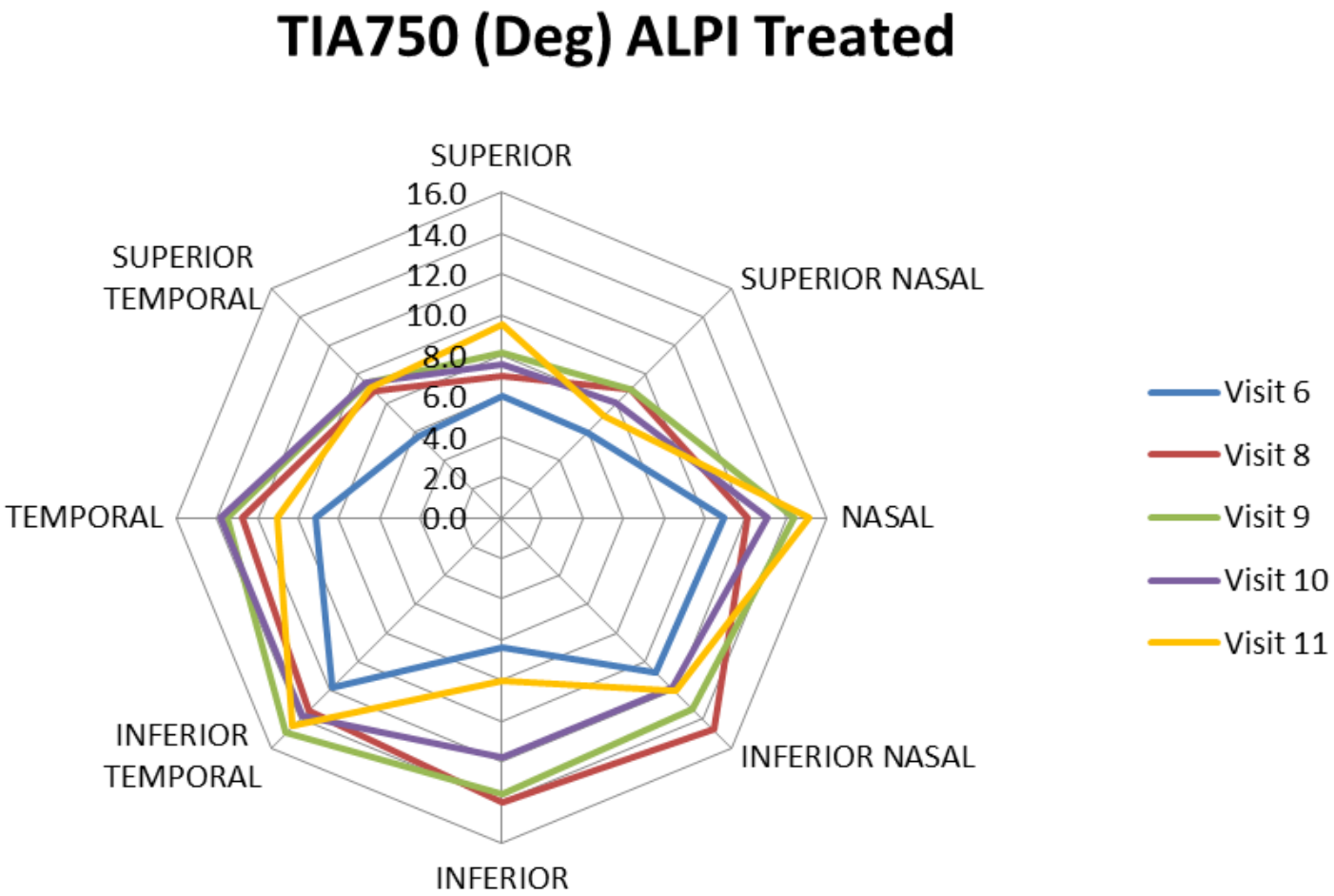

Figure 5.9 Dimensions for the parameter TIA 750 for all of the eight different sections in ALPI treated eye at visits 6, 8, 9, 10 and 11.

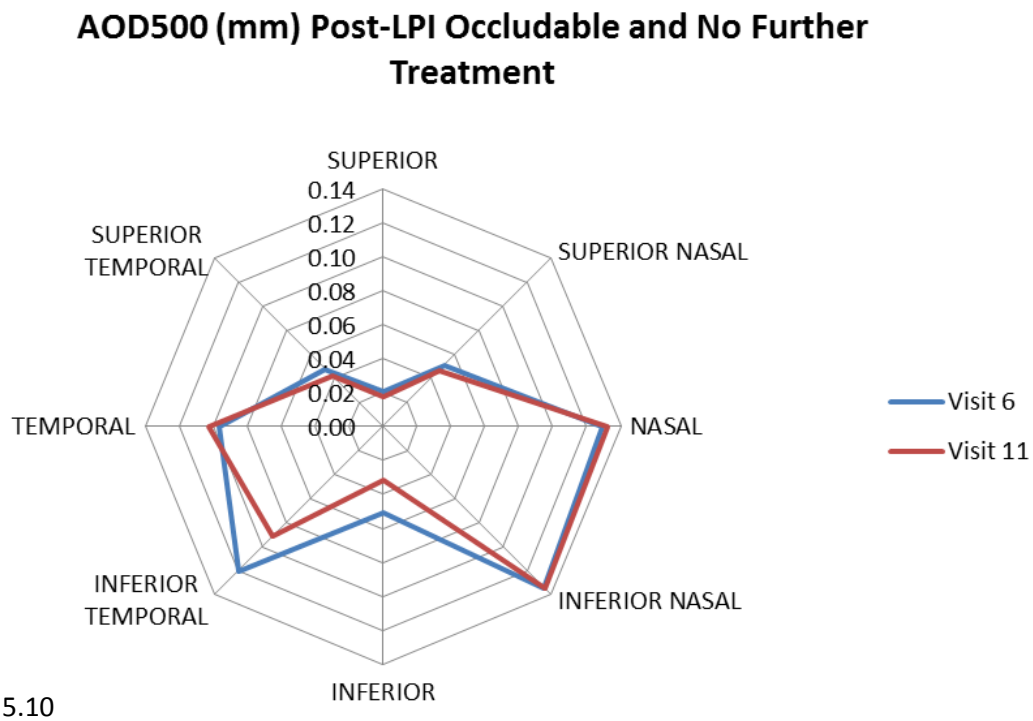

Figure 5.10

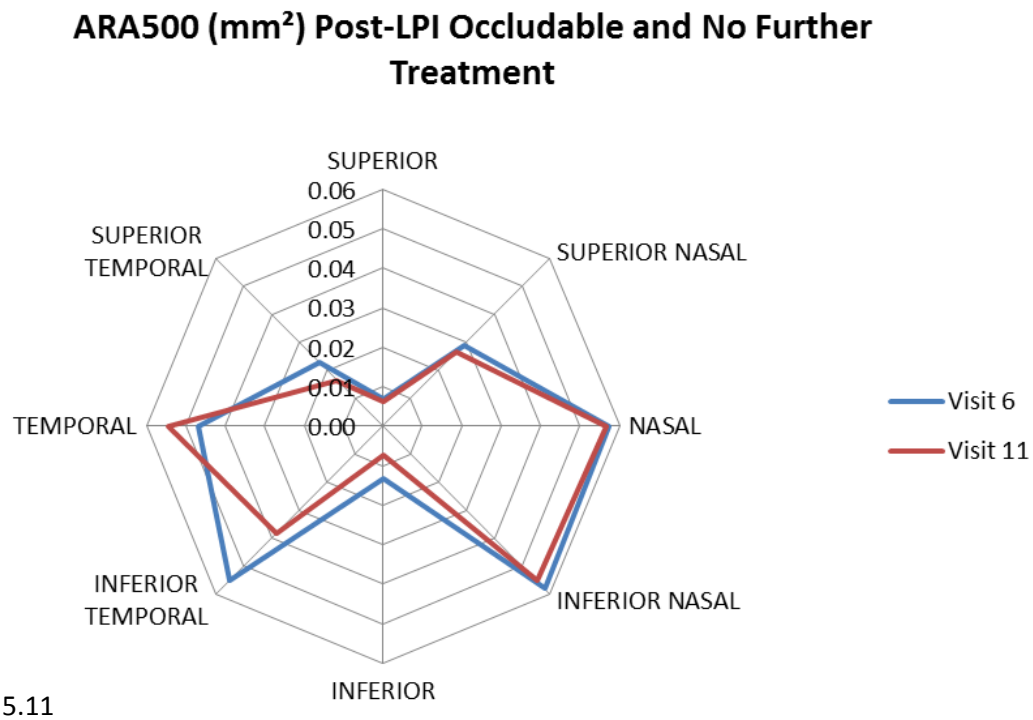

Figure 5.11

Figure 5.10 and 5.11 Dimensions for the parameter AOD and ARA 500 for all of the eight different sections in Occludable Untreated eyes at Visits 6 and 11.

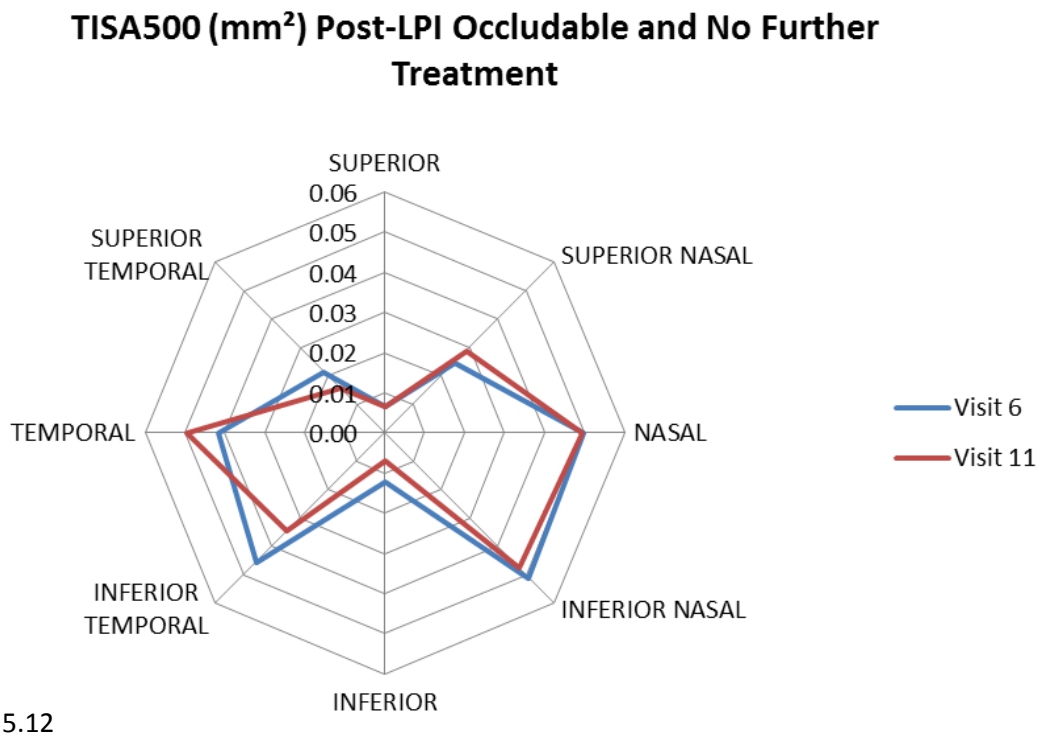

Figure 5.12

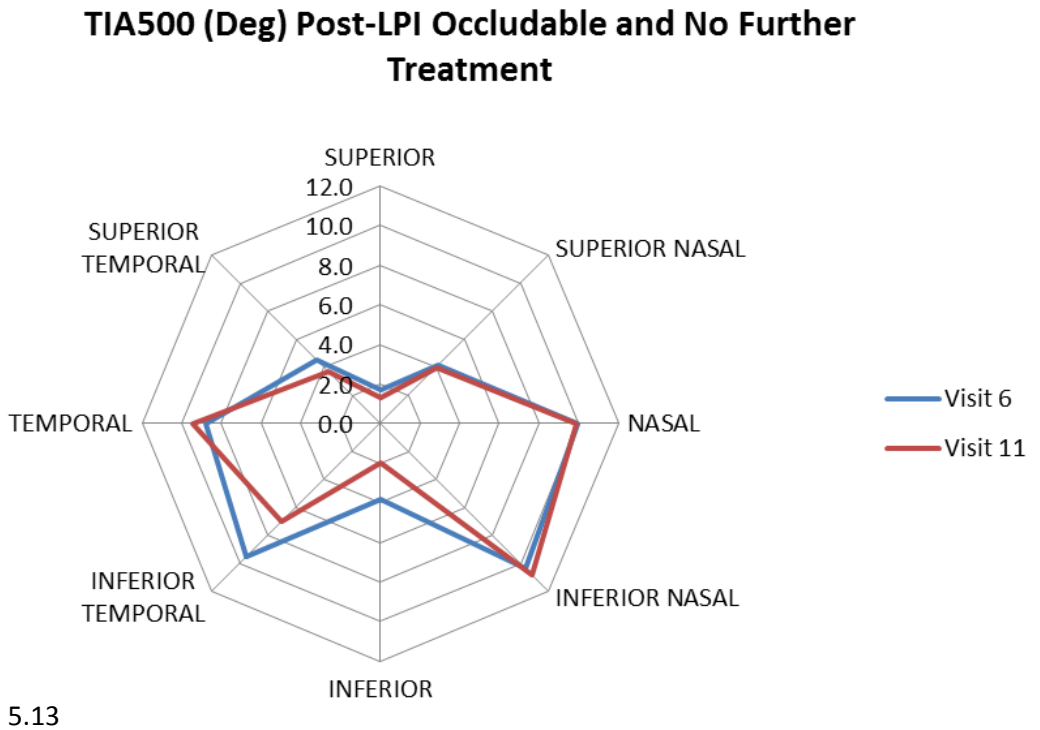

Figure 5.13

Figure 5.12 and 5.13 Dimensions for the parameter TISA and TIA 500 for all of the eight different sections in Occludable Untreated eyes at Visits 6 and 11.

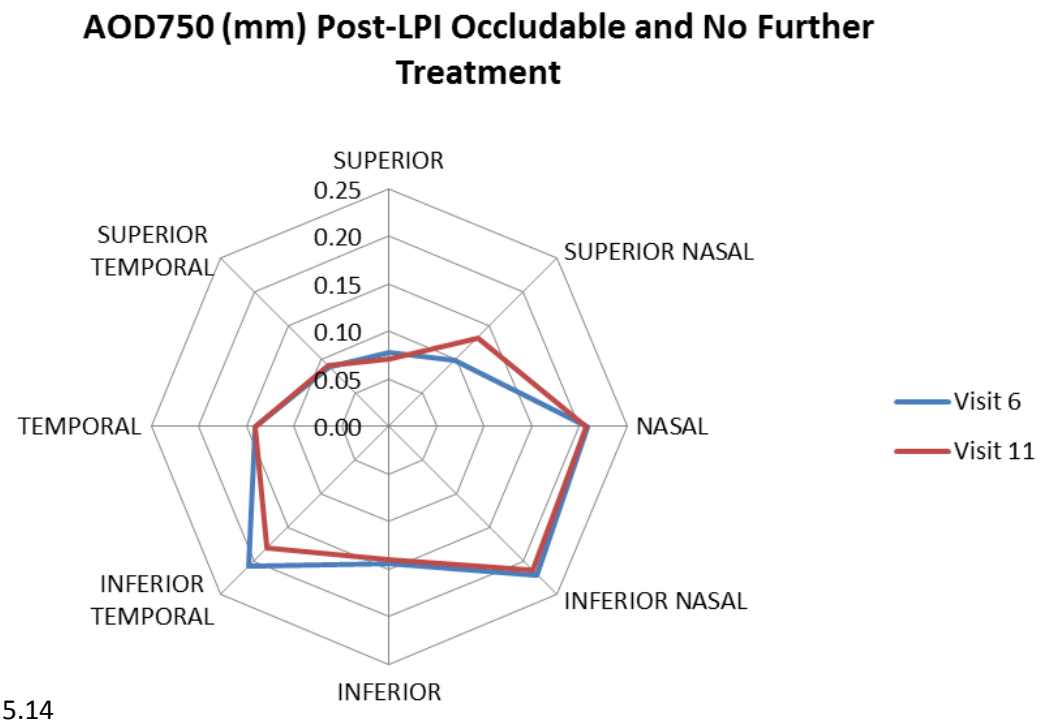

Figure 5.14

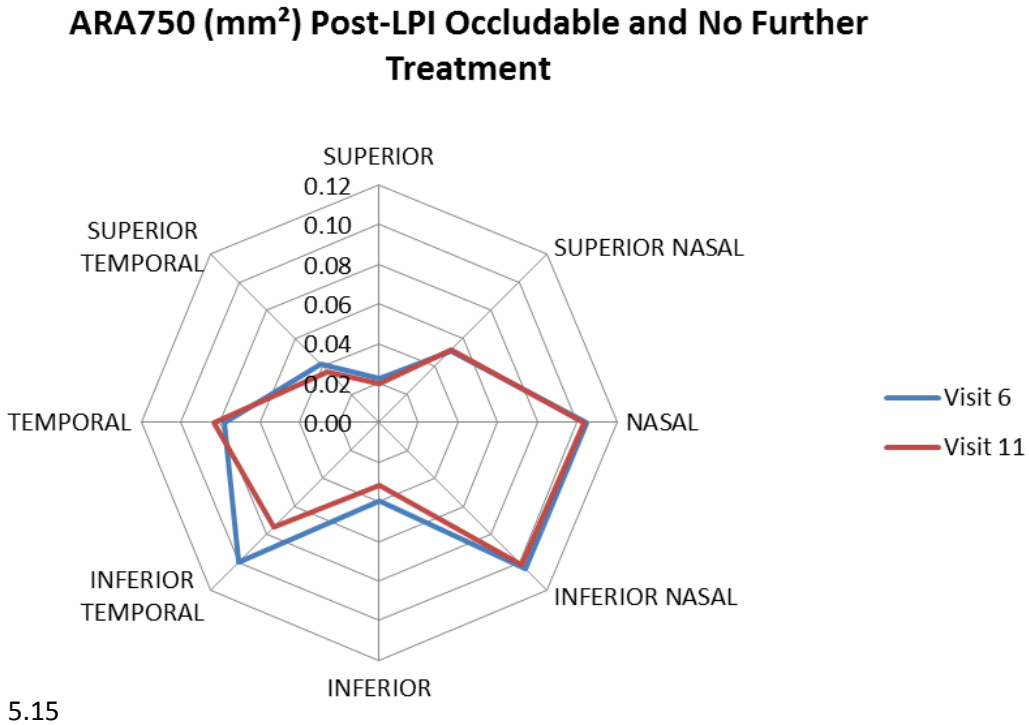

Figure 5.15

Figure 5.14 and 5.15 Dimensions for the parameter AOD and ARA 750 for all of the eight different sections in Occludable Untreated eyes at Visits 6 and 11.

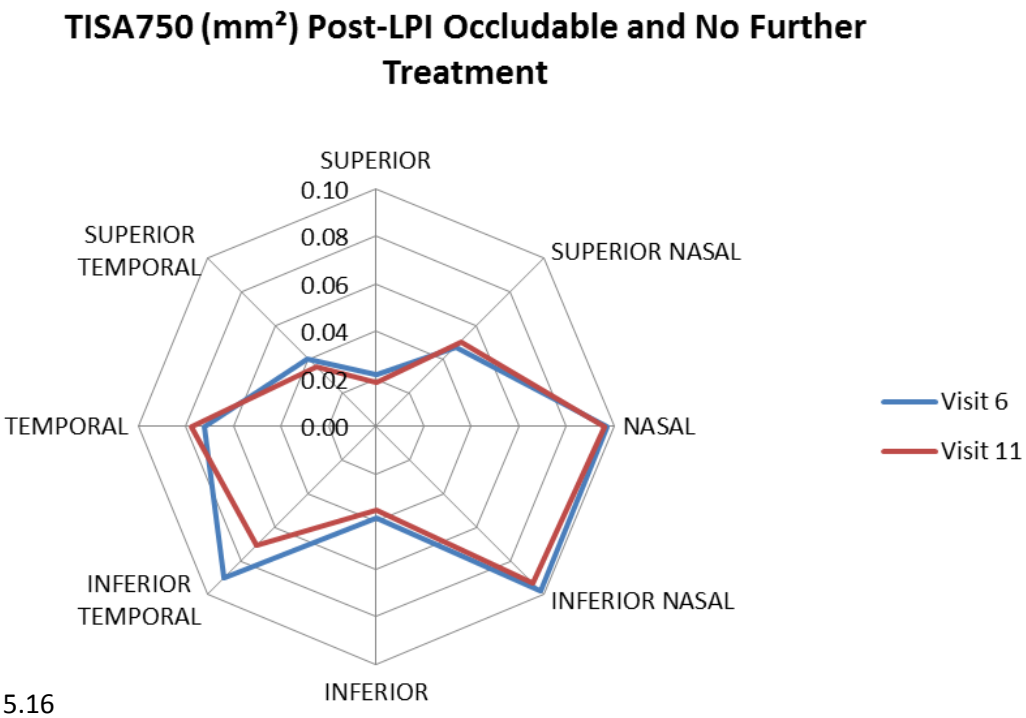

Figure 5.16

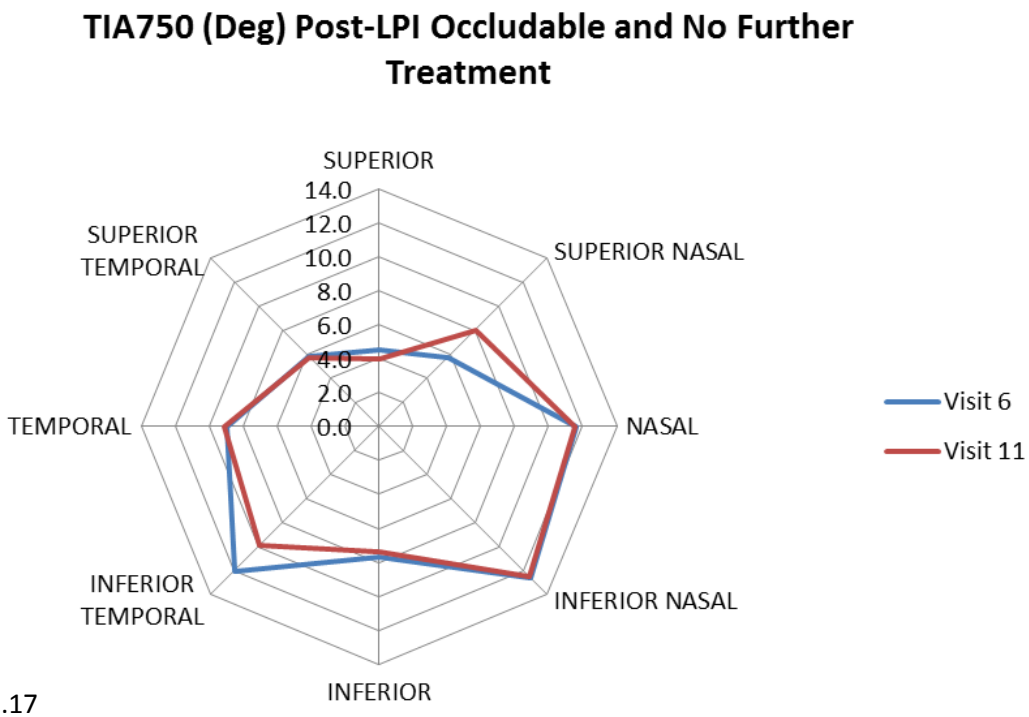

Figure 5.17

Figure 5.16 and 5.17 Dimensions for the parameter TISA and TIA 750 for all of the eight different sections in Occludable Untreated eyes at Visits 6 and 11.

5.1.4 Discussion

ALPI has shown to be effective in increasing the angle parameters dimensions when compared to the NFT group (the control group). This was confirmed by gonioscopy, where all the eyes that received the treatment changed from an occludable configuration (2 weeks before the treatment) to a non-occludable configuration 2.09 months after.

The novelty of these results is the presence of a control eye (NFT) against which to adjust the statistical model. This means that, should there have been random external factors modifying the angle parameters, these have been corrected for in this model. For these reasons, it seems that this is a more accurate investigation of the effect of the ALPI than those described in the already mentioned published research.

Furthermore the opening effect of the ALPI seemed to be, although non-statistically significant, correlated with time during the first two months after the procedure (time period of this follow-up). In other words, as time progressed the angle parameters increased. The proportion for this relationship was given by the value of the slopes in Table 5.3. To the best of one's knowledge there is only one study that has shown changes in one eye before and after ALPI using the OCT, but these changes were not quantified (Leung, et al., 2005).

A relationship between IOP after the ALPI and the angle parameters dimensions was not found in the majority of the parameters; when found, it was weakly correlated. Consequently, a relationship between rate of opening and level of IOP could not be verified. The reason for not looking into an association between parameters dimensions, time and IOP was due to the difference of time during the daytime when these pressures were measured in every participant. It has been already explained in this thesis (Section 4.2) how the diurnal IOP fluctuates in PAC and PACS patients (untreated and treated with LPI) and therefore this may have given inaccurate possible associations.

Chew and Yeo (1995) investigated the IOP levels of 11 PACG participants treated with ALPI who had already undergone LPI but whose angles remained occludable. All IOP measurements were made pre-laser and 1 hour, 1 week, 1 month, 3 months and 6 months post laser. They found that there was an initial reduction of IOP during the first week, but that it rose after 4 weeks following the procedure. A final comparison between the pre-laser IOP and that measured 6 months post-laser showed a decreased of IOP in 7 eyes. Aside from the fact that the characteristics of their patient sample differed from those in current research, it is not possible to compare their results with present data on account of the fact that the authors did not specify the time of day the IOP was measured at every visit or if this was taken at the same time for the same participant at every visit. Similar limitations may apply in a recent study by Sun, et al. (2010) who randomised 158

PAC/PACG participants into having LPI or LPI plus ALPI. They measured the IOP at baseline and at seven more visits during the following year. They found a reduction in IOP of approximately 6.66 mmHg in the LPI treated group and 7.8 mmHg in the LPI plus ALPI group one year after the procedures. However, they did not specify if these IOP measurements were taken at the same time of the day as in the pre-laser visit. The present study data from Section 4.2 shows that a diurnal fluctuation exists of around 6.34 mmHg (SD 2.21 mmHg) in successfully treated LPI eyes. If data by Sun, et al. (2010) were collected on LPI patients at different times of the day, the differences in IOP between the pre and post-laser measurements could well be explained through the diurnal IOP fluctuation. Diurnal fluctuation for ALPI treated patients in the present study is explored in the next section (Section 5.2).

Another study carried out by Lee, Choi, Kim and Choi (2011) in bilateral PACS subjects, randomised one eye to receive LPI and the fellow eye to receive LPI plus ALPI (same setting). The anterior chamber depth measured at 4 to 6 mm from the centre of the eye was significantly different between the two treatment groups, being the LPI plus ALPI the treatment with the higher deepening efffect. These differences were measured 1 week after the procedure and assessed with Pentacam. There were no statistically significant differences between groups in the IOP measured at baseline, 1 hour, 1 day, 1 week, 1 month and 3 months after the treatment, however, again, the time of IOP measurement was also not specified.

A further outcome for this thesis could have been a comparison for parameters and IOP levels between the ALPI treated group and the non-occludable post-LPI group.

5.1.5 Conclusion

ALPI has been shown to be effective in opening those angles that remained occludable after LPI. This has been tested using two techniques, gonioscopy and AS-OCT.

Although statistically non-significant there appears to be a relationship between an increase in the angle parameters and an increase in time after the procedure for at least the first two months.

5.2 Effect of ALPI on the intraocular pressure diurnal fluctuation after 2 months

5.2.1 Introduction

As explained in the introduction of section 5.1, the mechanism of lowering of IOP by ALPI is unclear although one would presume that reduction of the area of trabecular meshwork that is occludable by the iris is a major factor. In addition to measuring absolute IOP levels this thesis aimed to study the effect of ALPI on DIOP fluctuation. To date there is no published literature regarding the outcome of this objective, but it has been shown earlier in this thesis that there is an inverse association between DIOP fluctuation and the dimensions of the parameters in the different sections. It has been additionally shown that there is a widening effect caused by the ALPI in nearly all the parameters of 3 angle sections when compared to the untreated eye. One can hypothesise that there would be a decrease in such fluctuation in eyes treated with ALPI.

5.2.2 Methodology and Statistical Analysis plan

Prior to planning the statistical analysis, variability in the DIOP fluctuation due to time in this group of eyes was investigated:

In the Section 4.2 of this thesis, the effect of the Laser Peripheral Iridotomy (LPI) on the DIOP fluctuation was studied. DIOP fluctuation due uniquely to time was additionally studied prior to plan the statistical analysis. It was shown that there were no statistically significant differences (nor clinical) in the DIOP fluctuation measured 6 months apart in the fellow untreated eyes of those eyes that had only received LPI as laser treatment. However, in this section the eyes acting as control are those with post-LPI occludable angles that did not received further treatment (NFT group, n=10). There was therefore a need to know if the DIOP fluctuation was stable in this group of eyes.

If there was no variability in the DIOP fluctuation in the NFT group of eyes (used as control group) it would mean that comparisons between two different visits (Visit 1 and 11) could be performed.

A paired samples t-test was performed for DIOP fluctuation, peaks and troughs for the NFT group at Visit 1 compared to the same group at Visit 11. The differences were all lower than 1 mm Hg

and not statistically significant. The results for these comparisons can be found in the results section of this section.

The time elapsed between Visit 1 and Visit 11 for the NFT group was 6.61 months (SD 0.62 months) which was similar to that of the ALPI group, 6.52 months (SD 0.60 months).

Consequently, it was justified to use the NFT as the control group for the ALPI group (those eyes with post-LPI occludable angles that received ALPI as a further treatment). See the following figure (Figure 5.18) for a visual pathway of the participants after the two randomisations.

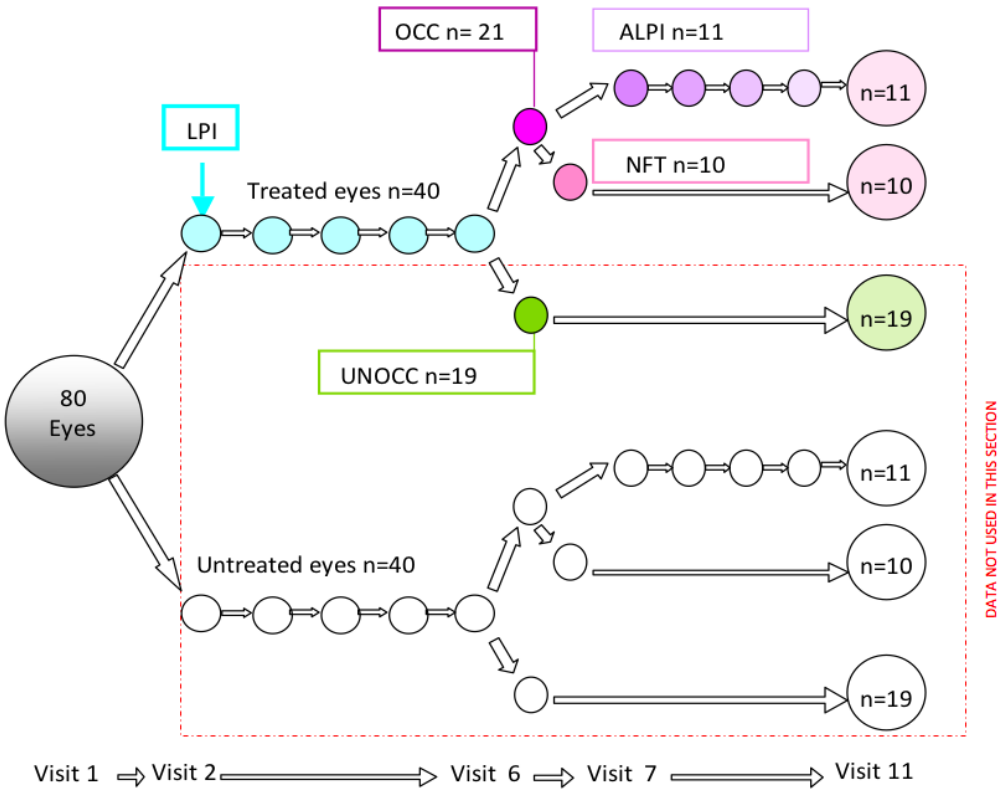

Figure 5.18.Participant pathway throughout the study. The upper half of the figure shows the pathway of those eyes randomised to receive Laser Peripheral Iridotomy (LPI) and the lower half of the figure shows the pathway of the untreated fellow eyes. The data enclosed in red boxes was not used in this section. Abbreviations in this figure: n= number of eyes in each group. LPI= Laser Peripheral Iridotomy. OCC= Post-LPI eyes with occludable angles. UNOCC= Post-LPI eyes with unoccludable eyes. ALPI= Eyes with post-LPI occludable angles that were further randomised into receiving ALPI. NFT= Eyes with post-LPI occludable angles that were further randomised into not receiving further treatment.

To test the hypothesis that ALPI would decrease the DIOP fluctuation:

The statistical analysis was designed to investigate the differences in DIOP fluctuation within the same eye before and after the ALPI (time lines: Visit 1 and Visit 11). As this group of eyes was already treated with LPI, it was necessary to isolate the effect of the ALPI. The way this was done was using the NFT (group of eyes with similar features as the ALPI group with the exception that they did not receive the ALPI). This was carried out using analysis of covariance at Visit 11 and adjusted for the differences in DIOP fluctuation for the two groups. If a statistically difference was to be found, this would have been due to the effect of ALPI solely.

The mean time between ALPI, carried out in Visit 7, and Visit 11 was 2.39 months, SD 0.29 months.

5.2.3 Results

Investigation of variability of the data found for DIOP fluctuation in the control group of eyes (NFT) between Visits 1 and 11:

Paired t-test was performed to compare the DIOP fluctuation, peaks and troughs between the NFT group at Visit 1 and Visit 11. No statistically significant differences existed and the differences in the means were lower than 1 mmHg. See following table (Table 5.5).

DIOP	NFT group Visit 1 Mean (SD)	NFT group Visit 11 Mean (SD)	Mean difference (SE)	T test P value
Fluctuation	6.83 (3.07)	6.61 (1.63)	0.22 (3.62)	0.859
Peak	22.11 (4.39)	21.55 (2.52)	0.55 (3.83)	0.675
Trough	15.28 (2.03)	14.94 (1.88)	0.33 (2.05)	0.638

Table 5.5. Paired Samples t-test comparing DIOP fluctuation, peaks and troughs between NFT group at Visit 1 and NFT group at Visit 11.NFT=no further treatment.

Results for the effect of ALPI on the DIOP fluctuation:

The analysis of covariance showed that there was a difference of 1.56 mmHg between the DIOP fluctuation found in the two groups, ALPI (Mean DIOP fluctuation at Visit 11=5.04 mmHg; SD=1.60 mmHg) and the post-LPI occludable angles left untreated (Mean DIOP fluctuation= 6.61 mmHg; SD=1.63 mmHg). This difference was statistically non-significant p=0.056.

To assess if this difference in fluctuation was due to a difference between peaks, troughs or due to both, further analyses were undertaken. One compared the peaks (Mean IOP peak at Visit 11 for ALPI group= 19.04 mmHg, SD 2.58 mmHg; Mean IOP peak at Visit 11 for NFT group= 21.55 mmHg, SD 2.52 mmHg) and the other compared the troughs between groups (Mean DIOP trough ALPI group= 14.00 mmHg, SD 2.00 mmHg; Mean DIOP trough NFT group= 14.94 mmHg, SD 1.88 mmHg). Analysis of covariance showed no statistically significant differences when comparing the DIOP troughs between groups (Mean difference between DIOP troughs=0.47 mmHg; p=0.578). When comparing the DIOP peaks, the mean difference between groups was found to be 1.35 mmHg, with this difference being no statistically significance, p=0.210. Table 5.6 contains all this information.

DIOP	NFT group Mean (SD)		ALPI group Mean (SD)		Mean difference (SE)	ANCOVA P value
	Visit 1	Visit 11	Visit 1	Visit 11		
Fluctuation (mmHg)	6.60 (2.99)	6.61 (1.63)	5.32 (2.20)	5.04 (1.60)	1.60 (0.78)	0.056
Peak (mmHg)	21.75 (4.30)	21.55 (2.52)	19.32 (2.79)	19.04 (2.58)	1.35 (1.04)	0.210
Trough (mmHg)	15.15 (1.96)	14.94 (1.88)	14.00 (2.70)	14.00 (2.00)	0.470 (0.83)	0.578

Table 5.6. Analysis of covariance (ANCOVA) comparing DIOP fluctuation, peaks and troughs between post-LPI eyes with occludable angles that were left without further treatment (NFT group) and those that received further treatment with ALPI (ALPI group) at Visit 11 adjusted for Visit 1 data. SD= Standard deviation. SE= Standard error.

5.2.4 Discussion

In this study ALPI was effective in lowering the DIOP fluctuation by 1.56 mmHg (p=0.056) after 2.4 months approximately after the procedure. This difference seemed to be due to the lower peaks in the ALPI group, meaning that those participants who were treated with ALPI seemed to have lower peaks than those with post-LPI participants with occludable angles who were left untreated.

The advantage of this investigation is to have a control group whose levels can be used to adjust the statistical models to. If this group had not existed only data collected at Visit 11 would have been compared.

It was interesting that the DIOP fluctuation found in Section 4.1 for the unoccludable post-LPI eyes (6.34 mmHg; 2.21 mmHg) was similar for those that were not treated with ALPI compared to those that were treated. Moreover, the ALPI treated group of eyes showed the lowest DIOP fluctuation compared to the other 3 groups at Visit 11 (non-treated eyes, post-LPI unoccludable

eyes, post-LPI occludable eyes). This would suggest that ALPI further reduced the DIOP fluctuation.

As mentioned in the Section 4.2 of this thesis, there have been several studies performed in angle closure participants, however, this is the first study assessing DIOP fluctuation in ALPI treated eyes; furthermore, it is the only study having a control eye of similar characteristics.

5.2.5 Conclusion

When considering eyes with occludable angles that do not become open on gonioscopy following LPI, a subsequent ALPI treatment may be effective in lowering the DIOP peaks and DIOP fluctuation when compared to the diurnal profiles of eyes that are not offered further treatment post-LPI.

5.3 Assessment of variability of ALPI effect depending on the angle sector

5.3.1 Introduction

Unlike LPI where the laser is used to create an iridotomy in a single site, the ALPI is applied over the 360 degrees of irido-trabecular angle circumference (20 to 24 shots aimed to contract/burn iris tissue but not to penetrate it). There is no published research assessing the effect of ALPI on multiple angle sectors with AS-OCT. One may hypothesise that the evenly-spaced circumferential laser applications would widen the anterior chamber angle to a similar extent circumferentially.

5.3.2 Methodology and Statistical Analysis plan

Analysis of variance followed by Tukey HSD (this analysis can be found in the attached compact disc) was used to statistically test the differences in angle parameters for the different 10 sections in light and dark conditions and before and after the ALPI (time points: Visit 6 (12.55 days, SD 5.24 days, before ALPI) and Visit 11 (2.09 months, SD 0.302, after ALPI)) in the 11 eyes that received the treatment.

5.3.3 Results

The analysis showed no statistically significant differences among the effect of ALPI on the parameters in the ten sections under study. The descriptive mean values for the difference in the parameter dimensions between Visit 6 and Visit 11 can be observed in Table 5.7 for the parameters in light conditions and in Table 5.8 for dark conditions.

LIGHT MEAN VALUES OF ALPI EFFECT	AOD 500	ARA 500	TISA 500	TIA 500	AOD 750	ARA 750	TISA 750	TIA 750
IRIDOTOMY POSITION	0.008 (0.041)	0.005 (0.013)	0.005 (0.012)	0.670 (3.336)	0.030 (0.065)	0.008 (0.021)	0.007 (0.022)	1.873 (4.066)
SUPERIOR	0.001 (0.034)	0.001 (0.013)	0.003 (0.012)	0.636 (3.611)	0.014 (0.044)	0.012 (0.029)	0.013 (0.028)	1.491 (3.233)
SUPERIOR- NASAL	0.022 (0.044)	0.004 (0.022)	0.005 (0.022)	2.740 (4.220)	0.014 (0.044)	0.012 (0.029)	0.013 (0.028)	1.491 (3.233)
NASAL	0.016 (0.063)	0.013 (0.033)	0.010 (0.025)	2.273 (5.658)	0.008 (0.076)	0.016 (0.048)	0.013 (0.043)	1.336 (5.221)
INFERIOR- NASAL	0.029 (0.079)	0.022 (0.029)	0.018 (0.026)	2.864 (7.718)	0.010 (0.084)	0.028 (0.045)	0.024 (0.042)	1.082 (5.592)

OPPOSITE IRIDOTOMY	0.064 (0.103)	0.026 (0.040)	0.025 (0.036)	3.955 (6.004)	0.077 (0.083)	0.047 (0.062)	0.045 (0.059)	3.800 (3.333)
INFERIOR	0.008 (0.053)	0.000 (0.030)	0.000 (0.030)	1.000 (4.468)	0.064 (0.089)	0.011 (0.040)	0.011 (0.041)	3.746 (4.436)
INFERIOR-TEMPORAL	0.037 (0.036)	0.021 (0.028)	0.023 (0.025)	4.555 (3.749)	0.036 (0.046)	0.033 (0.036)	0.035 (0.032)	3.246 (3.056)
TEMPORAL	0.040 (0.075)	0.029 (0.038)	0.026 (0.032)	4.073 (5.185)	0.045 (0.084)	0.037 (0.049)	0.034 (0.044)	3.146 (4.210)
SUPERIOR-TEMPORAL	0.048 (0.086)	0.017 (0.026)	0.017 (0.025)	4.382 (7.427)	0.064 (0.076)	0.033 (0.047)	0.034 (0.044)	4.127 (4.638)

Table 5.7. Mean value of the ALPI effect in the parameters in the 10 different sections measured in light conditions. The values in the table are mean values of the change between V6 (pre-ALPI) and V11 (post-ALPI). The standard deviation is the value within brackets. Minimum parameter mean value dimension for every section is boxed in blue and maximum value in red.

DARK MEAN VALUES OF ALPI EFFECT	AOD 500	ARA 500	TISA 500	TIA 500	AOD 750	ARA 750	TISA 750	TIA 750
IRIDOTOMY POSITION	0.001 (0.043)	0.009 (0.032)	0.006 (0.024)	0.300 (3.024)	-0.020 (0.058)	0.007 (0.040)	0.005 (0.032)	-1.180 (3.681)
SUPERIOR	0.028 (0.030)	0.012 (0.023)	0.012 (0.021)	2.550 (2.658)	0.046 (0.077)	0.025 (0.032)	0.025 (0.030)	2.922 (4.751)
SUPERIOR- NASAL	0.029 (0.045)	0.015 (0.027)	0.012 (0.023)	2.164 (3.640)	0.042 (0.086)	0.022 (0.037)	0.020 (0.033)	2.244 (5.338)
NASAL	0.030 (0.049)	0.015 (0.028)	0.013 (0.024)	2.573 (4.497)	0.056 (0.071)	0.026 (0.048)	0.024 (0.045)	3.370 (5.036)
INFERIOR- NASAL	0.057 (0.041)	0.019 (0.034)	0.017 (0.028)	5.309 (4.647)	0.035 (0.063)	0.029 (0.042)	0.028 (0.035)	2.450 (4.315)
OPPOSITE IRIDOTOMY	0.019 (0.068)	0.009 (0.034)	0.008 (0.026)	1.109 (4.145)	0.021 (0.032)	0.014 (0.044)	0.013 (0.037)	1.055 (1.831)
INFERIOR	0.031 (0.068)	0.001 (0.023)	0.002 (0.022)	2.200 (5.359)	0.030 (0.087)	0.010 (0.043)	0.010 (0.043)	1.636 (5.413)
INFERIOR-TEMPORAL	0.043 (0.072)	0.023 (0.022)	0.020 (0.018)	3.100 (6.612)	0.044 (0.065)	0.032 (0.031)	0.030 (0.028)	2.755 (4.477)
TEMPORAL	0.056 (0.064)	0.029 (0.035)	0.026 (0.032)	3.773 (6.445)	0.039 (0.060)	0.040 (0.044)	0.036 (0.039)	1.900 (4.050)
SUPERIOR-TEMPORAL	0.031 (0.029)	0.006 (0.010)	0.005 (0.010)	2.418 (2.354)	0.055 (0.046)	0.018 (0.016)	0.018 (0.016)	3.373 (3.086)

Table 5.8. Mean value of the ALPI effect in the parameters in the 10 different sections measured in dark conditions. The values in the table are mean values of the change between V1 (pre-ALPI) and V11 (post-ALPI). The standard deviation is the value within brackets. Minimum parameter mean value dimension for every section is boxed in blue and maximum value in red.

5.3.4 Discussion

ALPI resulted in angle opening (an increase in angle parameters) for all 10 sections in light conditions and in the majority of the parameters for dark conditions. This is consistent with the results found earlier in this thesis showing the statistically significant widening of the majority of the parameters due to ALPI effect.

The differences found between maximum and minimum values were relatively small and not statistically significant in both lighting conditions. This would appear to support the research hypothesis stating that there is a homogeneous effect of the ALPI throughout the angle sections.

However, to be able to confirm this statement one would need to obtain a perfect correlation between gonioscopy and AS-OCT parameters dimensions. This correlation would assert what is a relevant or an irrelevant change in dimension for a given parameter. Unfortunately, this information is not currently available in the literature, but is an interesting concept for future research.

5.3.5 Conclusion

There were no statistically significant differences between the 10 sectors of the anterior chamber angle when considering the angle-opening effect of ALPI. To date, no data exists in the literature to compare results of the present study with.

CHAPTER 6. Effect of Nd:YAG in addition to Argon energy on the corneal endothelium

6.1 Effect of Laser Peripheral Iridotomy (LPI) in addition to Argon Laser Peripheral Iridoplasty (ALPI)on the corneal endothelium

6.1.1 Introduction

The effect of Nd:YAG energy on the corneal endothelium when performing iridotomies has been extensively studied. However, the additional effect of argon laser peripheral iridoplasty on the endothelial cells has received little attention.

In addition, new techniques combining LPI and ALPI simultaneously as combined treatment of PACS (Lee, Choi, Kim and Choi, 2011), PAC and PACG (Sun, et al., 2010) have been described yet the possible impact of these techniques on the endothelium has been described by one report only (Sun, et al., 2010) who reported that the corneal endothelial cell count was not significantly reduced at 1 year follow up (from 2610.74/mm^2 at baseline to 2610.7/mm^2 after one year) but no details were given regarding the method used in this quantification. Little is known about how this cell density is affected in a shorter post-operative period. Should a patient require another type of intraocular surgery that may affect the endothelium after having received ALPI preceded by LPI, it would be advantageous to clinicians to understand or predict the changes to the endothelium through time.

One can hypothesise that there would be an initial decrease in cell density from baseline, followed by a gradual increase in endothelial cell density until baseline levels are regained.

6.1.2 Methodology and Statistical Analysis plan

The assessment of cell density and degree of polymegethism and pleomorphism in 7 different regions of the corneal endothelium (1 central and 6 peripheral: Superior, Superior-Nasal, Inferior-Nasal, Inferior, Inferior-Temporal and Superior-Temporal) were obtained with the TOMEY- 3000 non-contact specular microscope analysis software. More information about this device can be found in the methodology chapter (Chapter 2 of this thesis).

The statistical analysis was carried out in several statistical comparisons and divided in two parts.

The first part of the analysis was aimed to investigate the effect of the LPI on the corneal endothelium in terms of density of endothelial cells, pleomorphism and polymegethism compared to baseline. The measurements were taken before LPI was performed at Visit 1 (2.31 weeks; SD 2.34 weeks, pre-LPI) and after LPI at the following visits: Visit 2 (1:54 hours; SD 25 minutes, post-LPI), Visit 3 (1 day; SD 0.00, post-LPI), Visit 4 (1.10 weeks; SD 0.13 weeks, post LPI), Visit 5 (1.44 months; SD 0.18 months, post-LPI), Visit 6 (3.05 months; SD 0.27 months, post-LPI) and Visit 11 (5.83 months; SD 0.37 months, post-LPI).

The second part of the analysis aimed to investigate the effect of the ALPI on the corneal endothelium (same parameters studied as for the LPI and specified in the paragraph above). The data used in this part of the analysis was collected from eyes whose angles remained occludable 3 months after the LPI. Only 11 of these 21 eyes were randomised to receive the ALPI and the analysis focused on this group. Data from baseline, in this case Visit 6 (1.79 weeks; SD 0.75 weeks, pre-ALPI), and consecutive posterior visits, Visit 7 (1:32 hours; SD 31 minutes, post-ALPI), Visit 8 (1 day; SD 0.00, post-ALPI), visit 9 (1 week; SD 0.13 weeks, post-ALPI), Visit 10 (1.43 months, SD 0.18 months, post-ALPI) and Visit 11 (2.39 months; SD 0.29 months, post-ALPI) were used for the statistical analysis.

The objective was studied in two groups of eyes:

Group 1- Forty eyes treated with LPI and their untreated fellow eyes. The data for those eyes that had received the ALPI were excluded in Visit 11.

Group 2- 21 eyes with occludable angles after LPI, for which 11 received ALPI. Their fellow eyes were not included, but those occludable eyes that were randomised to not to receive ALPI (n=10) acted as the control eyes for the evaluation of the ALPI effect.

With the aim of studying the effect of the lasers through time, paired samples t-test was performed between the baseline visit and each of the consecutive visits. This analysis was performed in the treated and in the untreated fellow eye, using this latter as a control.

A second aim was to find if there were differences in the effect of these lasers when treated and untreated eyes were compared. This was achieved through analysis of covariance and adjusting all the models for the data found at baseline.

The mean total power used to perform the iridotomy was 16.11mJ (SD 10.879mJ), varying from 2mJ to 48mJ. The mean number of shots was 13 (SD 8.569) and the power setting mean value was 1.22mJ (Range 1.19 to 1.25mJ).

In the case of the ALPI, the minimum mean power used was 170mJ (SD 24.89mJ) and the maximum 239.09mJ (SD 59.74mJ) giving an overall power of 204.54mJ. The mean number of burns was 23.08 (SD 2.08) and this number varied from 20 to 26 burns.

6.1.3 Results

The effect of the LPI and ALPI on the corneal endothelium was investigated for each laser in 4 sub-results: 1. Effect on endothelial cell density; 2. Effect on endothelial average size (polymegethism); 3. Effect on percentage of hexagonal endothelial cells (pleomorphism) and 4. Effect on central corneal thickness. These effects were studied for LPI on Group 1 and for ALPI on Group 2 (these groups have already been specified above).

Descriptive statistics for these endothelial cell parameters at the different visits for Group 1 are given in Tables 6.1 to 6.7. The corresponding data for Group 2 can be found in Tables 6.8 to 6.14 in Appendix 1.

A. Effect of LPI on the corneal endothelium

A.1. LPI effect on endothelial cell density (number of cells/mm^2)

The majority of paired samples t-tests showed no statistically significant differences when comparing baseline (Visit 1) with the rest of the visits (Visit 2, 3, 4, 5, 6 and 11) in any of the 7 sampled areas. The only exception was found when comparing Visit 1 and Visits 3, 4 and 5 in the Superior area of the treated and untreated eyes, where there was a statistically significant loss of cell density. These statistically significant mean differences were smaller in treated eyes than those found in the fellow untreated eyes at Visit 3, but greater for Visits 4 and 5. However, when these differences between treated and untreated eyes were tested using analysis of covariance, there was no statistical significance.

Although not statistically significant, there was a trend for the endothelial cell density in the treated eye to start reducing at Visit 2, achieving a maximum reduction at Visit 3, begin a minor recovery at Visit 4, drop again at Visits 5 and 6 and achieve full recovery by Visit 11. Additionally, this trend seemed to be followed by the fellow untreated eye in the Superior-Nasal and Inferior-Nasal areas and partially in the Central, Superior and Superior-Temporal

areas. In the case of Inferior and Inferior-Temporal areas, the fellow eye's cell density levels were fluctuating in the opposite direction as to the treated eyes. See following graphs for a visual representation.

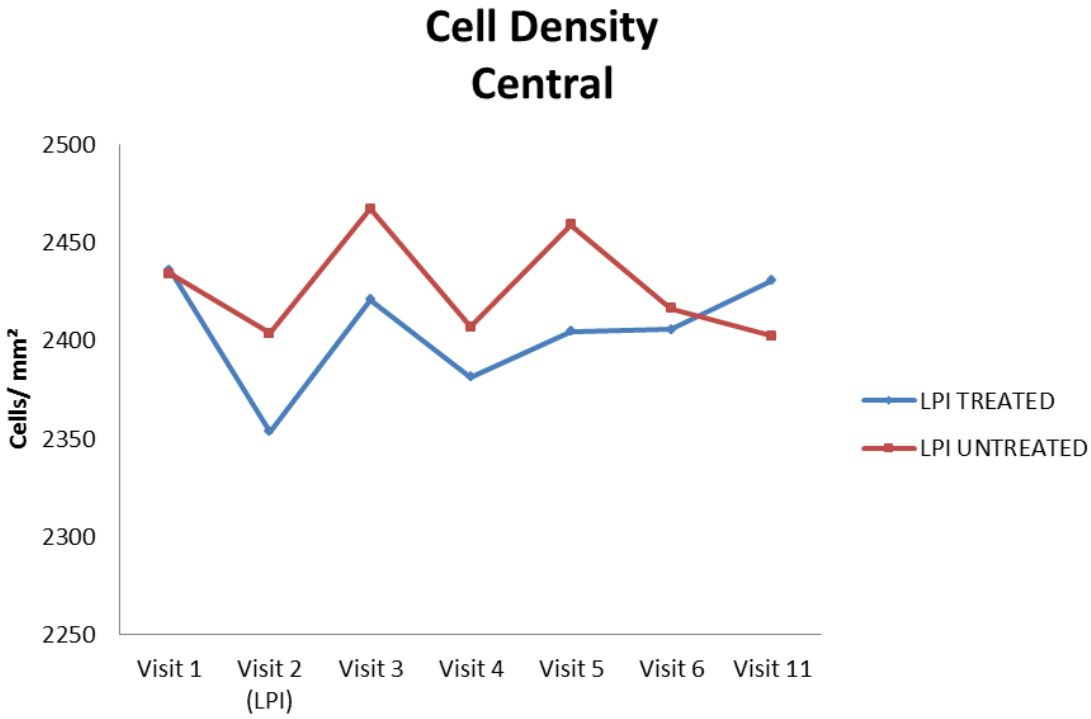

Figure 6.1. Descriptive mean values for cell density found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Central cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

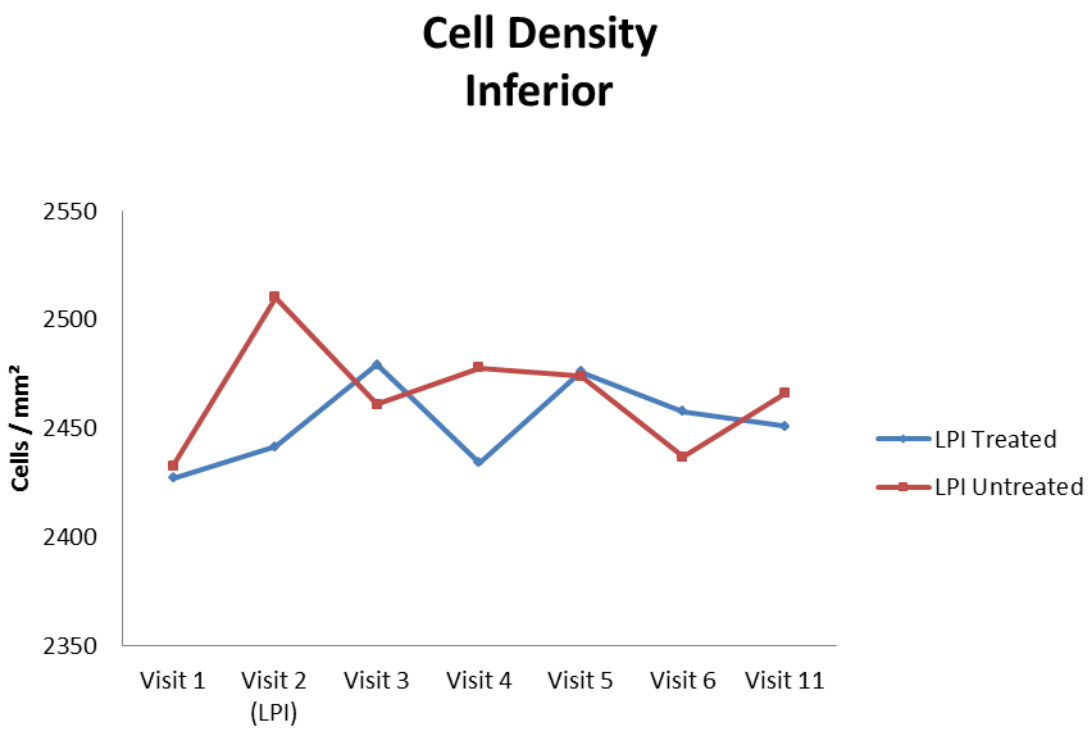

Figure 6.2. Descriptive mean values for cell density found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Inferior cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

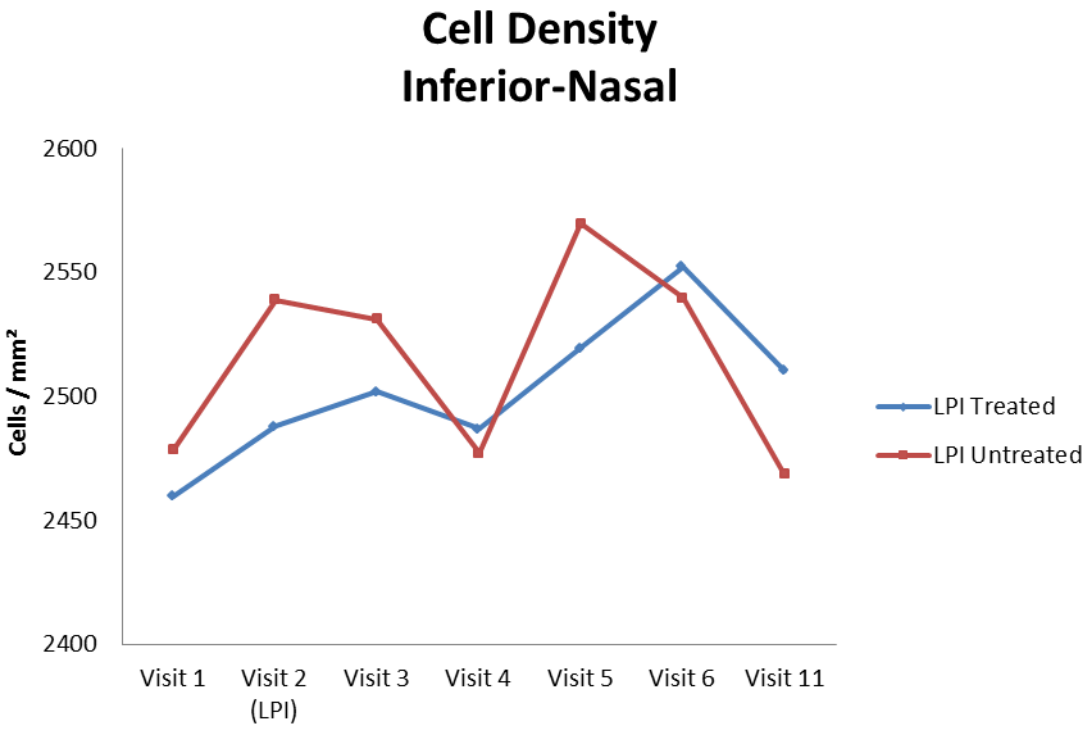

Figure 6.3. Descriptive mean values for cell density found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Inferior-Nasal cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

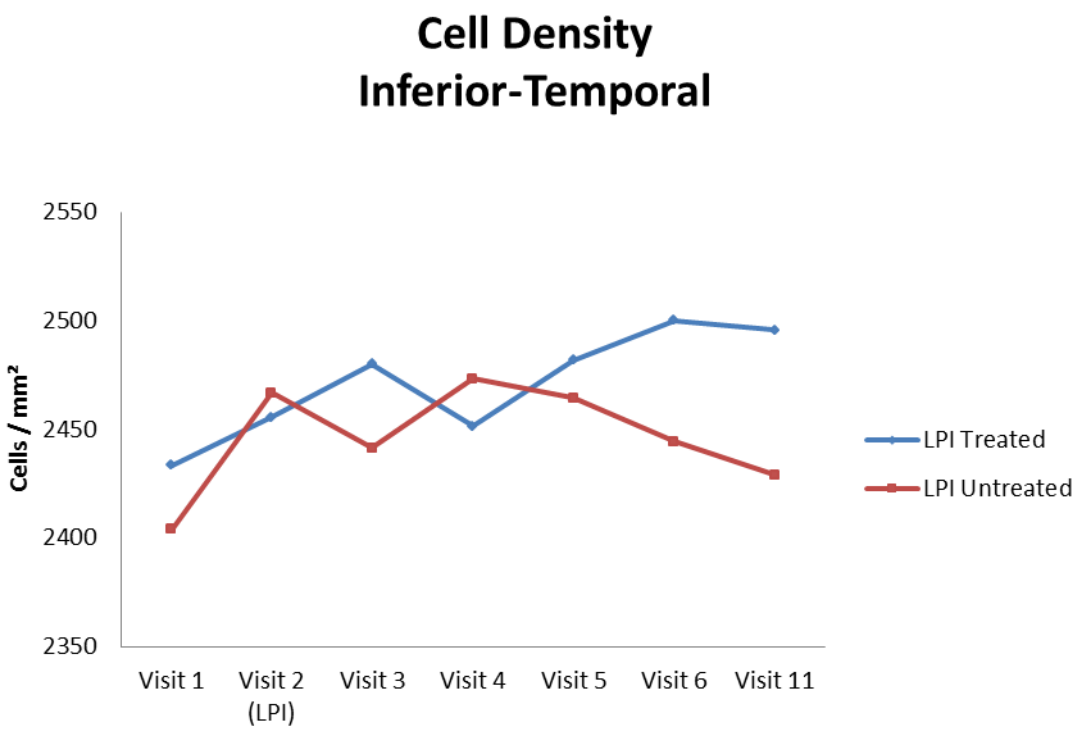

Figure 6.4. Descriptive mean values for cell density found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Inferior-Temporal cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

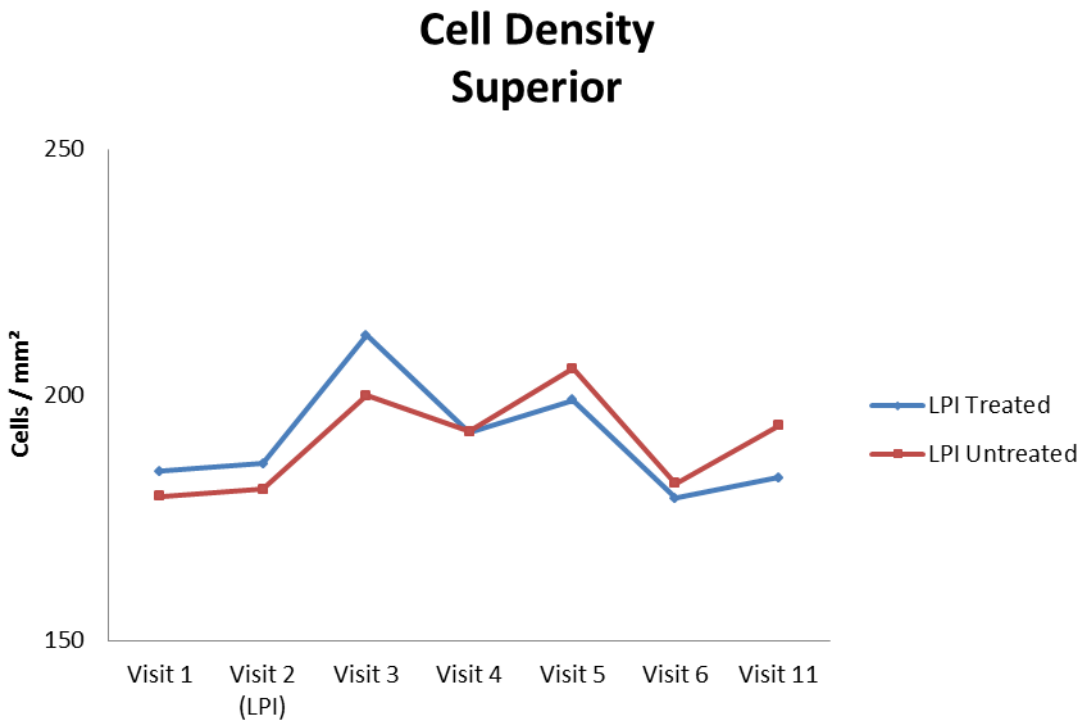

Figure 6.5. Descriptive mean values for cell density found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Superior cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

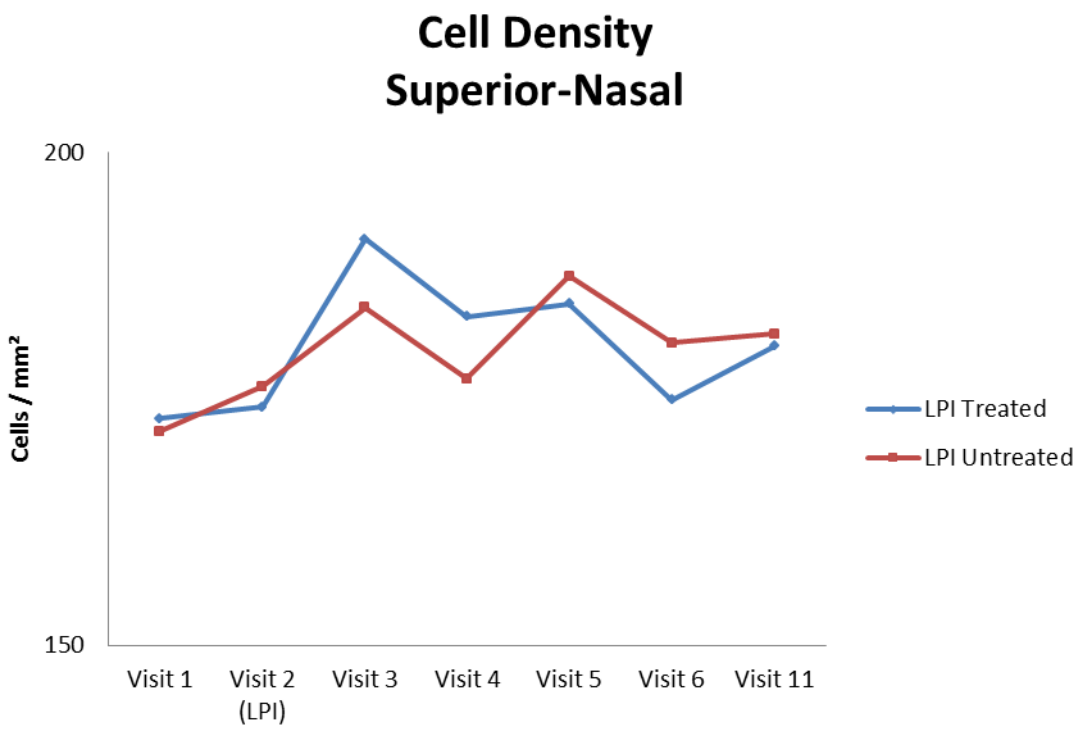

Figure 6.6. Descriptive mean values for cell density found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Superior-Nasal cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

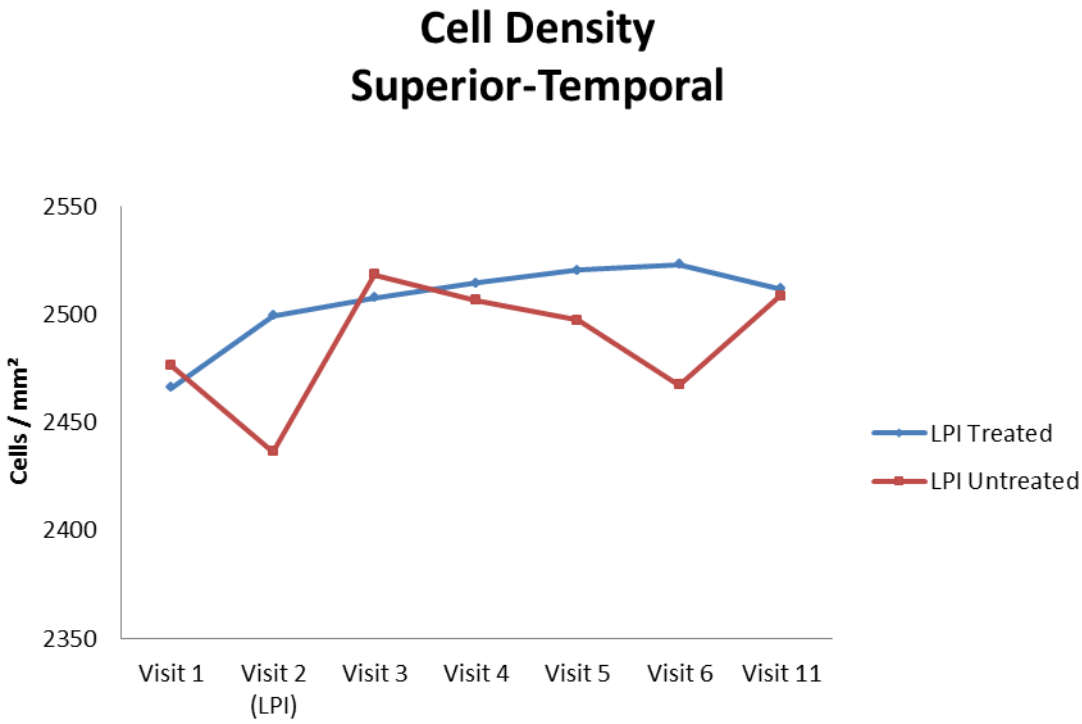

Figure 6.7. Descriptive mean values for cell density found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Superior-Temporal cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

A.2. LPI effect on endothelial average size, as an indication of polymegethism (μm^2)

There were very few statistically significant differences between baseline data and the rest of the consecutive visits:

- Central area: A decrease in cell area of 8.536 μm^2 (SD 21.929), p=0.049, was found at Visit 2 (1 hour after the LPI)

-Inferior-Nasal area: An increase in cell area of 12.387 μm^2 (SD 30.827), p=0.033, was found at Visit 6 when compared to baseline Visit 1

-Inferior-Temporal area: The cell area increased by 7.742 μm^2 (SD 21.085), p=0.050. This increase was found at Visit 6 when compared to baseline (Visit 1)

The most common trend followed by the treated eye rate of polymegethism was an initial increase between Visits 2 and 3, a mild recovery between Visits 4 and 5, a second increase in Visit 6 and a dramatic drop in Visit 11 for Superior, Superior-Temporal, Inferior-Temporal and Inferior corneal areas. However, a lack of recovery was found for the polymegethism rates in Central, Superior-Nasal and Inferior-Nasal corneal areas.

In the case of the untreated fellow eye, a trend was less obvious. Please see a visual representation for the different areas of cornea as follows:

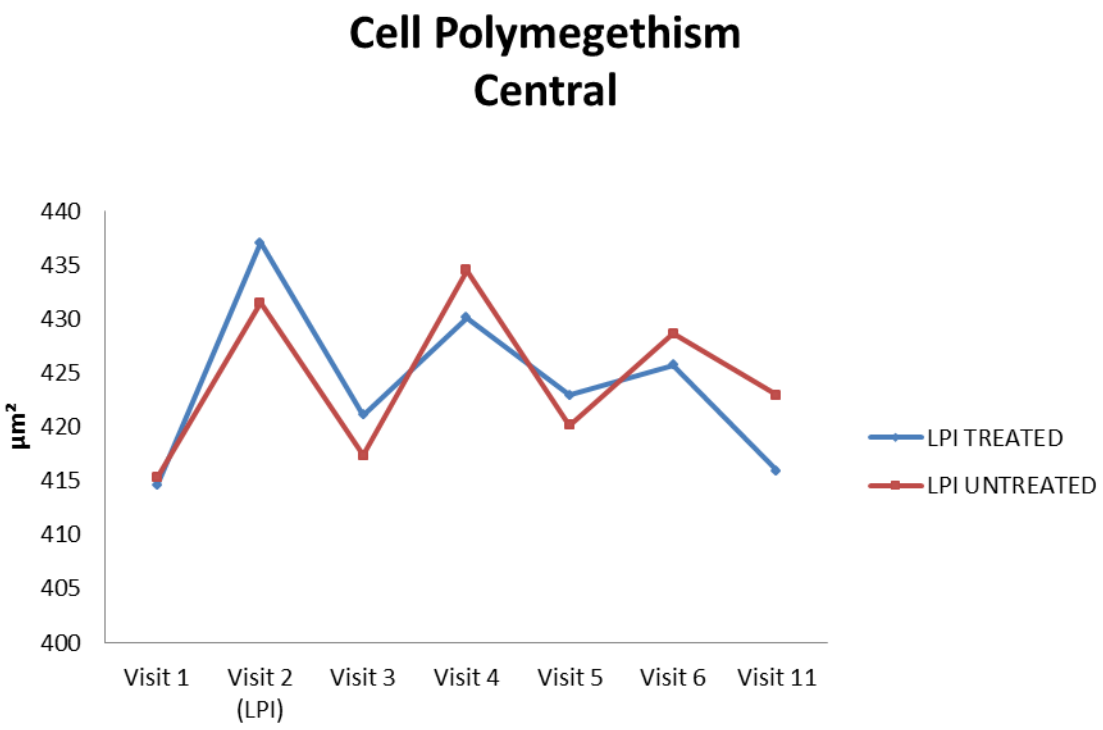

Figure 6.8. Descriptive mean values for endothelial polymegethism found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Central cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

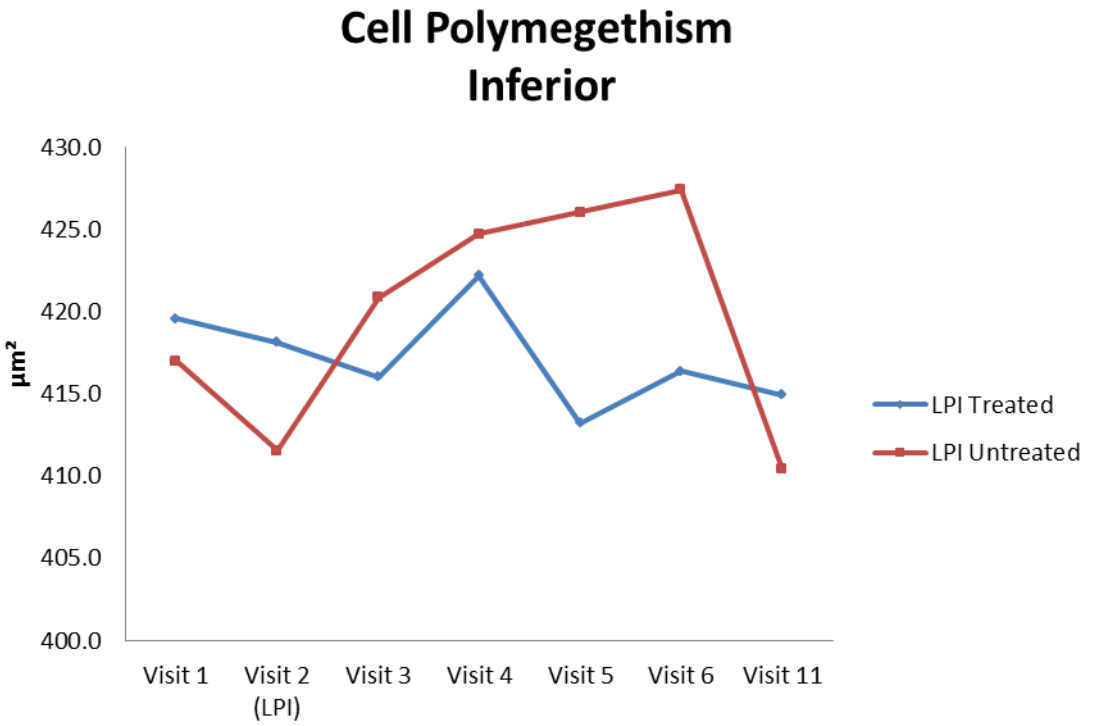

Figure 6.9. Descriptive mean values for endothelial polymegethism found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Inferior cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

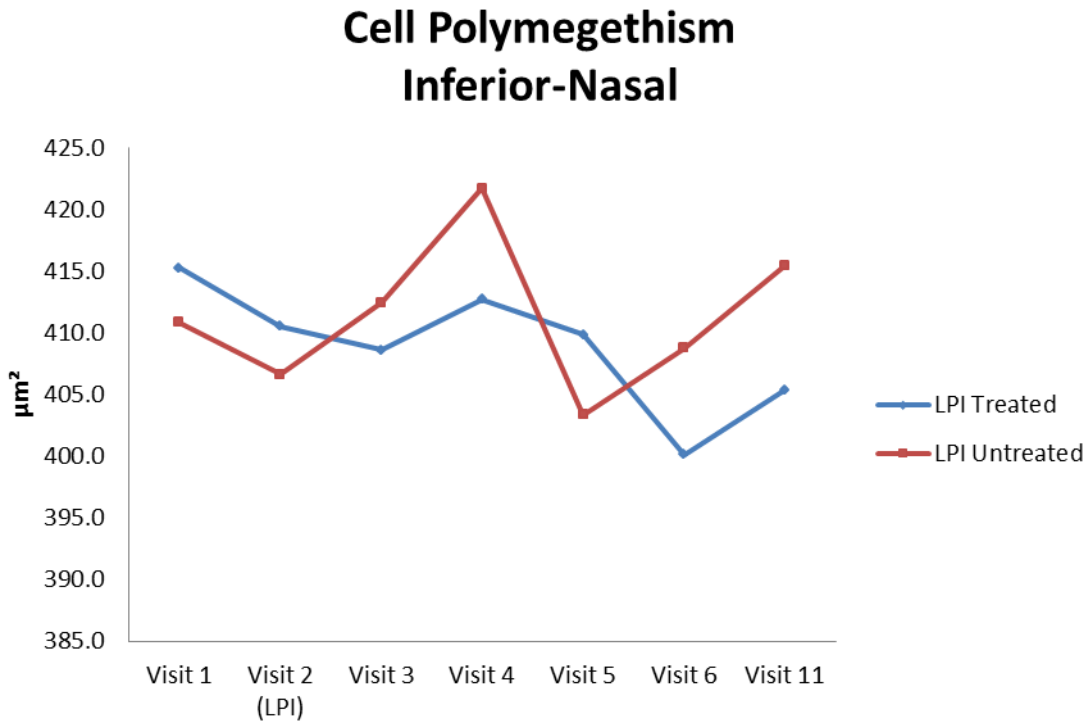

Figure 6.10. Descriptive mean values for endothelial polymegethism found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Inferior-Nasal cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

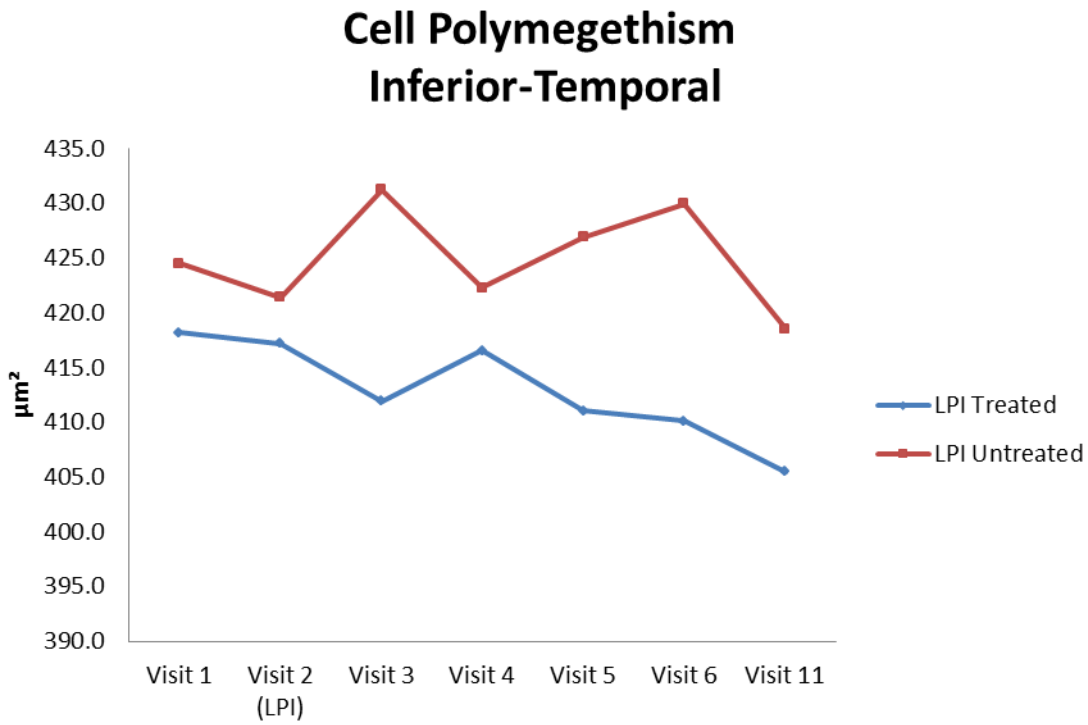

Figure 6.11. Descriptive mean values for endothelial polymegethism found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Inferior-Temporal cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

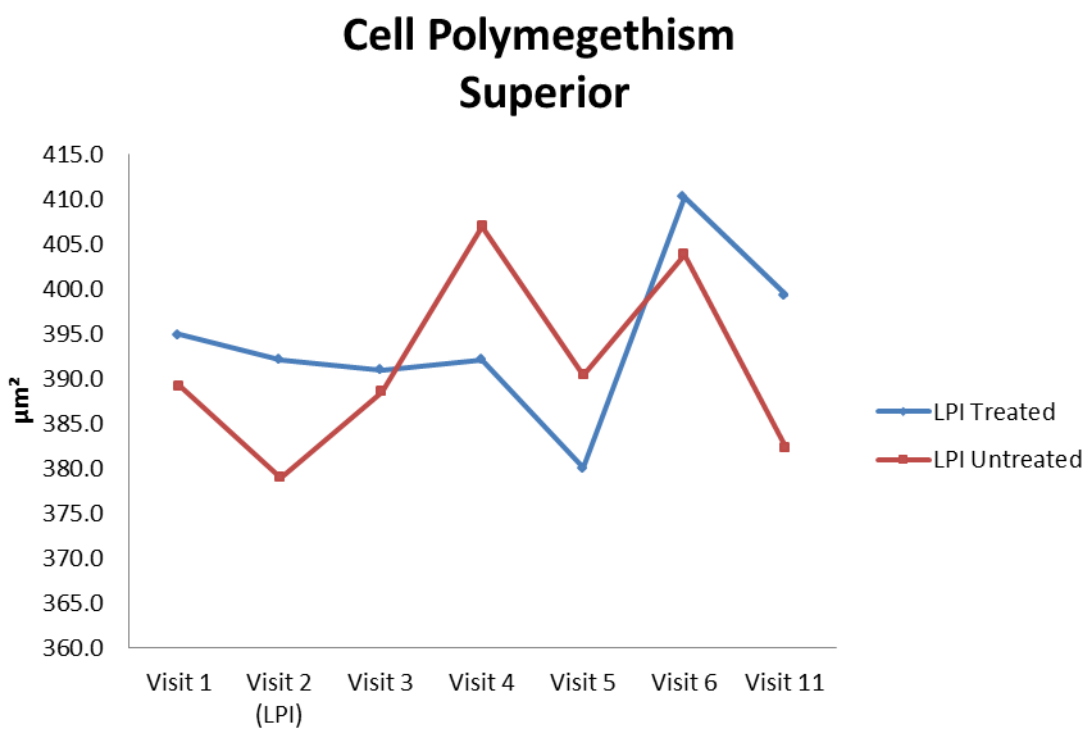

Figure 6.12. Descriptive mean values for endothelial polymegethism found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Superior cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

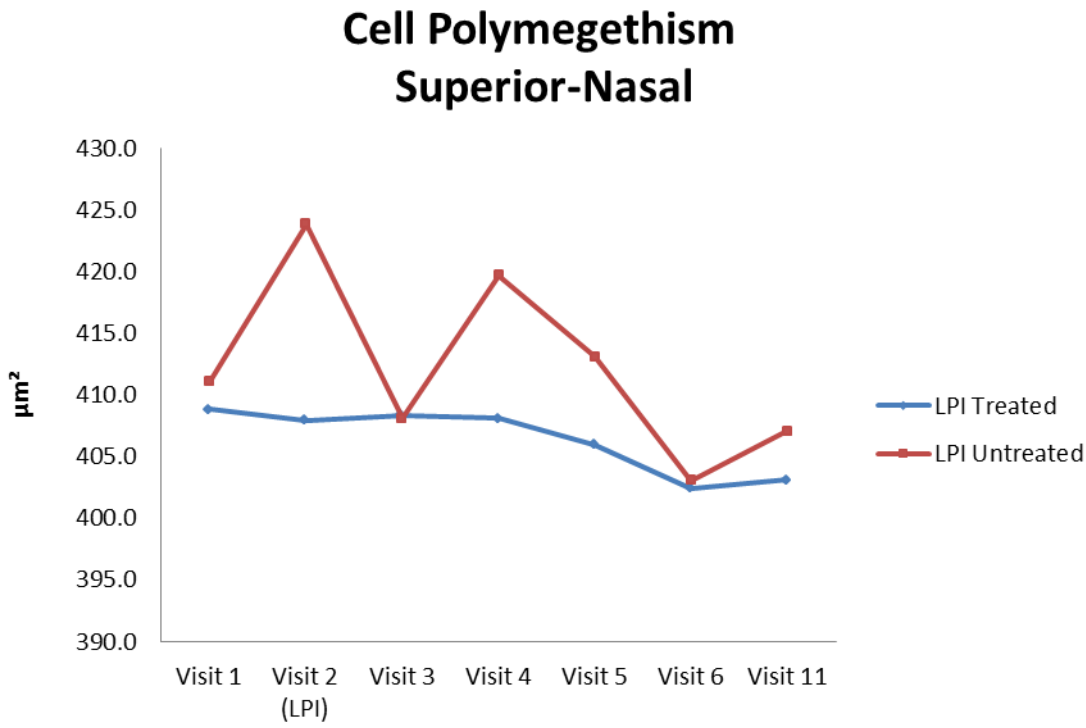

Figure 6.13. Descriptive mean values for endothelial polymegethism found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Superior-Nasal cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

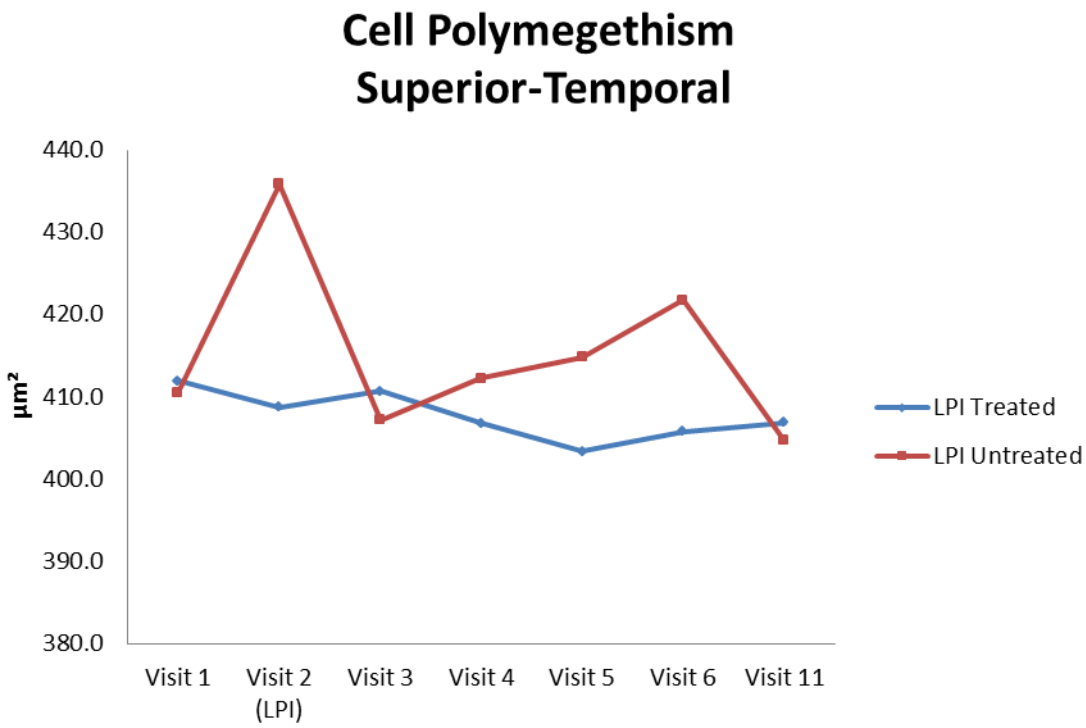

Figure 6.14. Descriptive mean values for endothelial polymegethism found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Superior-Temporal cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

A.3. LPI effect on percentage of hexagonal endothelial cells, pleomorphism (%)

The most common trend in the case of the treated eye was an initial reduction in pleomorphism between Visits 2 and 3, a mild recovery in Visit 4, before reducing again at Visit 5, ending with a more marked recovery in Visit 6 and Visit 11. In the case of the untreated fellow eye, the fluctuations through the visits were very similar to the ones described for the treated eye. This was confirmed statistically with the analysis of covariance where the differences in means were of ± 5% approximately and not statistically significant.

Please see a visual representation for the different areas of cornea as follows:

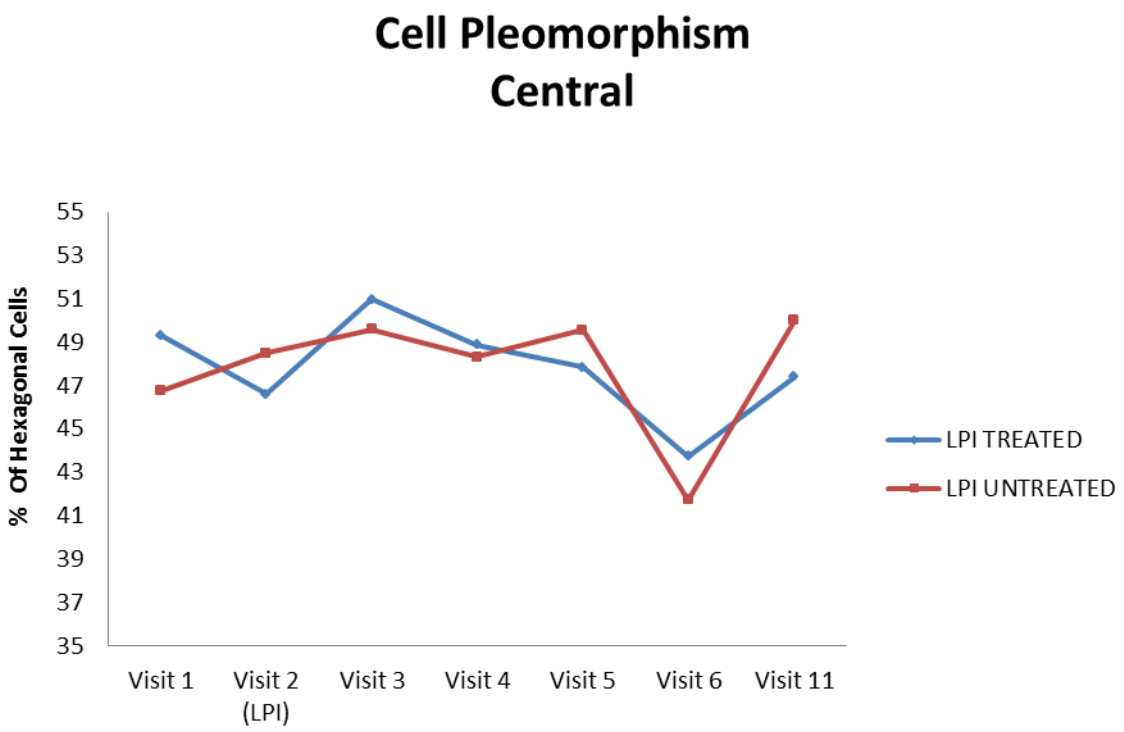

Figure 6.15. Descriptive mean values for endothelial pleomorphism found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Central cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

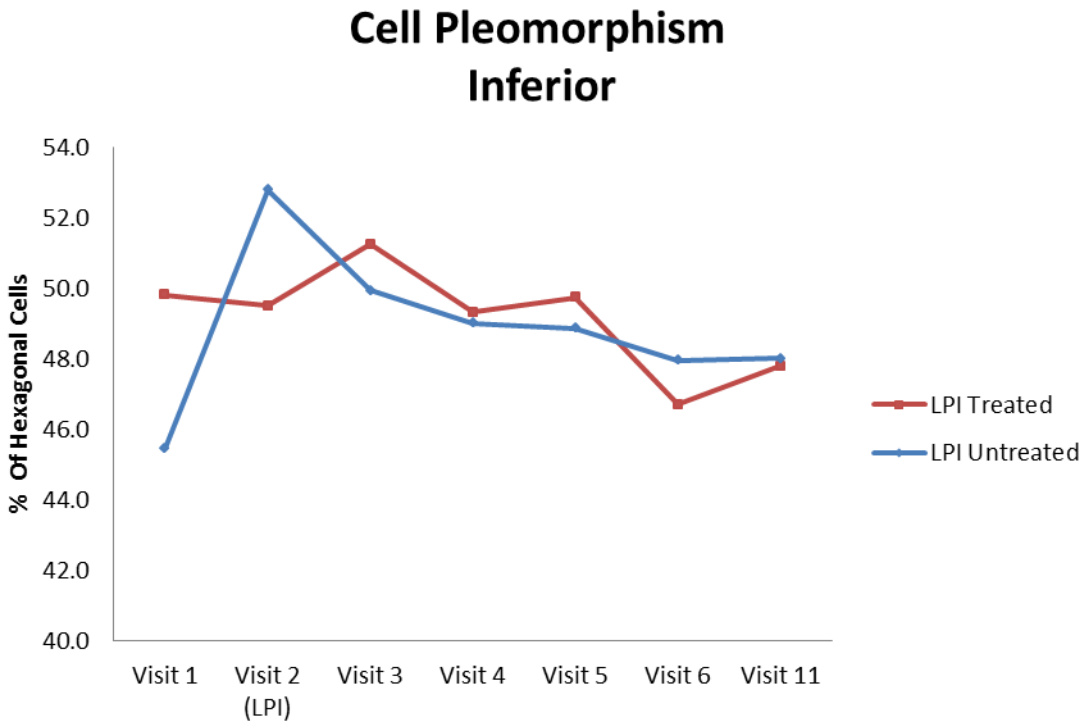

Figure 6.16. Descriptive mean values for endothelial pleomorphism found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Inferior cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

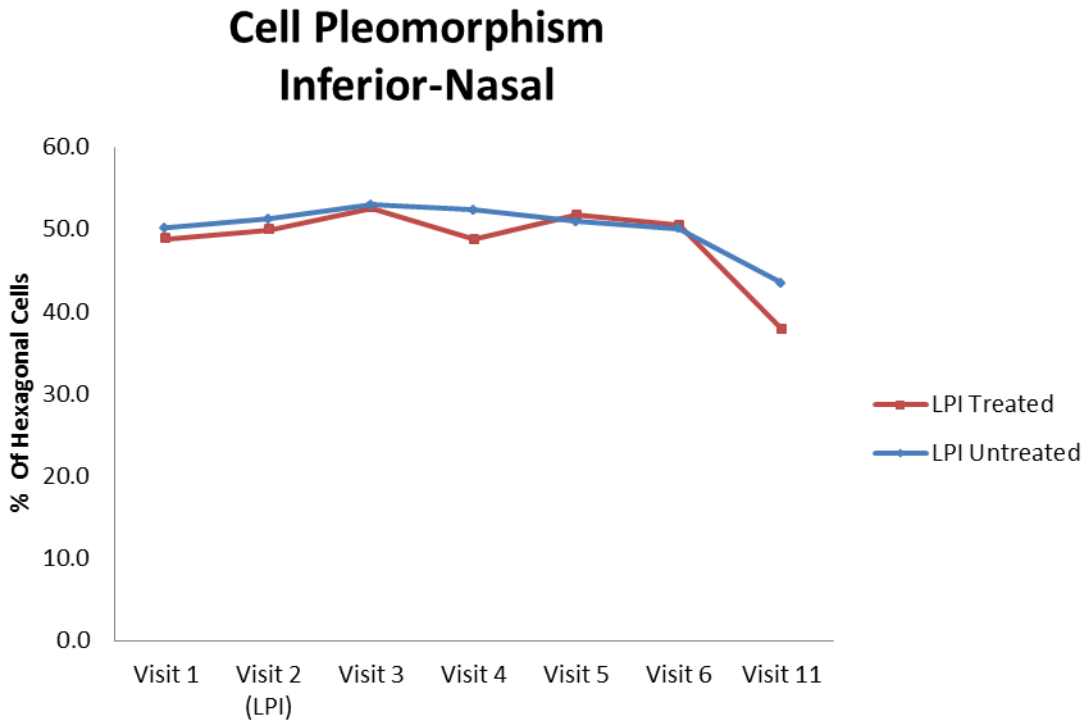

Figure 6.17. Descriptive mean values for endothelial pleomorphism found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Inferior-Nasal cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

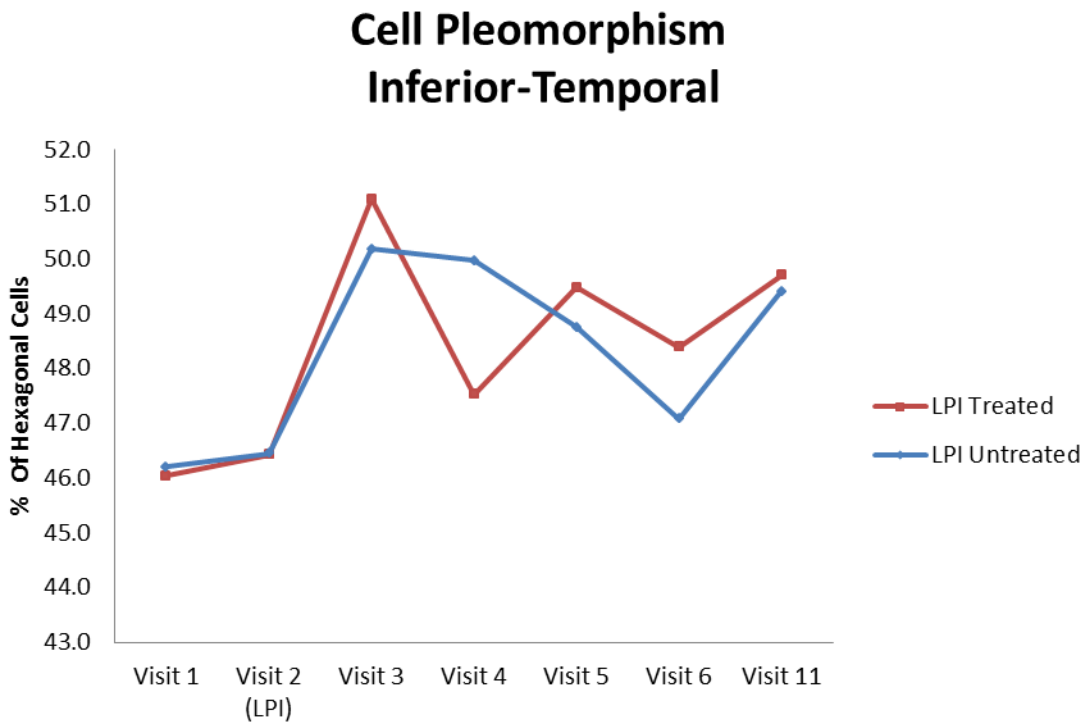

Figure 6.19. Descriptive mean values for endothelial pleomorphism found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Inferior-Temporal cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

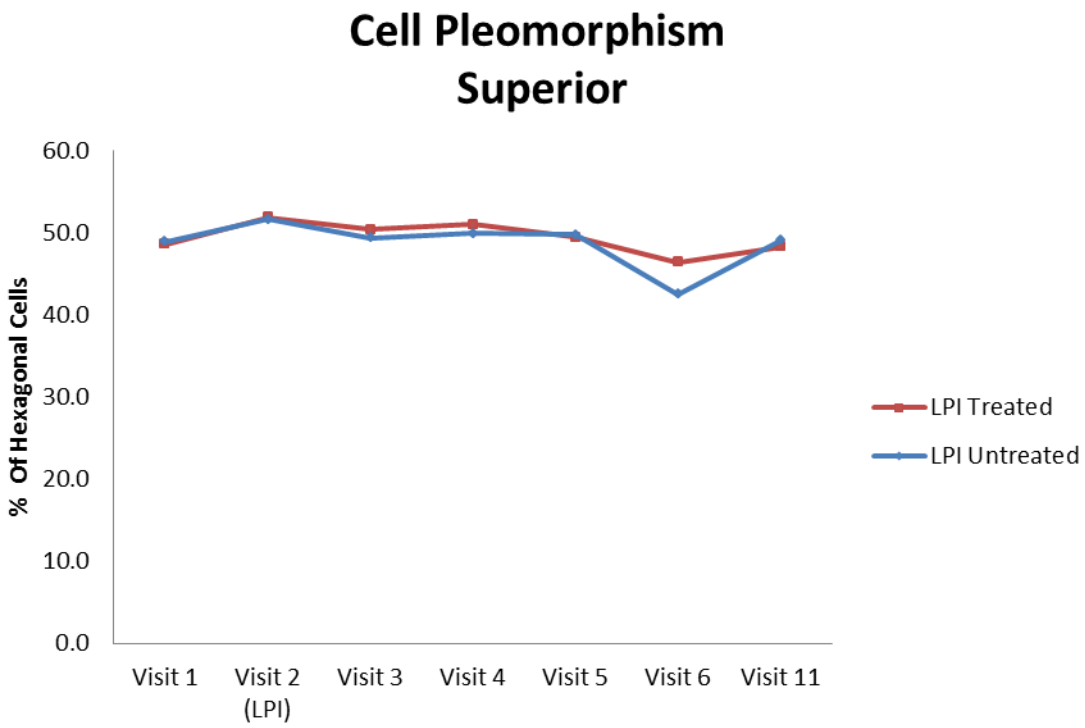

Figure 6.20. Descriptive mean values for endothelial pleomorphism found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Superior cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

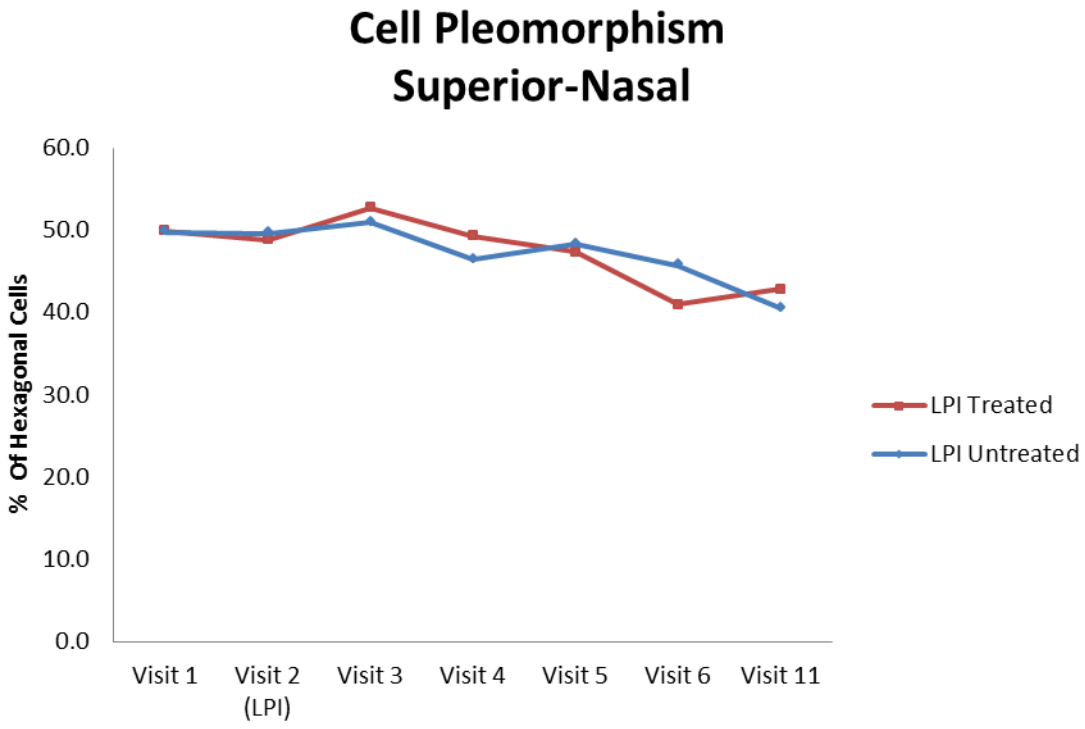

Figure 6.21. Descriptive mean values for endothelial pleomorphism found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Superior-Nasal cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

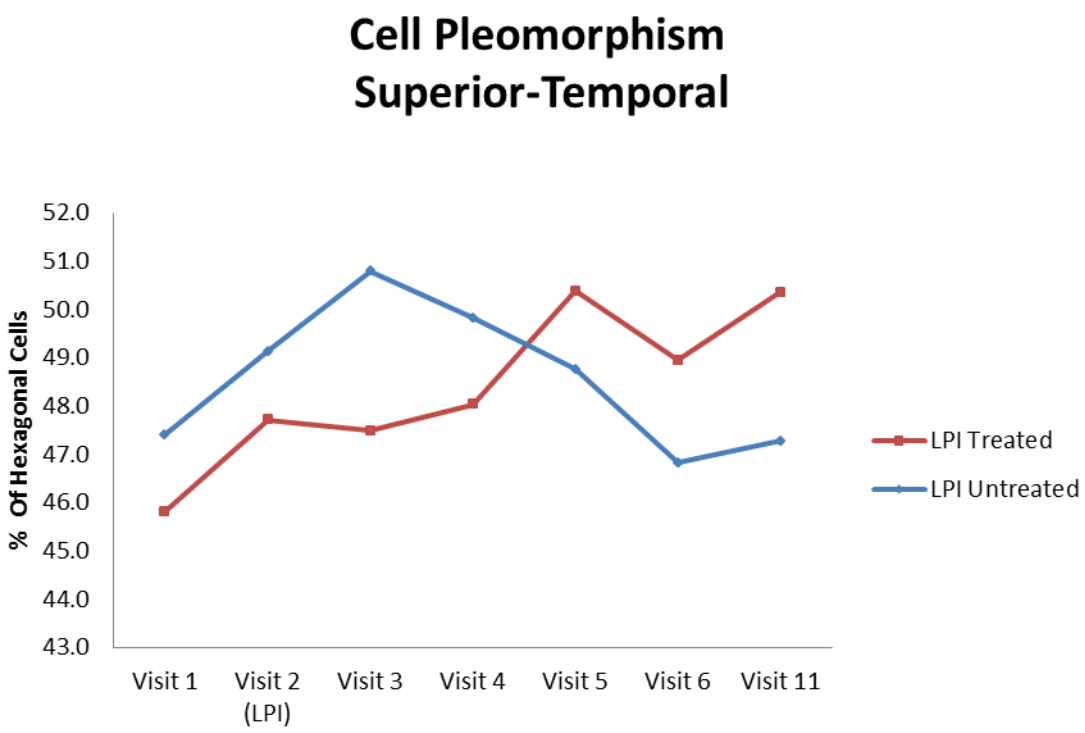

Figure 6.22. Descriptive mean values for endothelial pleomorphism found at Vists 1, 2, 3, 4, 5, 6 and 11 in the Superior-Temporal cornea for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

A.4. LPI effect on central corneal thickness (μm)

The corneal thickness data was only given when the measurement was taken in central cornea.

Paired samples t-test found statistically significant differences in central corneal thickness when comparing Visits 3 and 5 to Visit 1 for the treated and untreated eyes. The differences found for the treated eyes were not as marked as the ones found for the untreated eyes, but in any of the cases there seemed to be a loss in corneal thickness through those visits. Mean differences with paired t-test using for the treated eye, using Visit 1 as baseline, were of 13.769 μm (SD 12.206), $p<0.001$, at Visit 3 and of 4.852 μm (SD 10.654), $p=0.026$, at Visit 5. For the untreated eyes, these differences were of 9.000 μm (SD 2.685), $p<0.001$, at Visit 3 and of 3.138 μm (SD 8.101), $p=0.046$, at Visit 5. When these differences were tested by analysis of covariance no statistically significant difference was found. (The adjusted mean differences were found of 5.012 μm (SD 2.685), $p=0.068$, for Visit 3 and of 2.084 μm (SD 2.266), $p=0.362$ for Visit 5)

The trend followed by both groups of eyes was a very small reduction in corneal thickness in Visit 2, reaching a maximum reduction in Visit 3 and a very mild recovery through Visits 4 and 5, achieving partial to good recovery at Visits 6 and 11. In the case of the untreated group of eyes these differences were always less marked with the exception of the Visit 2.

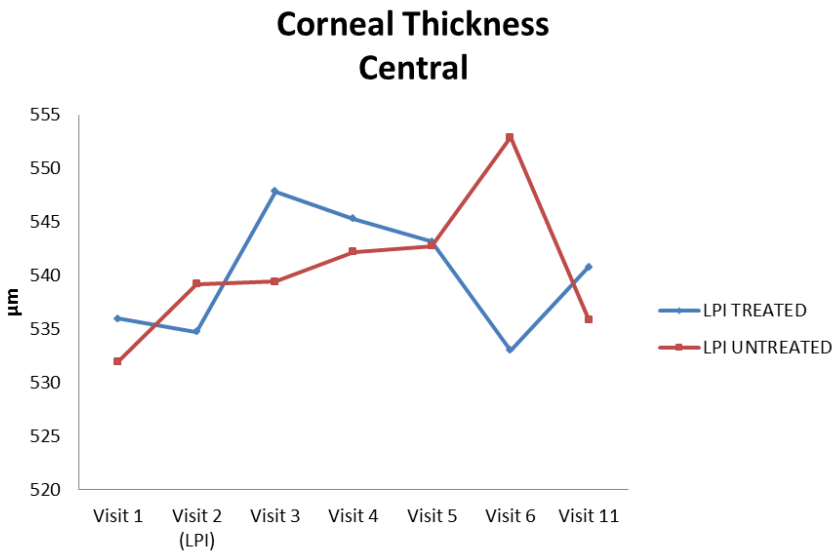

Figure 6.23. Descriptive mean values for central corneal thickness found at Vists 1, 2, 3, 4, 5, 6 and 11 for the eyes treated with Laser Peripheral Iridotomy (LPI) and their untreated fellows.

Paired Samples t-tests for every variable tested are given in Tables 6.8 to 6.14 (Appendix 1). The results for the analysis of covariance can be found in Tables 6.15 to 6.21 of the same Appendix.

B. Effect of ALPI on the corneal endothelium

B.1. ALPI effect on endothelial cell density (number of cells/mm^2)

When the mean values for cell density found at every visit for every corneal area were tested for statistically significant differences to baseline (Visit 1) using the paired samples t-test, few statistically significant results were found.

There were two main trends of change followed through time. The first and most common trend was a lack of change or increase of density in Visit 7, a decrease in Visit 8, a mild

recovery in Visit 9, and a decrease again in Visit 10 followed by a recovery in Visit 11 where there were frequently better values than in baseline. This trend was followed in all the areas under study with the exception of Inferior-Temporal and Superior-Temporal, where there was an increase of density in Visit 8, decreasing in Visit 9 and 10 and a final recovery in Visit 11.

The analysis of covariance showed a statistically significant difference (p=0.035) in the case of Superior and Superior-Nasal, were there was an increase of cell density (44 cells approximately) at Visit 11 when compared to baseline data at Visit 6.

See following graphs for a visual representation.

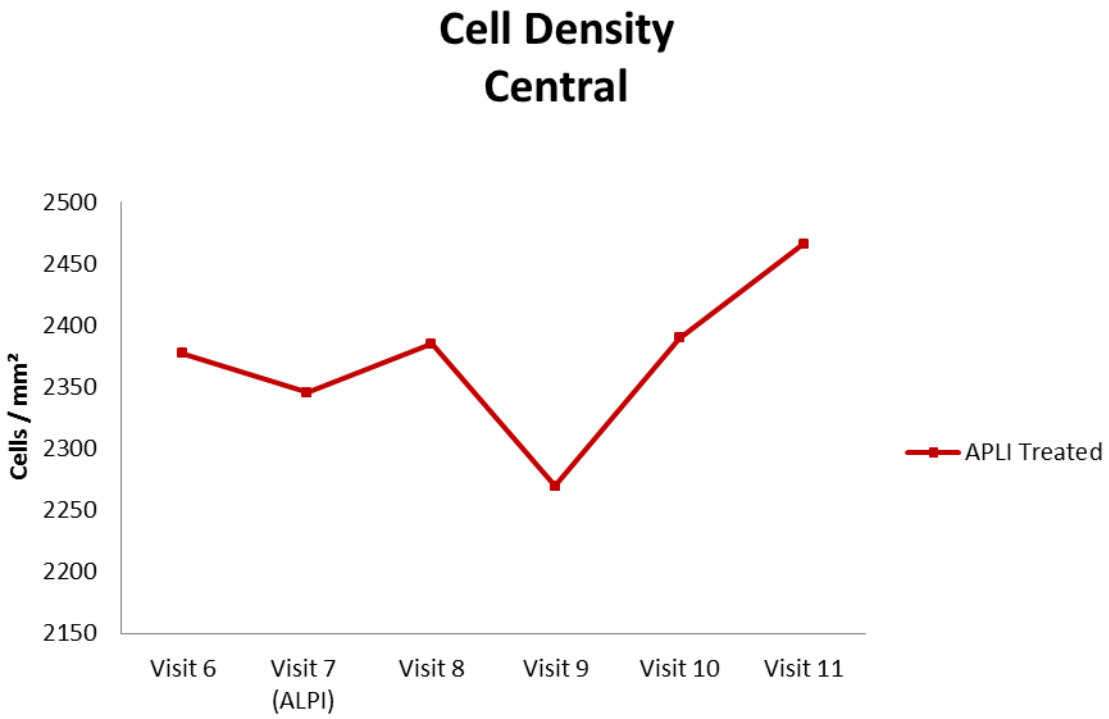

Figure 6.24. Descriptive mean values for cell density found at Vists 6, 7, 8, 9, 10, and 11 in the Central cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

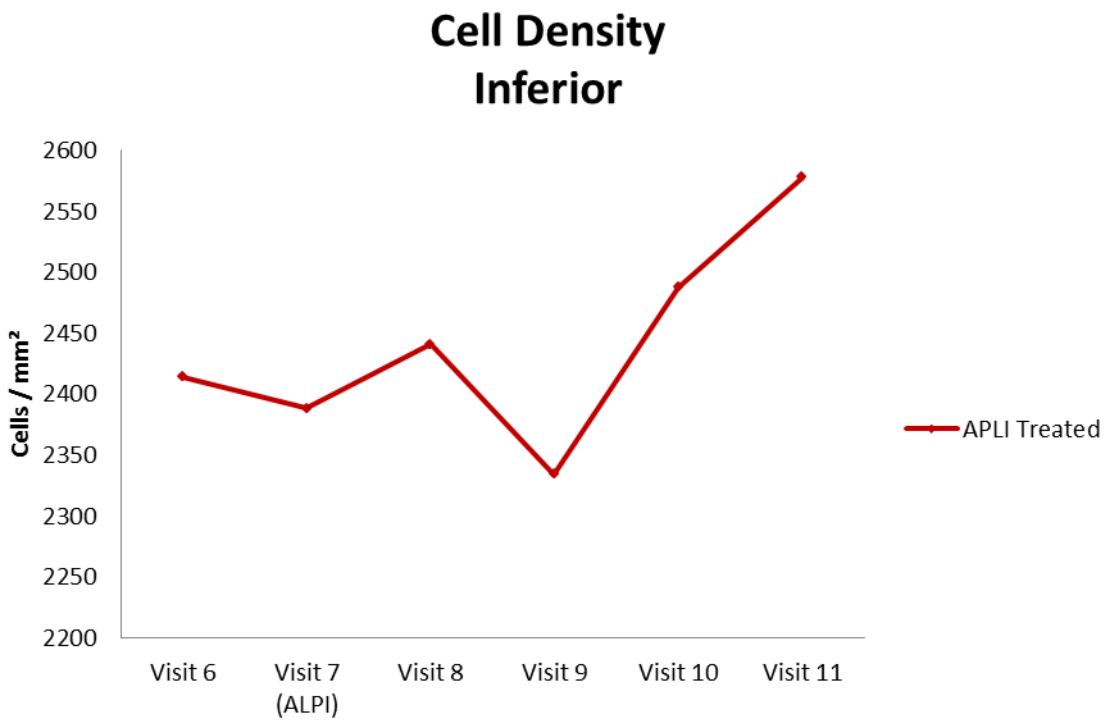

Figure 6.25. Descriptive mean values for cell density found at Vists 6, 7, 8, 9, 10, and 11 in the Inferior cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

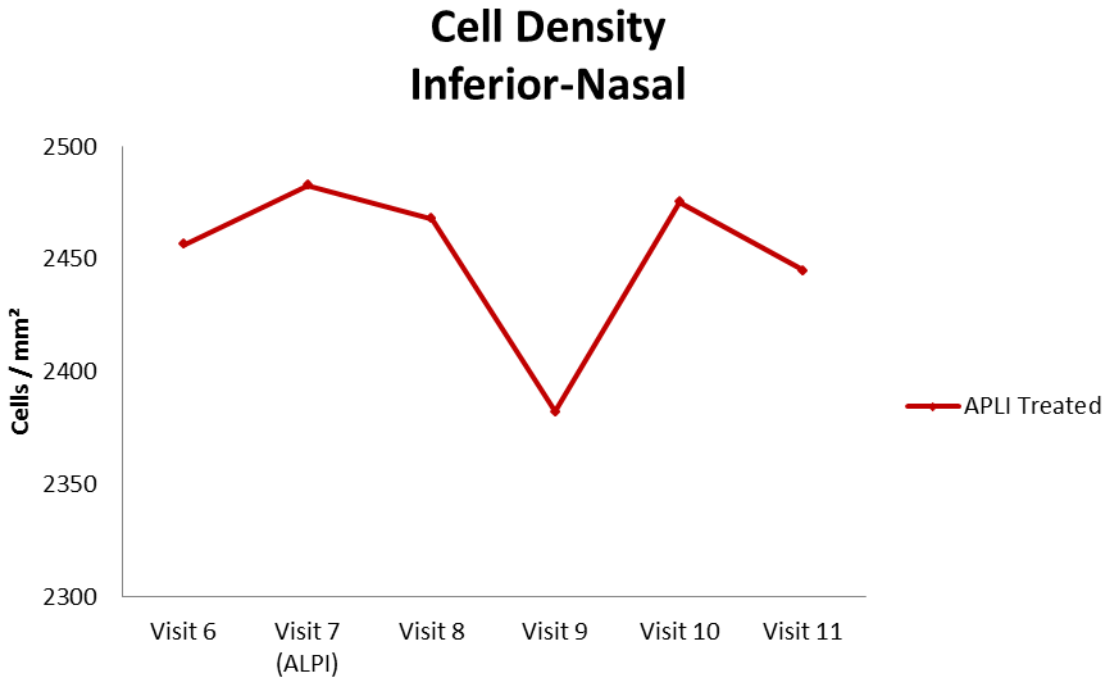

Figure 6.26. Descriptive mean values for cell density found at Vists 6, 7, 8, 9, 10, and 11 in the Inferior-Nasal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

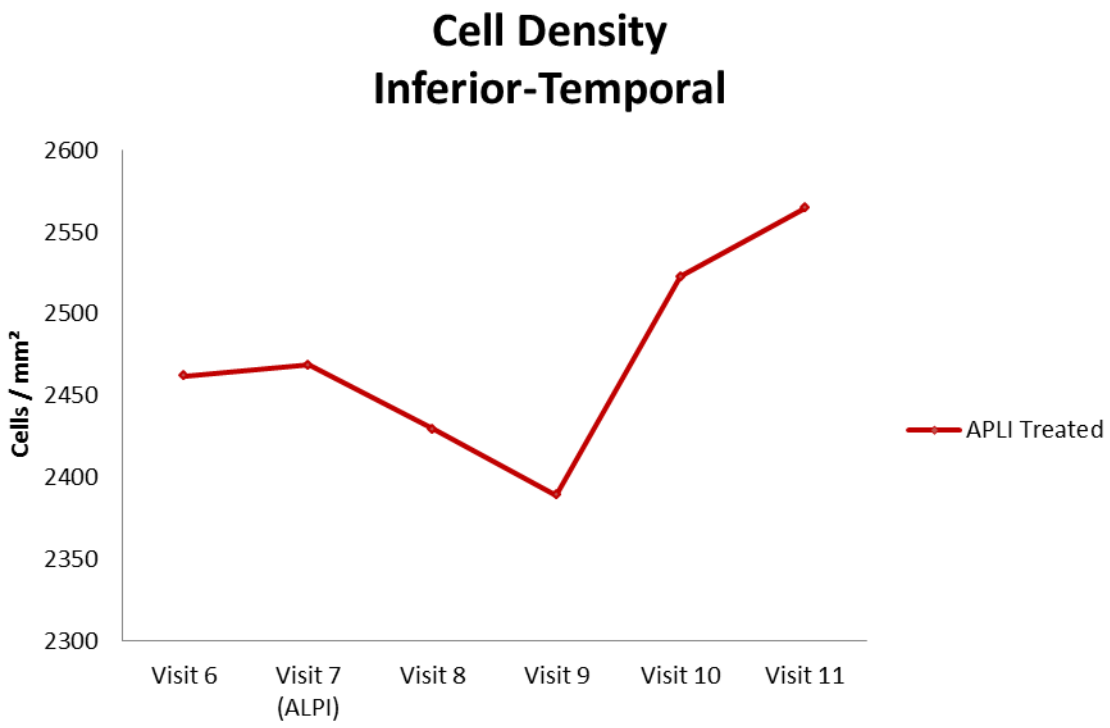

Figure 6.27. Descriptive mean values for cell density found at Vists 6, 7, 8, 9, 10, and 11 in the Inferior-Temporal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

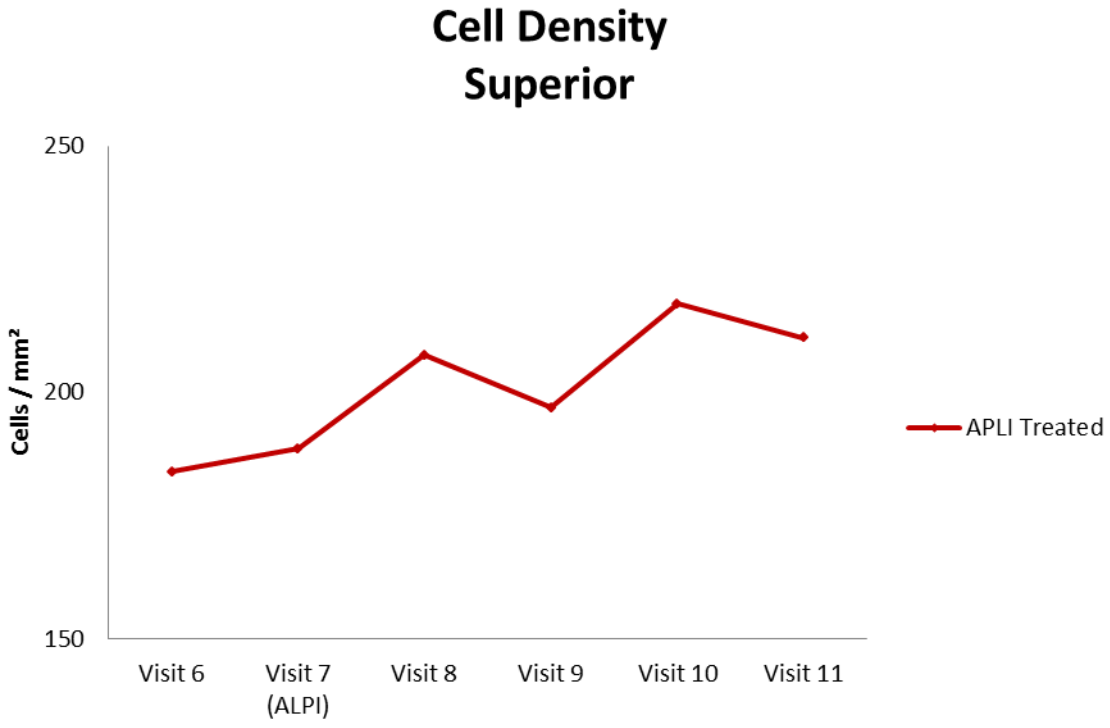

Figure 6.28. Descriptive mean values for cell density found at Vists 6, 7, 8, 9, 10, and 11 in the Inferior-Temporal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

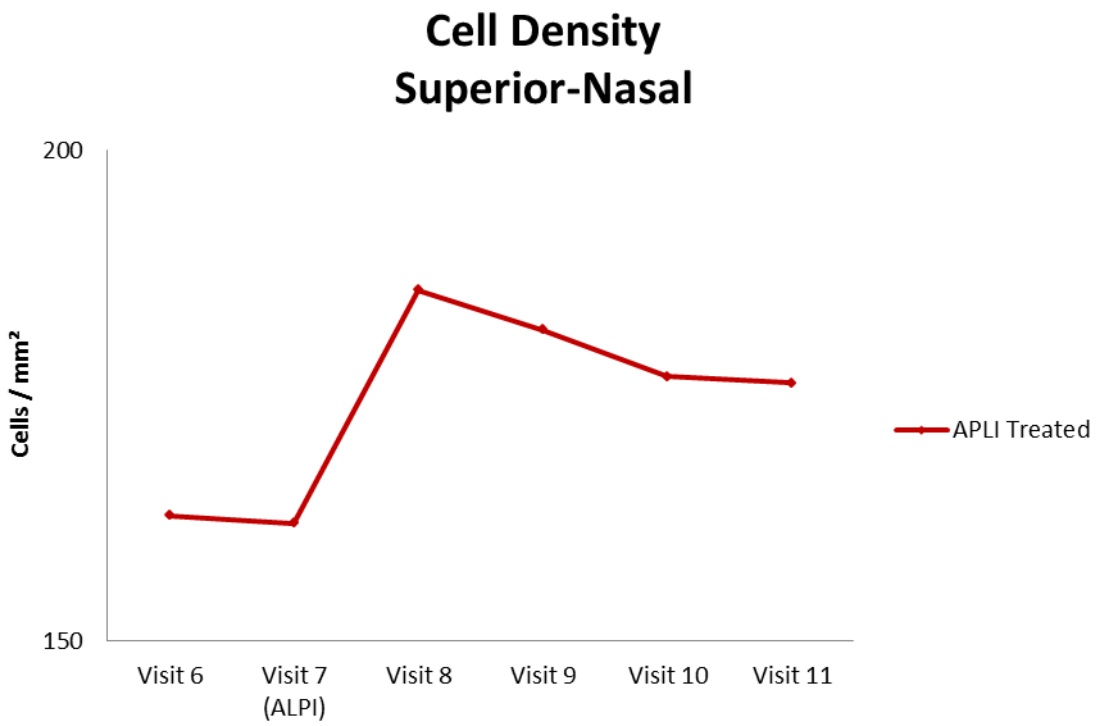

Figure 6.29. Descriptive mean values for cell density found at Vists 6, 7, 8, 9, 10, and 11 in the Superior-Nasal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

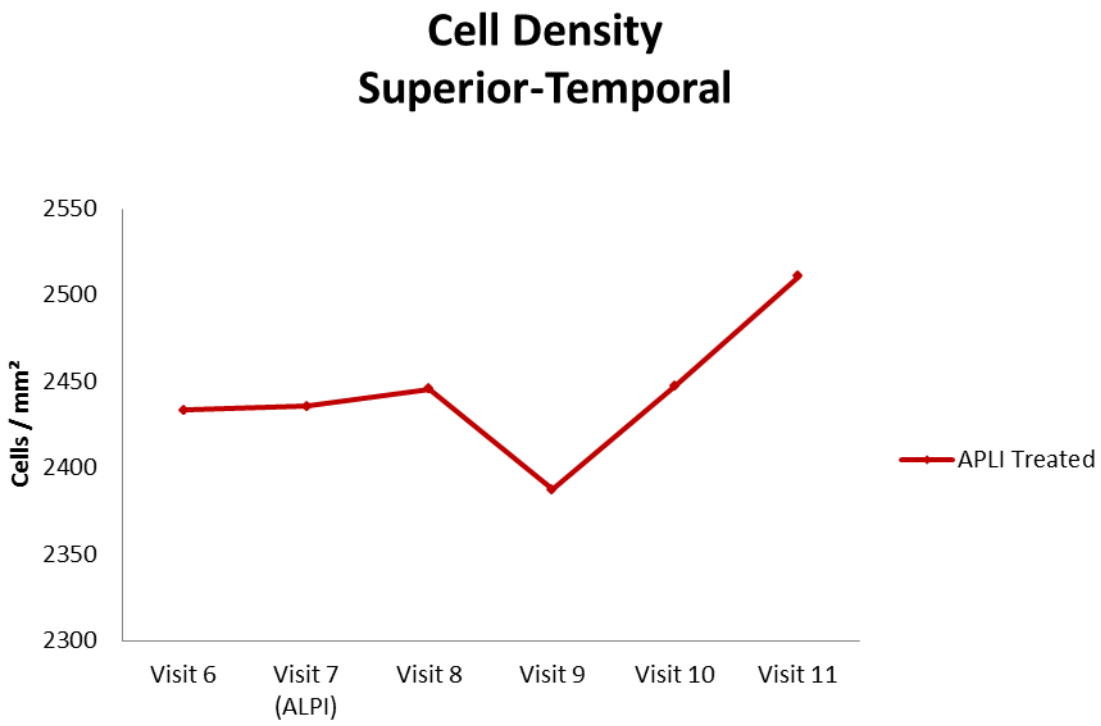

Figure 6.30. Descriptive mean values for cell density found at Vists 6, 7, 8, 9, 10, and 11 in the Superior-Temporal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

B.2. ALPI effect on endothelial average size, as an indication of polymegethism (μm^2)

Again very few differences tested with paired samples t-test were statistically significant and they were only found in the Superior-Temporal area.

The interesting finding with polymegethism was that there appeared to be a trend in the opposite direction to cell density for the same areas tested. Meaning that, as expected, when the density of endothelial cells increased, the polymegethism decreased in the same areas under study.

Analysis of covariance found a statistically significant difference in the polymegethism found in Visit 11. This was lower than that found in Visit 6 (the average size cell was 25.811 μm^2 smaller in Visit 11 when compared with Visit 6 data, p=0.033).

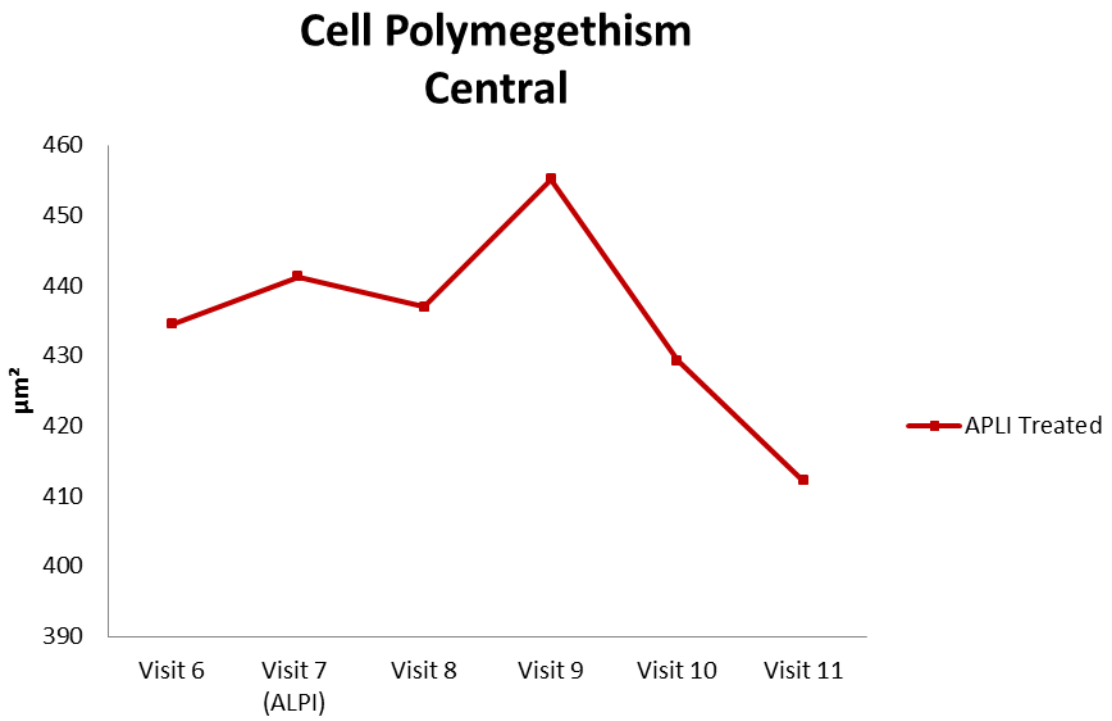

Figure 6.31. Descriptive mean values for cell polymegethism found at Vists 6, 7, 8, 9, 10, and 11 in the Central cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

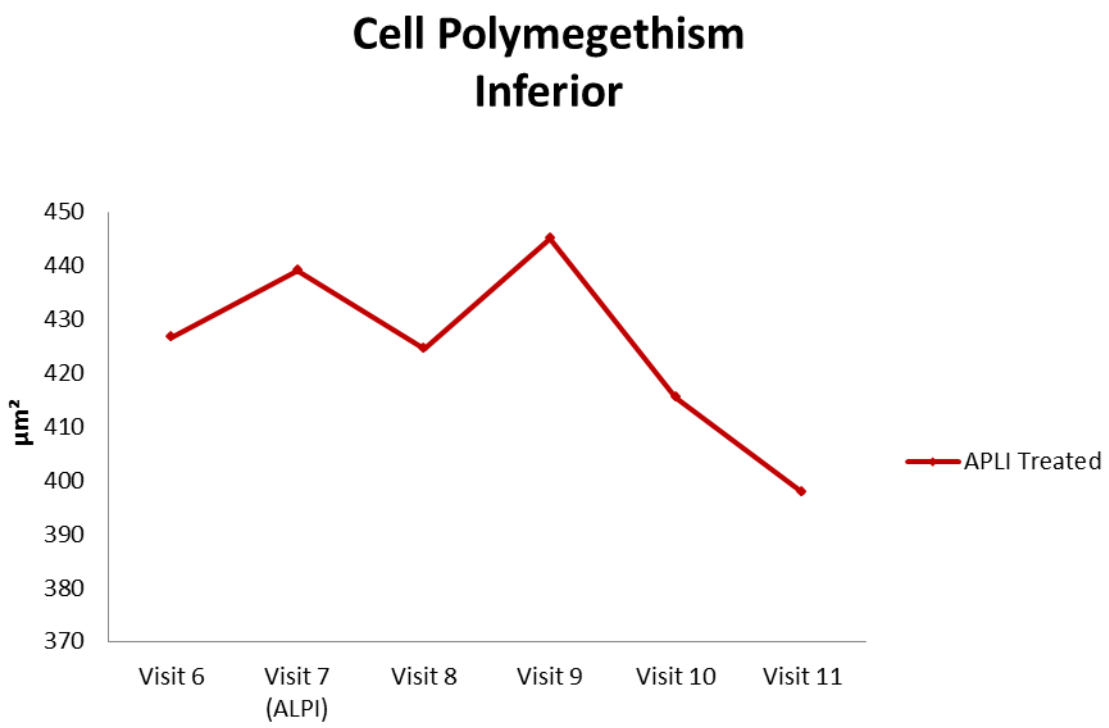

Figure 6.32. Descriptive mean values for cell polymegethism found at Vists 6, 7, 8, 9, 10, and 11 in the Inferior cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

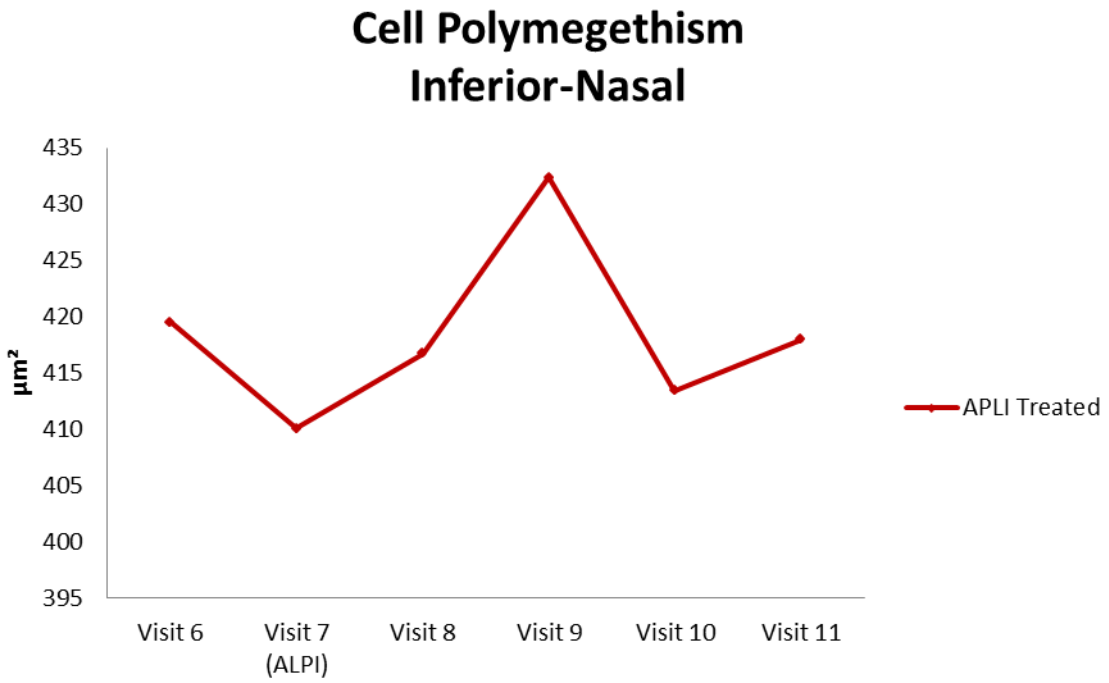

Figure 6.33. Descriptive mean values for cell polymegethism found at Vists 6, 7, 8, 9, 10, and 11 in the Inferior-Nasal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

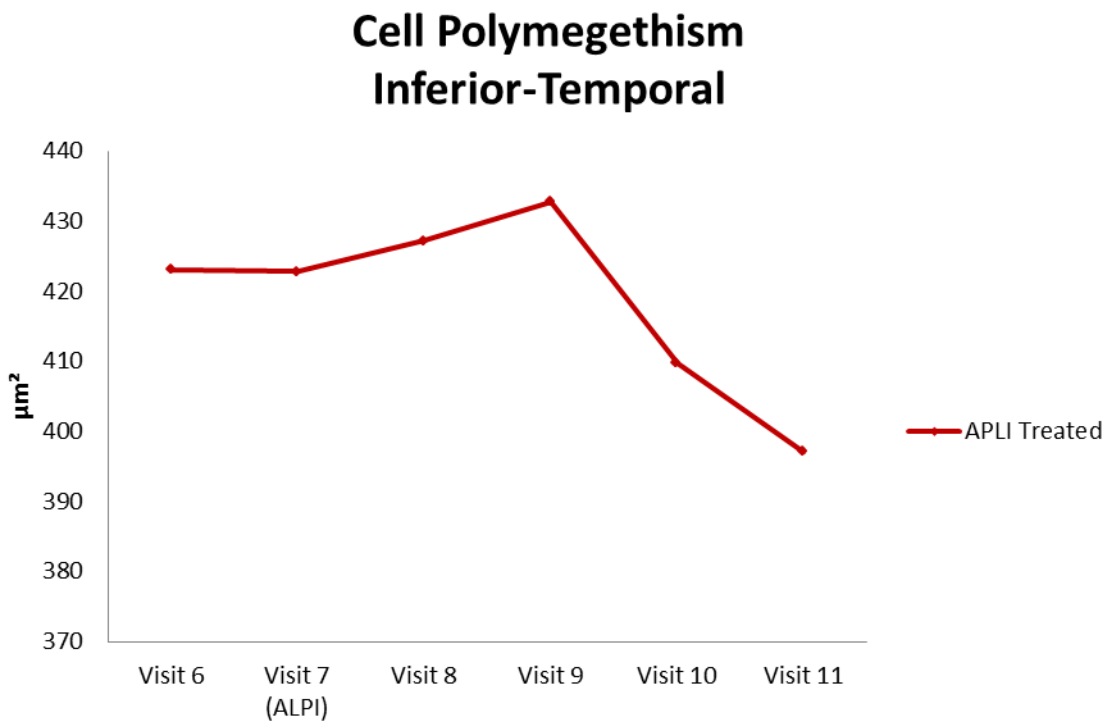

Figure 6.34. Descriptive mean values for cell polymegethism found at Vists 6, 7, 8, 9, 10, and 11 in the Inferior-Temporal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

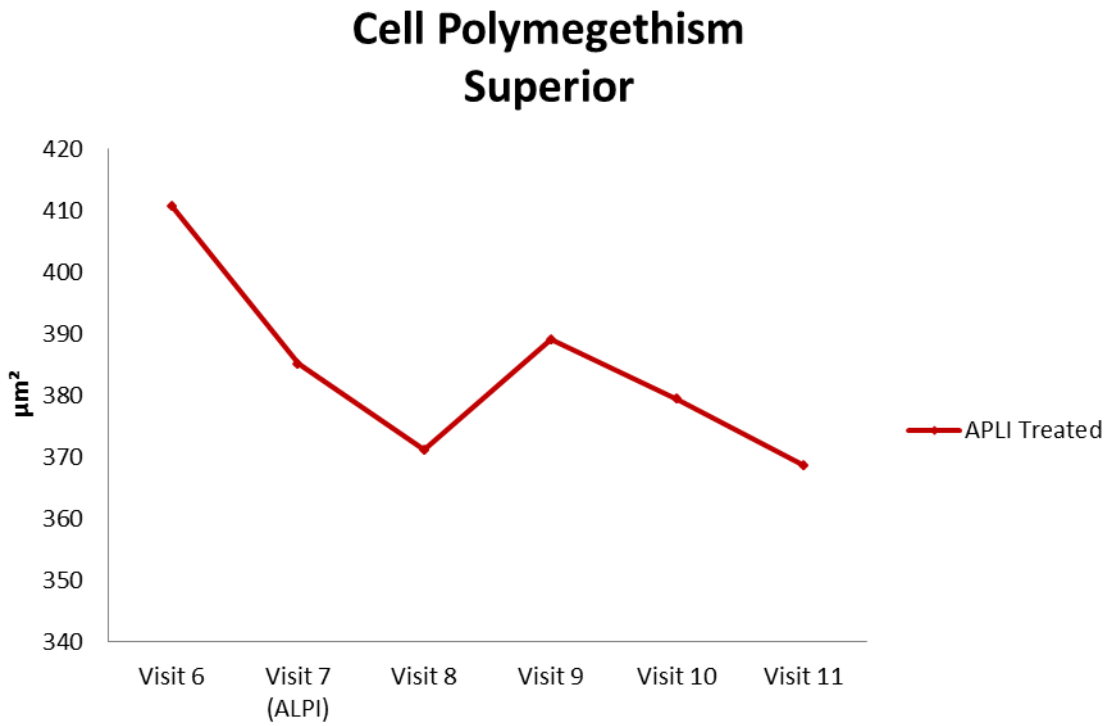

Figure 6.35. Descriptive mean values for cell polymegethism found at Vists 6, 7, 8, 9, 10, and 11 in the Superior cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

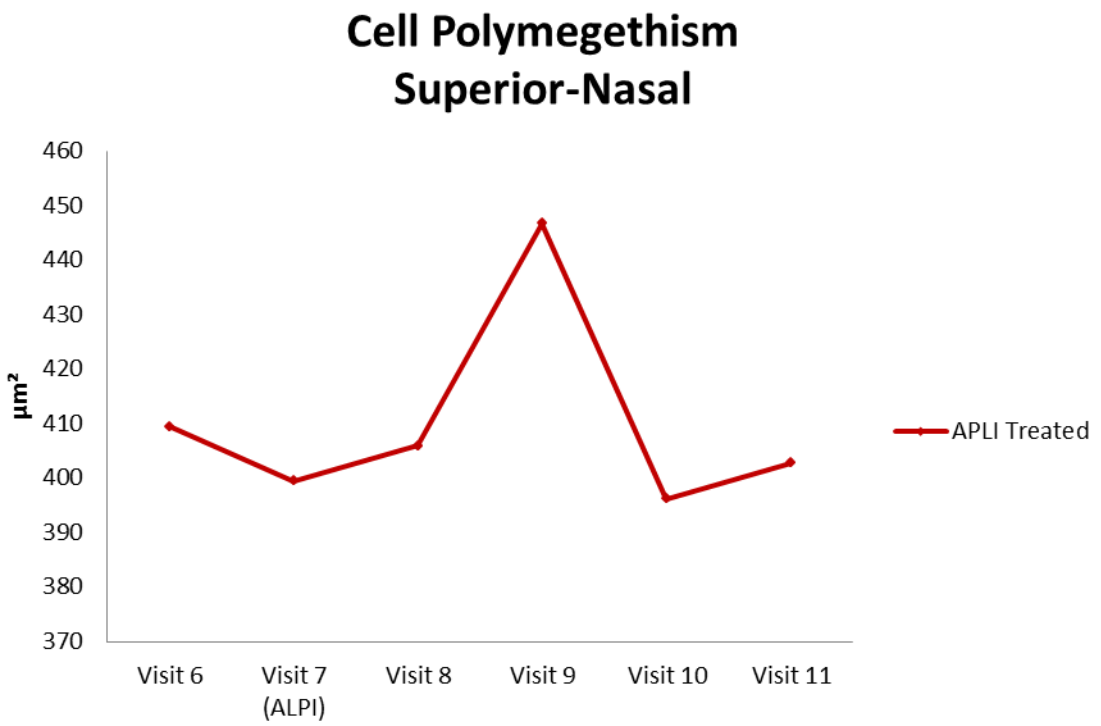

Figure 6.36. Descriptive mean values for cell polymegethism found at Vists 6, 7, 8, 9, 10, and 11 in the Superior-Nasal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

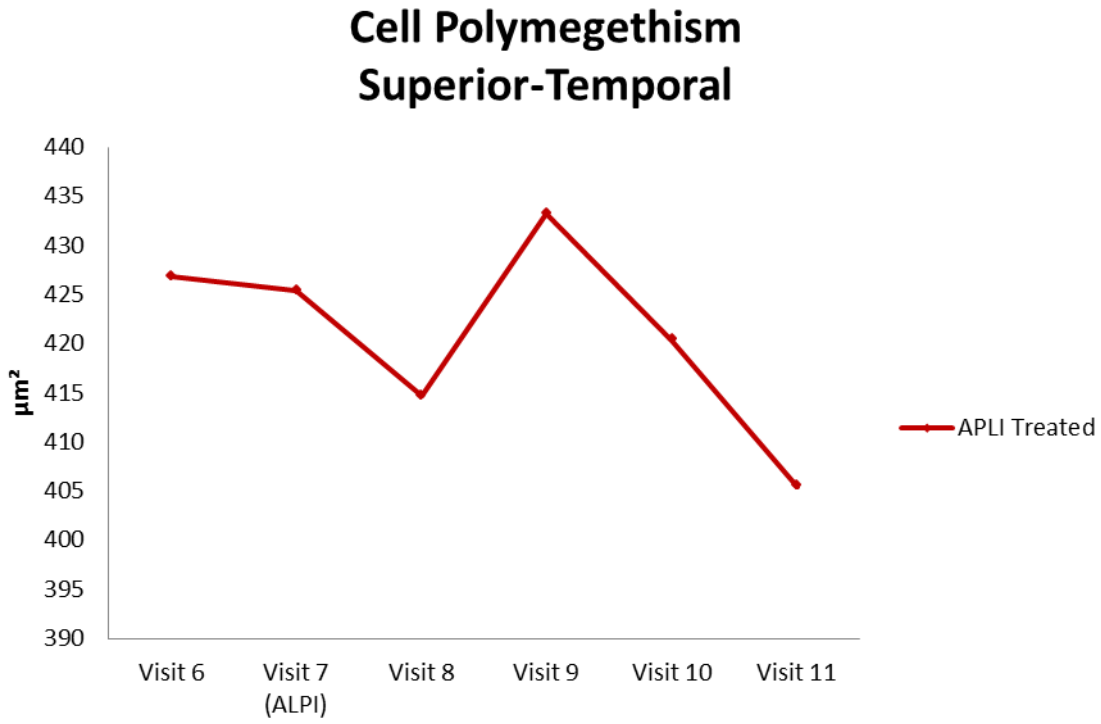

Figure 6.37. Descriptive mean values for cell polymegethism found at Vists 6, 7, 8, 9, 10, and 11 in the Superior-Temporal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

B.3. ALPI effect on percentage of hexagonal endothelial cells, pleomorphism (%)

Paired samples t-test showed 3 different trends for the areas under study.

In the case of Central and Superior sectors, there was a reduction in pleomorphism in Visit 8, a mild recovery between Visits 9 and 10 and a mild drop at Visit 11. However, in the case of the Central area, the pleomorphism fluctuated with negative values after Visit 7 and in the case of the Superior the values were always positive. The Superior-Nasal, Inferior-Nasal and Inferior-Temporal areas experienced an initial drop in the pleomorphism, more frequently found at Visits 8 and 9 and an increased in Visits 10 and 11 until completed recovery. The Inferior and Superior-Temporal areas showed a decrease in Visits 7, 8 and 9, and increase in Visit 10 and a new decrease in Visit 11. However, this decrease achieved lower levels than baseline in the case of Inferior area and higher for the Superior-Temporal.

The only statistically significant result for these comparisons was found in the Superior-Temporal area when comparing Visit 9 to baseline (Visit 6). Additionally, no statistically significant results were found with analysis of covariance when comparing Visit 11 to baseline. See following graphs for a visual representation.

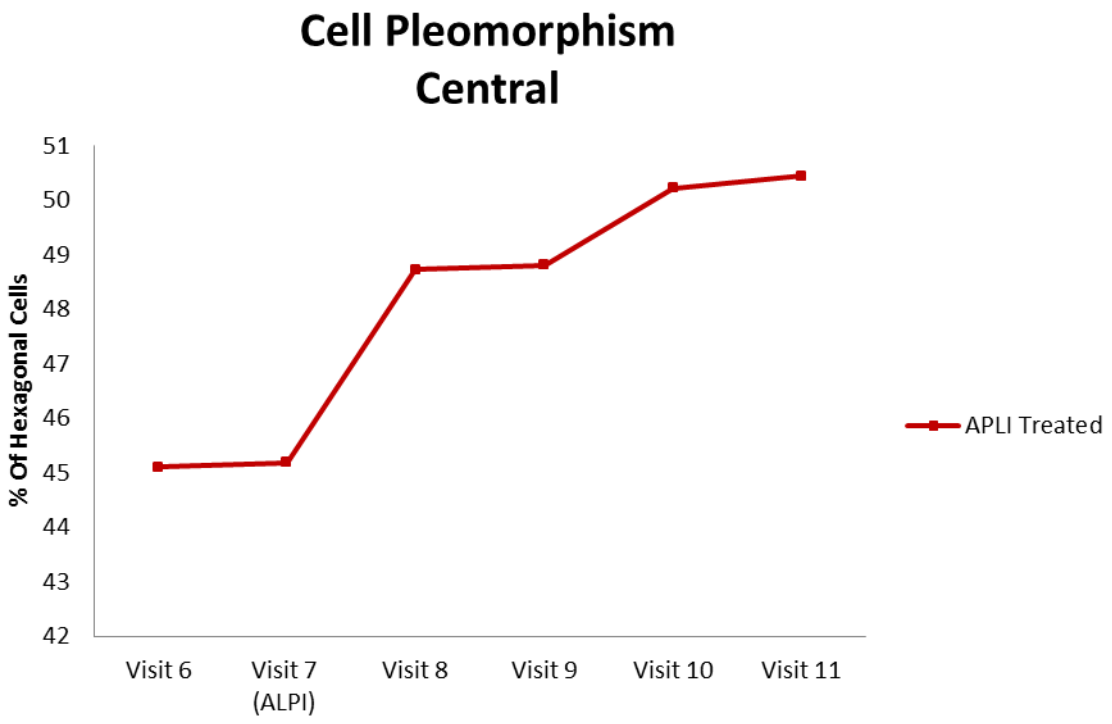

Figure 6.38. Descriptive mean values for endothelial pleomorphism found at Vists 6, 7, 8, 9, 10, and 11 in the Superior-Temporal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

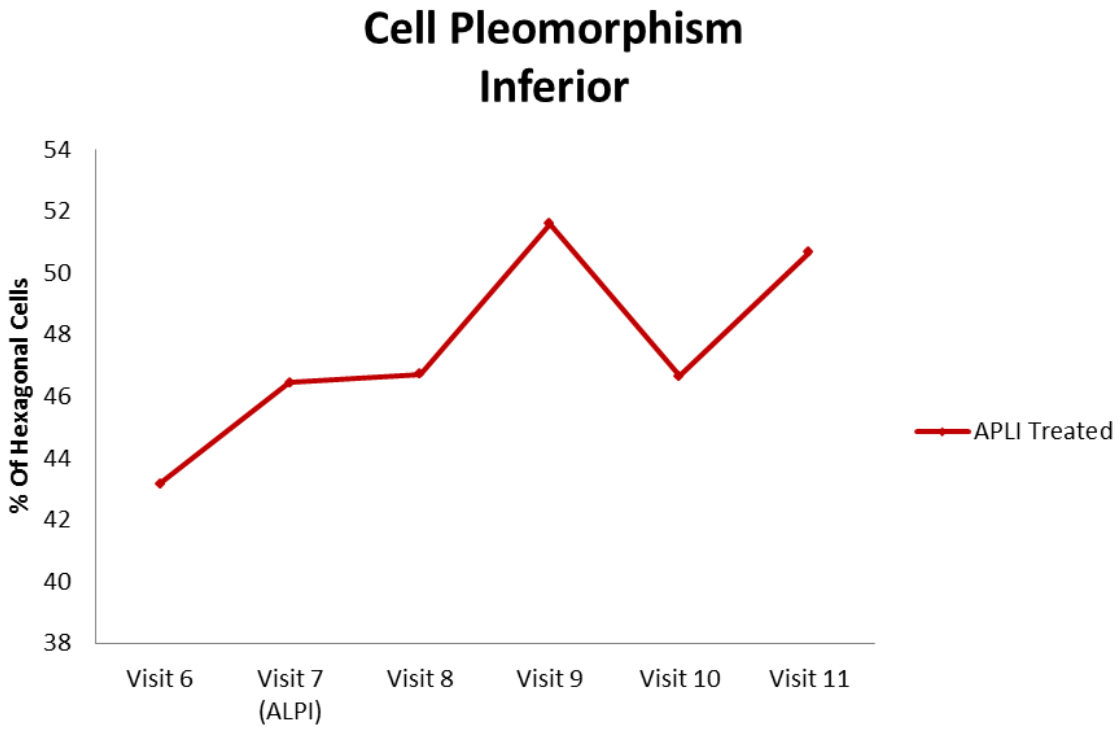

Figure 6.39. Descriptive mean values for endothelial pleomorphism found at Vists 6, 7, 8, 9, 10, and 11 in the Superior-Temporal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

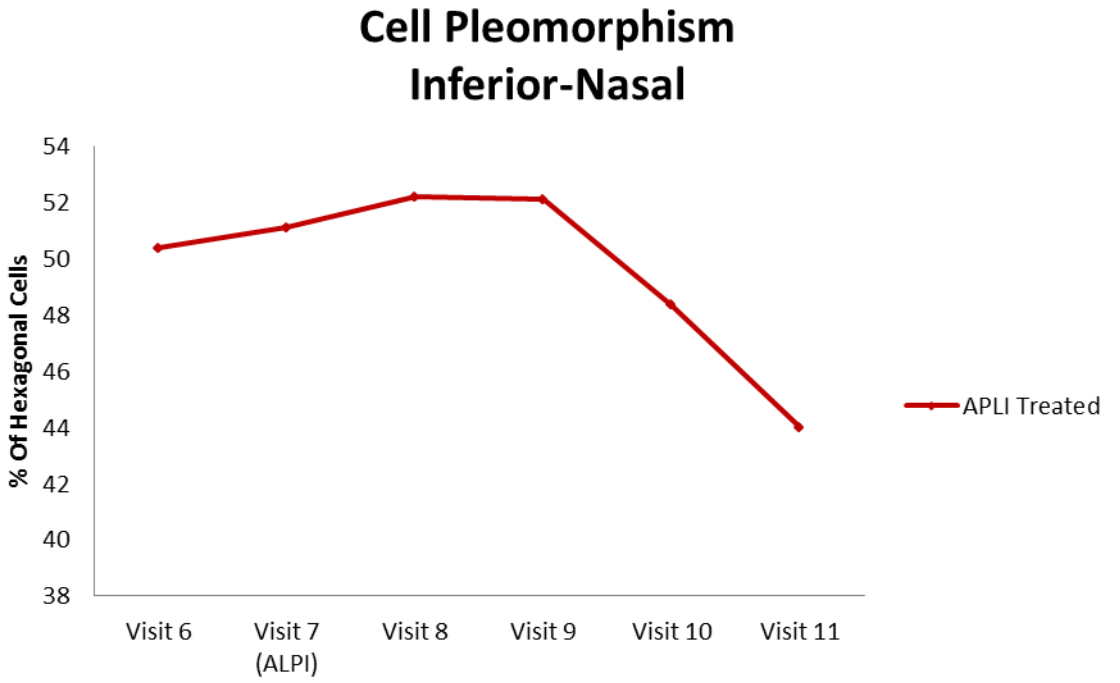

Figure 6.40. Descriptive mean values for endothelial pleomorphism found at Vists 6, 7, 8, 9, 10, and 11 in the Inferior-Nasal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

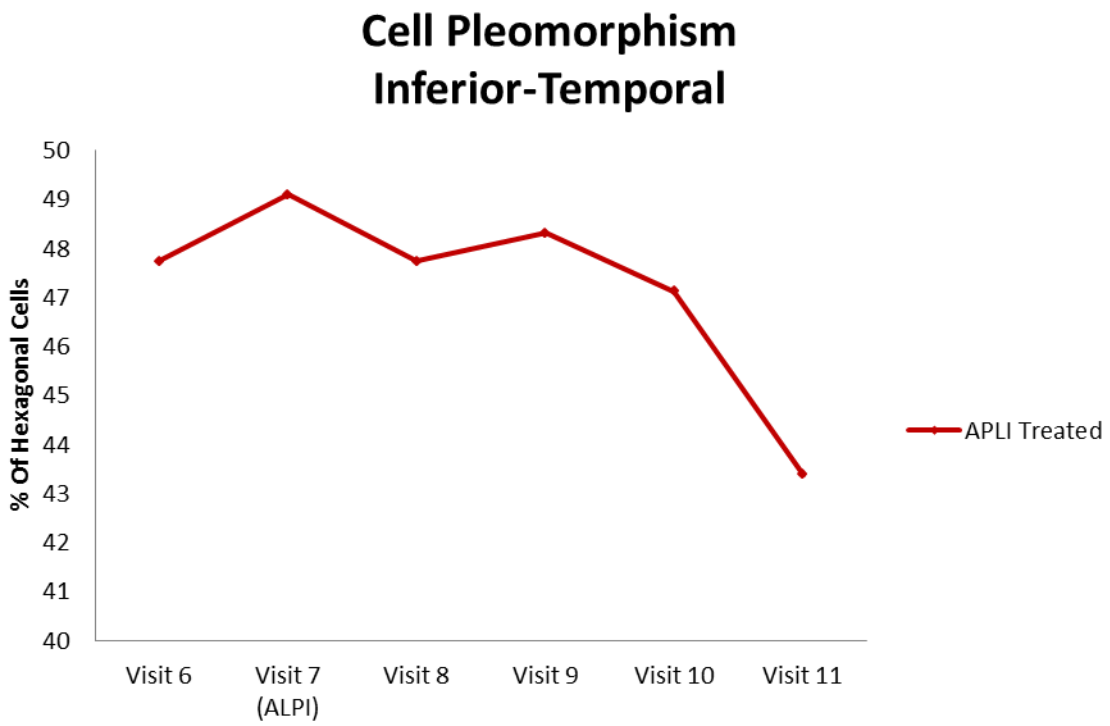

Figure 6.41. Descriptive mean values for endothelial pleomorphism found at Vists 6, 7, 8, 9, 10, and 11 in the Inferior-Temporal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

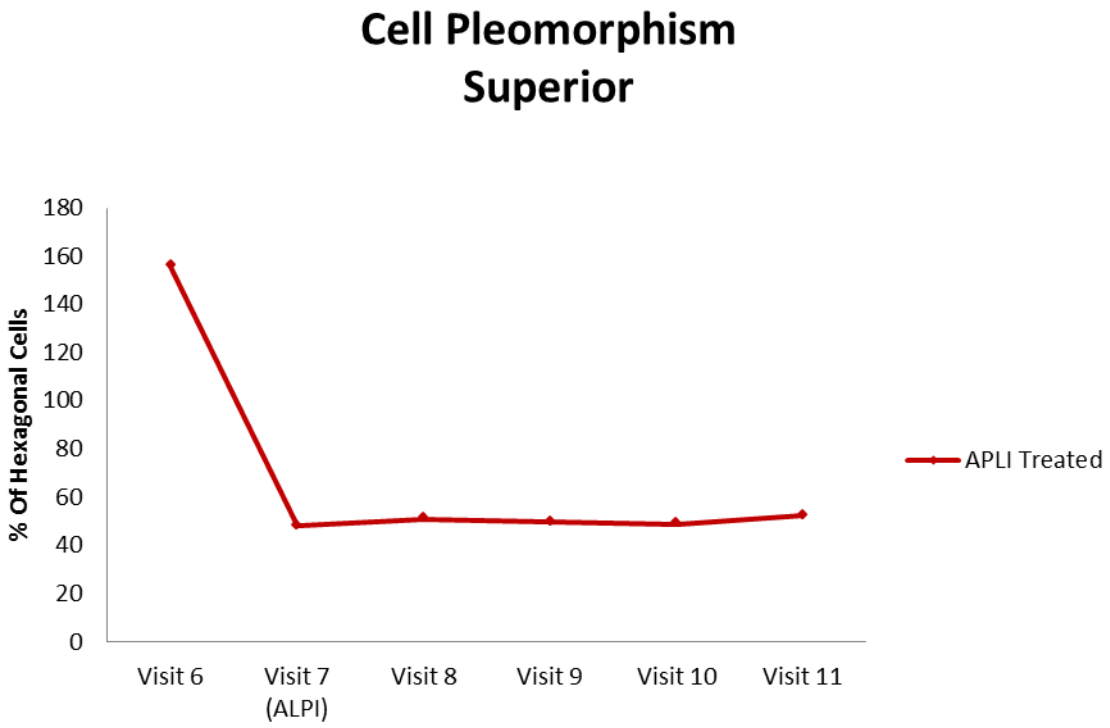

Figure 6.42. Descriptive mean values for endothelial pleomorphism found at Vists 6, 7, 8, 9, 10, and 11 in the Superior cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

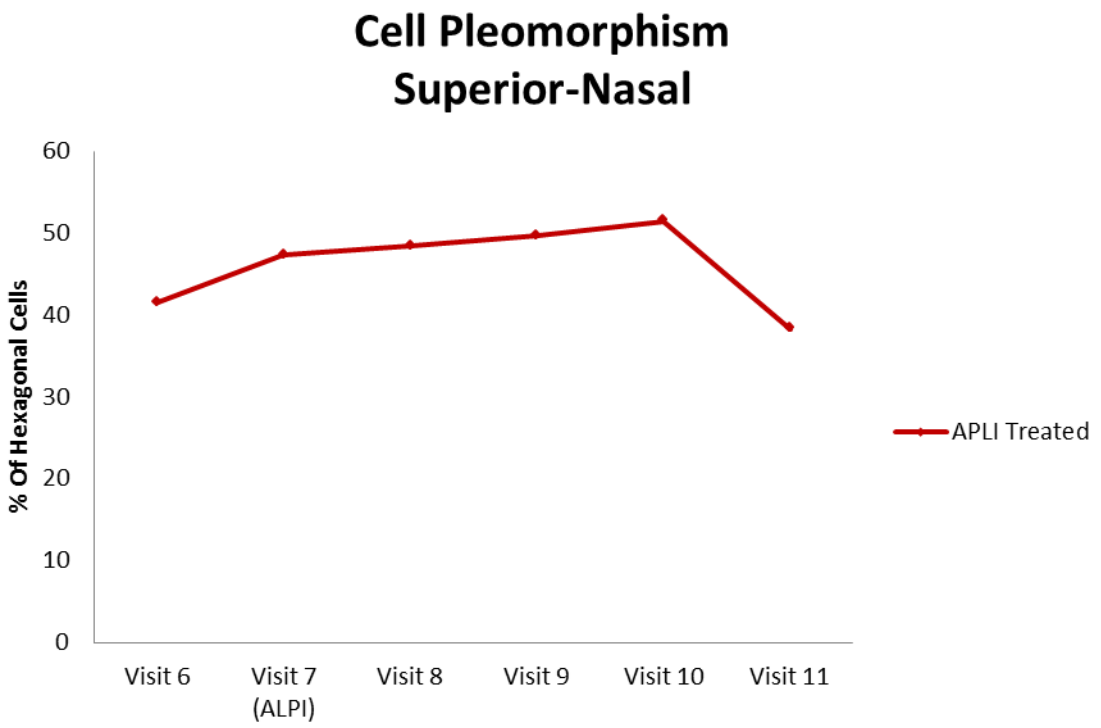

Figure 6.43. Descriptive mean values for endothelial pleomorphism found at Vists 6, 7, 8, 9, 10, and 11 in the Superior-Nasal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

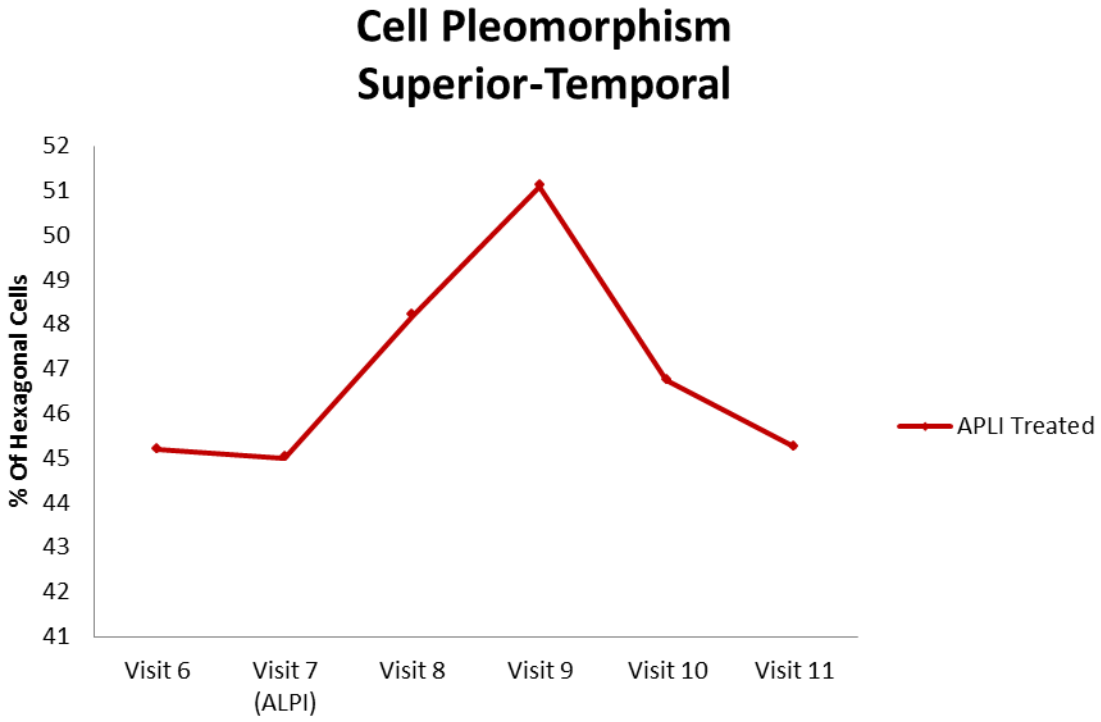

Figure 6.44. Descriptive mean values for endothelial pleomorphism found at Vists 6, 7, 8, 9, 10, and 11 in the Superior-Temporal cornea for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

B.4. ALPI effect on central corneal thickness (μm)

There seemed to be a decrease in the central corneal thickness at Visit 7 that recovered through Visits 8 and 9 until achieving an increase of thickness at Visits 10 and 11. These differences were not statistically significant as tested with paired samples t-test. The mean differences between Visit 6 (baseline) and Visit 7 was a decrease of 6.333 μm (SD 23.532), p=0.443; at Visit 8 and 9, this difference decreased to 5.750 μm (SD 8.860), p=0.109, and to 2.714 μm (11.470), p=0.554, respectively.

Analysis of covariance also did not show any statistically significant result.

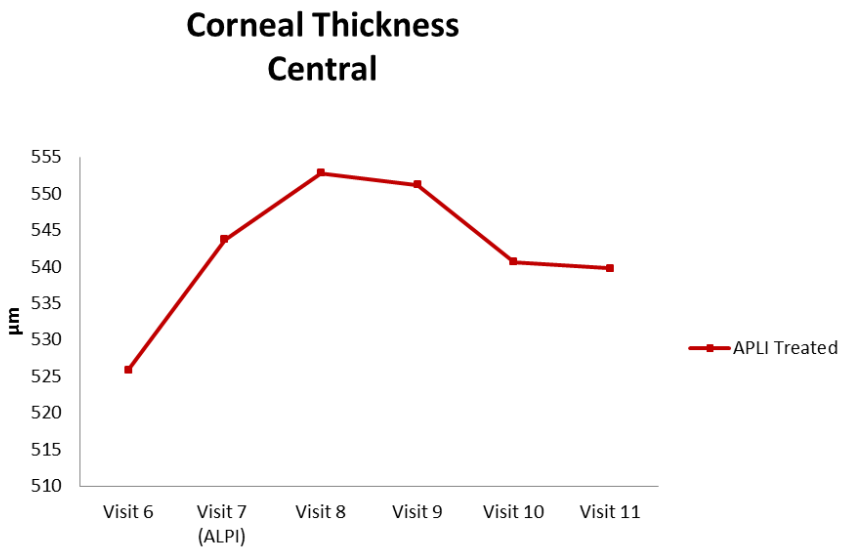

Figure 6.45. Descriptive mean values for central corneal thickness found at Vists 6, 7, 8, 9, 10, and 11 for the eyes treated with Argon Laser Peripheral Iridoplasty (ALPI).

Paired Samples t-tests for every endothelial parameter tested can be found in Tables 6.22 to 6.28 (Appendix 1). The results for the analysis of covariances can be found in Table 6.36, in the same Appendix.

6.1.4 Discussion

In the present study, LPI was found to have no statistically significant effect on the corneal endothelium cell density, polymegethism and pleomorphism. Furthermore, in the very few cases

were there was a statistically significant difference, it was unlikely to have been caused by the effect of the Nd:YAG laser as similar changes were occurring in the untreated eyes.

Several published reports have shown similar outcomes when studying the effect of the LPI on the already mentioned corneal endothelial parameters. Pollack, et al. (1984) examined the same endothelial cell parameters one month after the iridotomy was performed with Nd:YAG and found there were no changes in the case of animal endothelium (cytomologus monkeys) and a lack of change in cell count in the case of human endothelium (21 eyes of 21 patients). Wishart, et al. (1986) found that there was no pre versus post-LPI change in the central endothelial cell density in 14 of 16 eyes that undertook the procedure. Two eyes of the same patient showed immediate and localised endothelial changes that were not persistent at 3 months after the LPI. The total average of energy used to perform an iridotomy with the Nd:YAG was 22mJ. The post-LPI measurements time-points varied, for some patients these were taken immediately after the procedure and between 1 and 4 months and for others only the last measurements were taken.

However, endothelial damage caused by the Nd:YAG laser iridotomy has been described in the literature. Kerr-Muir and Sherrard (1985) described endothelial lesions in all the 16 treated eyes (this sample was diagnosed with chronic narrow angle glaucoma). The average of the total energy used to perform the iridotomy was 42.62mJ (range from 2.04mJ to 170.4mJ- this information has been calculated from the data showed in their table). Specular microscopy was measured prior to the iridotomy and immediately after, although four of the cases were followed up several days after to monitor possible changes. These four eyes showed normal adjacent endothelium spreading into the damaged areas.

More recently, some studies have shown endothelial damage secondary to iridotomies created with Nd:YAG lasers. Kozobolis, Detorakis, Vlachonikolis and Pallikaris (1998) found statistically significant changes after the LPI. All 10 eyes of 10 patients were treated with the Nd:YAG laser to perform an iridotomy using an average of energy of 30mJ. Five areas of cornea were sampled pre-operatively and at 1 day, 1 week, 1 month and 6 months after the procedure. Their study found a statistically significant decrease in cell density in the Superior-Temporal area when comparing pre-LPI to the data collected 1 month after the treatment. Additionally, 6 months post-LPI Central and Superior-Temporal areas showed a statistically significant decrease in cell density when compared to the pre-operative data. The rest of the sampled corneal areas at the different visits showed no statistically significant changes. No information about the number of lost cells was

given in their report. The corneal thickness changes were statistically significant when measured 1 week post-LPI in the Superior-Temporal quadrant. This finding was not clinically significant. The polymegethism and pleomorphism were measured on central endothelium only. The polymegethism decreased statistically significantly at 1 and 6 months post-LPI and an increase in pleomorphism was found only at 6 months post-LPI. The rest of the follow up visits showed statistically insignificant results for these endothelial parameters.

Additionally, Wu, Jeng, Huang and Lin (2000) found a decrease in cell count when assessing the endothelium after Nd:YAG iridotomy. They prospectively studied 31 eyes of 21 patients with occludable angles who were undergoing LPI as a prophylactic treatment. The mean energy used to perform the iridotomies was 63.5mJ (Range from 22.4mJ to 120.3mJ). When the cell density was measured at 1, 3, 6 and 12 months after the YAG LPI and compared to baseline, statistically significant losses of cells were found in every follow up visit with the exception of the 3 months post-procedure visit. Their analysis was based on the average of cell density found in 5 different areas of cornea. The maximum loss of cells was found to be as much as 70 cells (SD 89 cells) at the last visit (1 year after the LPI).

Kozobolis, Detorakis, Vlachonikolis and Pallikaris (1998) further suggested that there might be a relationship between endothelial damage and the amount of energy used to perform the iridotomy. Wu, Jeng, Huang and Lin (2000) tested this hypothesis using their data on endothelial cell density but their model resulted statistically insignificant. Nevertheless, if proven, this would have given a possible explanation for the differences between the reports supporting the idea of a significant change in the endothelium after Nd:YAG iridotomy and the present research thesis' findings as a much lower level of energy was used to perform the iridotomies in the latter study.

Moreover, a marked limitation of the last two mentioned publications (Kozobolis, Detorakis, Vlachonikolis and Pallikaris, 1998; Wu, Jeng, Huang and Lin, 2000) is the absence of a fellow control eye and, therefore, it would be difficult to determine if these differences were actually due to the effect of the Nd:YAG iridotomy or due to a normal decrease as the cornea ages with time.

Marraffa, et al. (1995), found an association between the distance from the endothelium over the iridotomy site to the Nd:YAG iridotomy in the iris and a reduction in endothelial cell density per linear millimetre on the temporal corneal area. The data was taken before and 1 week after LPI. This agrees with the results found at Visit 4 (1 week after LPI) in the present study, where there was a mean loss of approximately 21 cells/mm^2 in the treated eyes and 11 cells/mm^2 in the untreated (statistically insignificant).

To effectively assess change in cell density the mean values for every variable measured should be taken into account (Descriptive statistics can be found from Tables 6.1 to 6.7 in Appendix 1). In the case of the density of endothelial cells lost after the LPI, the difference in cell density in the treated eyes compared to baseline achieved a maximum of 69 cells lost per mm^2. For the fellow untreated eyes, this difference in cell density when compared to data at baseline was a maximum of 83 cells lost per mm^2. If the mean value of endothelial cell density is considered, the values are commonly of the order of 2500 cells per square millimetre for the majority of the seven sampled areas. These 69 and 83 lost cells would represent a minimal change in such values (less than a 3% and 3.5% respectively). The Superior or Superior-Nasal showed a significantly lower cell density at baseline than other sampled areas (approximately 180 cells per square millimetre), but the changes were lower too, representing a maximum loss of 32 cells, nearly an 18%. Nevertheless, this was considered a systematic error of the specular microscope; it is not plausible to have 180 cells/mm^2. A change in density of 95 cells/mm^2 has been previously considered of small clinical significance in corneas showing baseline densities of approximately 2500 cells/mm^2 (Panek, Lee and Christensen, 1991). Furthermore, focal corneal oedema has been observed in cases when the cell density reached levels of 300 to 900 cells/mm^2 after argon laser iridectomy at a time interval from 18 to 42 months (Jeng, Lee and Huang, 1991).

In the present study the maximum increase in polymegethism (as measured by average cell size) was observed in the untreated eye; values of approximately 15μm^2 and 14μm^2 larger cell dimensions were found in the Inferior-Temporal and Inferior area respectively. The maximum loss in pleomorphism was noted for the untreated eye on the Inferior cornea (approximately 7% loss when comparing Visit 2 and Visit 1; $p=0.021$). This change was a rare finding as the losses were expected to be found in the treated group. The pleomorphism in the treated eye was fluctuating without following a clear pattern. If the changes in polymegethism were compared with its descriptive statistical mean values found at baseline, they would represent a maximum of a 32% increase of the baseline polymegethism. If the same comparison is performed for the pleomorphism maximum losses, this would represent a maximum of 26.5% loss of the baseline pleomorphism.

Changes in the human normal corneal endothelium with time have been described in the literature. Bourne, Nelson and Hodget (1997) followed 42 adult subjects over a period of 10 years. The same specular microscope was used throughout the study. The area/areas of sampled corneal endothelium were not specified (presumably central position). They found that, over that period, statistically significant losses in endothelial cell density of 176 cells/mm^2 (SD 149

cells/mm^2) were shown with an increase in polymegethism (indicated by the coefficient of variation of cell area) of 0.03 (SD 0.03) and a decrease in pleomorphism (percentage of hexagonal cells) of a 4% (SD 7%). The change in these parameters per year was estimated to be 16 cells/mm^2 (SD 14 cells/mm^2), 0.003 (SD 0.003) and 0.3% (SD 0.7%) respectively. There was no change in the corneal thickness.

This agrees with results found in the present study, where a slightly greater change for the different endothelial parameters have been described during the 6 months follow up for the different sampled areas. However, at 6 months time from baseline nearly all the endothelial parameters found in the treated and untreated group achieved similar levels as those found at baseline. The most marked exception to this assertion was a decrease in cell density of approximately 50 cells/mm^2 and an increase in the average cell area of approximately 10 μm^2 in the Inferior-Temporal position of the treated group of eyes.

To summarise the present study; the losses or recovery of endothelial cells of eyes treated with the Nd:YAG laser seemed to vary in the same pattern as in the untreated eye. This was additionally tested with the analysis of covariance, showing that although there were some differences in cell density (a maximum of 84.7 cells), none of the different for the cell density in the seven areas resulted statistically significant. Similar results were observed for central corneal thickness and degree of pleomorphism and polymegethism. Therefore, there is a possibility that these endothelial cell parameters may have changed through time and that LPI performed with this level of energy is not affecting these changes. This would, nevertheless, need corroborating with a larger sample size.

In the case of the effect of ALPI, only comparisons with the same eye with time were performed, as the fellow eye of the participant was not included. The eyes that were treated with ALPI had been previously treated with LPI. If only the ALPI effect was to be studied, only those eyes that despite of LPI remained occludable but received no further treatment could act as control eyes. The limitation of the present study results of the ALPI effect on the endothelial parameters is that there was no control eye for Visits 7, 8, 9 and 10. However, it was possible to have these control eyes data at Visits 6 and 11.

Using the data from the control eyes, statistically significant differences between the ALPI treated group and the post-LPI occludable group were found. These results suggested that there is a higher cell density in the ALPI treated eyes than in the control eyes for the Superior and Superior-Nasal areas and that there is a higher average of cell size in the ALPI treated group in the Inferior-Nasal area.

As in the case of the LPI, there were fluctuations of corneal endothelial parameters with time. Very few of these changes were statistically significant and none of them were clinically significant based on the reports commented for the LPI (mentioned earlier in this section). The maximum loss of cell density found after ALPI was 89 cells/mm^2. This result was statistically significant and was observed in the Superior-Temporal area (representing a loss of 3.7% from baseline data). The maximum change in polymegethism and pleomorphism was observed in the Inferior-Nasal and Inferior areas. When these changes were compared with baseline data, they represented an increase in polymegethism of a 3% and a reduction in the number of hexagonal cells of a 20.6% (both results were statistically non-significant). The corneal thickness changes represented a 0.4 to 1.1% difference from baseline.

There is very little published literature regarding the effect of ALPI on the corneal endothelium. However, there have been at least two published reports on the effect of Argon Laser Trabeculoplasty (ALT) on the corneal endothelium, the only other commonly applied argon laser to anterior segment structures. Hong, Kitazawa and Tanishima (1983) studied 10 eyes with primary open angle glaucoma. They performed contact specular microscopy on central cornea prior to ALT and at one week, 4 weeks, 3 months, 6 months and one year after the procedure. The number of burns during the ALT ranged from 92 to 107 with an average energy of 200mJ. A statistically significant increase of cell size of approximately 12% was observed after one year. They attempted a correlation between the change in this parameter and the energy delivered during the ALT procedure, but their data were statistically insignificant. Thoming, Van Buskirk and Samples (1986), studied 22 eyes of 17 patients that were treated with ALT. Ten eyes were left untreated and acted as control. Specular microscopy was performed prior and once after the procedure (from 9 to 17 months after). The total mean energy delivered on the anterior trabecular meshwork varied from 3.5 to 0.9J with a mean number of burns of 88. No significant difference was found in any of the three parameters measured in central cornea, cell area, cell density, percentage of hexagonality and shape factor (how close the shape of the cell is to the shape of a circle) in the treated and control eyes. The results for these two papers are consistent to those found in the present study and for similar length of time. However, a longer follow up would be needed to assess the results that these authors found at approximately one year after the ALT. This could form a basis for future study.

Therefore, the results from the present study are the first comprehensive report on the effect of ALPI on the corneal endothelium.

There are some limitations related with the instrumentation used in this section. The limitations for the Tomey 3000 Specular Microscope and its repeatability are explained in the Appendix 3 of this thesis.

One other limitation of this study is the duration of the follow up. If there are further or stable changes on the endothelial parameters in Caucasian PAC and PACS treated eyes (either with LPI or ALPI), this remains unknown.

6.1.5 Conclusion

The endothelial cell parameters under study fluctuated during the 6.5 months that the study lasted and these fluctuations were not clearly related to the LPI or ALPI effects. The fluctuations were small compared to the mean value of the tested corneal endothelial parameter. Furthermore, these small variations in cell parameters are most likely to be caused by bias using the specular microscope (the limitations of this devices are discussed in Appendix 3 of this thesis).

CHAPTER 7. General Discussion

The present study thesis involved Caucasian individuals with bilateral occludable anterior chamber angles.

This is the only study that has described the diurnal intraocular pressure (DIOP) characteristics in patients with untreated Primary Angle Closure (PAC) and/or Primary Angle Closure Suspect (PACS).

It has been shown that this sample of PAC/PACS Caucasian patients generally present a peak of IOP in the early morning and these levels decrease throughout the day, showing a moderate second peak in the early afternoon. When compared to previous published literature, these eyes had diurnal intraocular pressure curves similar to normal healthy eyes (Wilensky, 1991; Liu, et al., 1999). When these curves were compared to those of eyes with early glaucomatous changes, the curves were also similar (peaks and troughs within similar diurnal times) with the glaucomatous DIOP curve demonstrating higher levels of IOP during the day (Liu, Zhang, Kripte and Weinreb, 2003).

In 24-hour IOP assessments, it has been reported that patients with early glaucomatous changes and without treatment presented an IOP peak at 5:30 am when the patient is lying supine during nocturnal hours (Liu, Zhang, Kripte and Weinreb, 2003). Hughes, Spry and Diamond (2003) also found that the peak of IOP occurred outside office hours in 51.7% of 29 glaucoma patients under therapy. Barkana, et al. (2006) found similar results to Hughes and colleagues. 69% of their glaucomatous sample had a peak of IOP outside office hours. However, new evidences (Quaranta et al., 2010) suggest that there is not a real difference between the IOP measured during the day and the nocturnal one. The peak of IOP in this study was situated at 10:00 hours. There is no published report on the 24-hour IOP behaviour for eyes with PAC/PACS. It is for future research to find how representative the DIOP found in this study is of a 24-hour cycle in these patients.

Although Liu and colleagues did not specify the characteristics of the sample in terms of gonioscopic findings, their work suggested that DIOP within higher limits than those found in healthy eyes may be associated to factors related to progression to a glaucomatous stage (Liu, Zhang, Kripte and Weinreb, 2003). In the case of angle closure, factors such as presence of peripheral anterior synechiae (PAS) have been related to a more serious stage of the condition (Foster, Buhrmann, Quigley and Johnson, 2002). Furthermore, PAS have been associated with

trabecular meshwork histological damage (Sihota, et al., 2001). Therefore, the presence of PAS and its relationship with higher DIOP fluctuation needed to be investigated. The present study found a statistically significant positive relationship between higher IOP measurements taken during the majority of the diurnal hours and the amount of PAS present in an eye. Additionally, the average difference between IOPs found in the DIOP of eyes without PAS and those with PAS was 1.5 mmHg ($p=0.043$). Consequently, it can be concluded that primary angle closure patients with a higher presence of PAS (covered degrees of the irido-trabecular circumference) will exhibit higher levels of diurnal intraocular pressure.

Previous literature has stated that there is an increase of IOP when a patient adopts either a supine or a head-down position (Friberg, Sanborn and Weinreb, 1987). It was additionally found that an increase in IOP due to these postural changes was directly related to an increase in the episcleral venous pressure. It was justified to suggest that individuals in the present study with narrow angles, where the aqueous humour outflow may be more limited, would exhibit higher IOP levels after being in the supine or prone position than those with open angles described in previous reports. As higher levels of IOP after postural changes have been related to a more advance damaged of the visual field in glaucomatous patients (Kiuchi, Motoyama and Oshika, 2010), it was of interest to know how PACS/PAC eyes in the present study reacted to the effects of postural changes. The difference in IOP between the pre-supine and the post-supine levels in this cohort of untreated PAC/PACS individuals was 1.70 mmHg (SD 2.12; $p<0.001$).

This result was similar to that found by Lam and Douthwaite (1997) for normal healthy Chinese eyes. They found that after 8 minutes in the supine position, the difference between the pre and post-supine was of approximately 1.40 mmHg. Although this difference was not analysed statistically, the similarity between the result found in their study and the present one is of interest. This may be explained when looking the differences in instrumentation. Lam and Douthwaite (1997) used the Pulsair 2000 which averaged IOP measurements have been found to be within $\pm$3mmHg 79% of the times when compared to the Goldmann tonometer (being this last tonometer the one used in the present study) (Moselay, et al., 1993). It is possible that the differences in IOP found as a result of the supine position may have been due to the variability of the device when compared to the Goldmann tonometer. Other studies performed in healthy eyes show even higher rates of change in the IOP, a difference of 4.11$\pm$1.82mmHg was found with contact tonometry (Buchanan and Williams, 1985). The duration of the test was not specified. However, even if it had been longer than in the present study (5 minutes in supine position), this

may not fully explain this difference. The reason based on the study performed by Yamabayashi, et al., (1991), were other group of normal eyes presented changes of 4.4 mmHg (SD 2.0) straight after laying on the supine position and it remained unchanged for the next 30 minutes. A possible explanation for these differences may be a result of the demographical differences between samples. The age range for the subjects participating in the study by Lam and Douthwaite (1997) and in Buchanan and Williams (1985) was of 19 to 26 and of 21 to 25 years old respectively. The age range among the participants of the present study was of 25 to 77 (Average 59.6 years old). Although there is no information about subjects' age in Yamabayashi's study, had these been younger subjects, it remains for future research to find a possible association between higher levels of IOP after adopting a supine position and age of the individual.

Regarding the dark room provocation test results (DRPT), the resulting average increase in IOP levels was 3.05 mmHg (SD 2.85) after the patient had adopted a prone position for 15 minutes in the darkness (illumination <0.01 lux). Previous published reports show higher levels for normal eyes after a similar test and duration. Walick, Kragh, Ward and Crawford (2007) found changes of approximately 10 mmHg when a patient was left in a prone position for at least 10 minutes. Lam and Douthwaite found an increase of approximately 6.5 mmHg after 8 minutes in the same test with levels of illumination of 360 lux (this increase IOP was not statistically tested). It was surprising to find that patients with untreated PAC/PACS eyes were exhibiting lower levels in the DRPT as they had the additive effect of the presence of narrower angles. One probable explanation for this observed lack of effect may be the different methods used to measure the IOP. While Walick and colleagues and Lam and Douthwaite were taking the measurements with the patient at all times positioned prone, in the case of the present study the IOP was measured in the sitting position before and after the test. Although care was taken in measuring the IOP immediately before and after the DRPT and in darkness, it is possible that the patients in the present study showed higher levels while they were lying on the prone positions and that these may have been modified after adopting the sitting position.

As mentioned earlier, the amount of PAS influenced the levels of the DIOP curve in this study sample. It is therefore possible that PAS may have had similar effects on the levels of IOP measured after the patients have been lying on the supine or prone position. This was investigated in the present study, finding that there were no differences between eyes with PAS and those without PAS for the supine IOP and the DRPT. Furthermore, when an association

between the degree of PAS present in the iridotrabecular angle and higher levels of IOP was investigated with regression statistical models, these showed no association for neither of the resulting IOPs, the supine or the DRPT.

The results for the DIOP curve for the untreated PAC/PACS in the present study showed an average difference between the maximum and the minimum IOP measured during the day. This difference is known as DIOP fluctuation and it was of approximately 6 mmHg (SD 2.70 mmHg) in this study's sample. This level of DIOP fluctuation is higher than those described for non-glaucomatous eyes with open angles previously described in the published literature. Liu, Zhang, Kripte and Weinreb (2003) found a DIOP fluctuation of 4.0 mmHg (SD 0.3mmHg) for their 'normal' sample of eyes of a mixed ethnicity and Sihota, et al. (2005) found rates of 4.83mmHg (SD 2.46) for a sample of the same characteristics although no ethnicity was specified. These differences may be explained through a possible higher resistance to aqueous humour outflow in eyes with narrow angles compared to those presenting open angles. This suggested a possible relationship between higher DIOP fluctuation and narrower dimensions of the irido-trabecular angle. This relationship was investigated in the present study using a swept-source OCT (CASIA OCT) for quantifying the angle parameters.

It has been found that for the vast majority of the angle parameters there was an inverse association between DIOP fluctuation and dimensions of the 8 angle sections sampled (Superior, Superior-Nasal, Nasal, Inferior-Nasal, Inferior, Inferior-Temporal, Temporal and Superior-Temporal). Baskaran, et al. (2009) studied the DIOP fluctuation in three Asian angle closure groups who had previously been treated with LPI (mean time 31.3 weeks, SD 2.33 weeks, previous to the study). The three groups, PACS, PAC and PACG presented a DIOP fluctuation of 3.75 mmHg (SD 1.24 mmHg), 4.53 mmHg (SD 2.33 mmHg) and 5.44 mmHg (SD 2.4 mmHg) respectively. These differences in fluctuation between groups, which were statistically significant, suggested that the DIOP fluctuation would be higher as the condition progressed to more serious stages. This was further confirmed when the authors additionally found a direct association between this fluctuation and the clock hours of PAS and the pattern standard deviation of the visual field.

In the present study, there was no association between the presence of degree of PAS and higher DIOP fluctuation. Although, it is true that Baskaran and colleagues' data had a high degree of

scatter and the association PAS~DIOP fluctuation was weak (R^2 0.139), there is not an obvious explanation for these differences in the outcome of both studies.

Untreated eyes of PAC/PACS Caucasian participants in the present study exhibited similar DIOP curves to other 'normal participants' previously described, but higher DIOP fluctuation.

The reason for always including the 8 angle sections in the statistical analysis of this thesis is down to statistically significant differences found among the 8 angle sections of the untreated group of eyes (Superior, Superior-Nasal, Nasal, Inferior-Nasal, Inferior, Inferior-Temporal, Temporal and Superior-Temporal). The Superior section was found to be the narrowest when compared with the rest of the sections and the Nasal, Inferior-Nasal and Temporal sections were the widest independently of the lighting conditions. Additionally, Superior and Superior-Nasal sections and the Inferior sector were statistically significantly different in light and darkness. This result would only affect those investigations that may not have used the data of all the sections, where investigators have averaged the angle dimensions and attempted to find associations with other parameters such as PAS. An example is the study by Su, et al. (2007) which reported a correlation between the mean value of the parameters in 3 sectors (Inferior, Nasal and Temporal) with AS-OCT and the PAS found in 4 sectors (Superior, Nasal, Inferior and Temporal) on gonioscopy. It is unknown what contribution to the correlation the Superior sector dimensions would have made or if this sector was statistically similar to any other of the sectors. It is consequently important to study the homogeneity of the angle sections present on any study sample before averaging them to use regression/correlation models.

Laser Peripheral Iridotomy (LPI) and Argon Laser Peripheral Iridoplasty (ALPI) have been reported in previous studies to have a widening effect of the irido-trabecular angle in Caucasians (Moster, et al., 1986; Mansouri, Buneger, Bagnoud and Shaarawy, 2009; Ang and Wells, 2010; López-Caballero, et al., 2010; Antoniazzi, Pezzotta, Delfino and Bianchi, 2010). Therefore, it was of interest to assess a possible further benefit of these two lasers, a decrease in the DIOP fluctuation. This is another novel piece of research as this has not been studied previously, with the notable use of the fellow eye as a control eye to truly assess the effect of these two lasers. In the case of the LPI, had there been a decrease in the DIOP fluctuation, it would have explained the lower DIOP fluctuations found by Baskaran and colleagues.

In the present study, the DIOP fluctuation measured pre and post LPI was 6.46 mmHg (SD 3.02 mmHg) and 6.43 mmHg (SD 2.02 mmHg), respectively, and in the case of ALPI was 5.32 (SD 2.20 mmHg) pre-laser and 5.04 (SD 1.60 mmHg) post-ALP. When these differences were adjusted with those belonging to their corresponding untreated fellows, there were no statistically significant differences between the DIOP fluctuation measured pre-laser (ALPI or LPI) and the DIOP fluctuation found after both lasers. It can be argued that in the case of the present study the differences between groups were adjusted for their control eyes, but this is the only manner in which the effect of the lasers can be isolated. The lower levels of DIOP fluctuation described by Baskaran, et al. (2009) in LPI treated PAC/PACS were thought to be down to ethnicity differences in ocular biometry. No current literature has studied differences in DIOP fluctuation in individuals of different ethnicity. One study in healthy young adults of diverse ethnicity (52% Caucasian, 36% Asian, 9.3% Hispanic and 12.6% Black) found an inverse correlation between axial ocular length and higher levels of 24 hours IOP fluctuation (Loewen, Liu and Weinreb, 2010) and other study has suggested that Caucasians eyes have a deeper anterior chamber when compared to Chinese eyes (Wang, et al., 2011). Baskaran's patient sample was mainly Chinese. It was unexpected that the present Caucasian sample showed higher rates of DIOP fluctuation. After comparing both studies in detail there is no explanation for these differences.

Nevertheless, there is a considerable DIOP fluctuation in Caucasian PAC/PACS eyes even after LPI or ALPI treatments. It is important for future research in similar samples that if IOP is measured only once in the follow-ups it should be measured within similar diurnal time-hour as baseline (pre-procedure).

This raised the question of whether the LPI and the ALPI had an effect on the IOP levels when these were compared to the fellow untreated eyes. This research question has never been addressed as in the present study since previous reports have only followed up the treated eye.

When adjusting the data for differences in the fellow eye, the present study has demonstrated that there is not an evident association between rate of opening of the angle and time elapsed since the LPI was performed. Furthermore, such association was only statistically significant for the angle parameters found in the Inferior-Temporal section of the angle. There was also a lack of association for this rate of opening and the IOP levels, although the Inferior-Temporal section was an exception. In the case of Caucasian eyes, the studies generally agree in an increase of the

dimensions of the parameters in LPI treated eyes when compared to baseline (Moster, et al., 1986; Mansouri, Buneger, Bagnoud and Shaarawy, 2009; Ang and Wells, 2010; López-Caballero, et al., 2010; Antoniazzi, Pezzotta, Delfino and Bianchi, 2010). There has been some disagreement about the effect of the LPI on the IOP. While López-Caballero, et al., (2010) reported a decrease in IOP and an association between this and the opening of the angle 1 month post-LPI, Moster, et al. (1986) found that the IOP of all of their LPI treated patients returned to baseline IOP levels within the first week and remained unchanged for 3 months. The present study's results are more similar to those found by López-Caballero, et al., (2010). The most probable reason may have been due to the higher degree of similarity between the samples. While the patient sample in the study by Moster et al. comprised 80% glaucomatous eyes of different types (a mixture of primary open angle glaucoma, primary chronic angle-closure and primary acute angle closure glaucoma individuals, but only one case with occludable angles), the López-caballero study involved a mixture of primary angle closure glaucoma, primary angle closure or eyes presenting occludable angles.

In the case of the ALPI, the present study investigated a relationship between the rate of opening caused by this laser in a given eye and the time elapsed since the procedure. Although the treated eye presented a significant wider angle dimensions than the control eye (not treated with ALPI, but previously treated with LPI), it was not possible to show an association between this difference in opening and time. There was again a lack of statistically significant association between rate of opening of the angle parameters and IOPs.

Previous reports about the effect of the ALPI on the iridotrabecular angle are scarce and when looking for studies performed in Caucasian population there is no supporting published literature.

In Asian populations there are three reports on the effect of the ALPI. The study carried out by Lee, Choi, Kim and Choi (2011) on PACS; on PAC and PACG eyes, performed by Sun, et al. (2010) and one case report on PACG by Leung, et al. (2005).

There appears to be an agreement in the widening effect of the ALPI between the case report studied by Leung and the study carried out by Lee and colleagues. Furthermore, Lee, Choi, Kim and Choi (2011) performed the only study using the fellow eye as a control eye although the models were not adjusted for differences at baseline. Additionally Sun, et al. (2010) found a decrease in the IOP as an effect of the ALPI; but it is unclear if DIOP fluctuation was taken into account.

Due to the different rate of opening that every section presented 6 and 3 months after the LPI or ALPI, respectively, it was unexpected to find no statistically significant differences in the widening effect of these lasers depending on the angle section studied. Furthermore, the maximum widening effect of both lasers was commonly found in the inferior sections. As the iridotomy was placed in the superior sections at all times a higher widening of this section was expected. It is difficult to find an obvious reason for this finding and maybe fluid dynamics holds the answer.

This study did not found an obvious affection of the endothelial cell density, polymegathism or pleomorphism after LPI or ALPI.

Although some studies have reported corneal endothelial damage after LPI (Kerr-Muir and Sherrard, 1985; Kozobolis, Detorakis, Vlachonikolis and Pallikaris, 1998; Wu, Jeng, Huang and Lin, 2000) it has been suggested that such damage is directly related to the amount energy used to create the iridotomy (Marraffa, et al., 1995). Due to the low levels of energy used in the present study to create the iridotomies, it was unsurprising to not to find clinically significant changes in these parameters. A change in such parameters due to time has been described (Bourne, Nelson and Hodget, 1997) and if there would not have been a control eye to adjust with, this may have had an influence in the results.

This is the first study reporting on the effect of ALPI on the endothelium parameters mentioned earlier. There has been only been one report by Sun, et al. (2010) were the endothelial cell density seemed to remaine unchanged 1 year after the procedure. As in the case of the LPI, the changes on these parameters were of little clinical significance.

There are some limitations to this study. In the case of the results showed for the effect of the LPI and ALPI on opening the angle, only the first 6 months and 3 months after the procedure were under study respectively. Therefore, the association found between the angle opening rate and time and between the same rate and IOP levels would only be valid for these periods of time.

Additionally, the images obtained with the CASIA OCT were only those taken in dark conditions. The aim was to emulate similar lighting conditions to those in which IOP is taken.

It has to be addressed that in the statistical analysis use to assess the effect of the ALPI on the treated angle and the association between such effect and time and IOP, there was a lacking of some of the control eye data. It was, therefore, not possible to provide the same precision as when investigating similar effects in the case of the LPI.

The same examiner (LSP) took all the IOP measurements for this group of participants throughout the study. The only limitation derived from these measurements is the fact that the examiner recorded the measurements as they were taken, meaning the examiner was not masked to the IOP result.

It needs to be also mentioned that the examiner analysing the images with the CASIA OCT (LSP) was not masked to the gonioscopical results after LPI treatment. However, possible bias was minimised, as the scans were analysed visit by visit (i.e. 160 scans in Visit 1 After completion, 80 scans in Visit 3. After completion, 80 scans in Visit 4 and so on).

Intraobserver repeatability for the CASIA OCT has been described in this thesis, showing better results than the ones previously described in the literature for the same device and measurements (Appendix 3). Some limitations as natural ocular cyclotorsion have been observed with the CASIA OCT. Although, this cannot be acknowledged as a limitation of this device but as an advantage for being able to be detected, it means that there has been a limited precision when taken the angle measurements. Therefore, the examiner cannot be absolutely certain that the measurements have been taken in the exact same section of the angle at the different visits. It is surprising that this limitation has not been described previously. With the new technologies designed for iris tracking and recognition so commonly used in refractive surgery, this should be an enhancement to be included in the future software of the CASIA OCT.

Regarding the specular microscopy, the benefits and limitations have been described in this thesis (Appendix 3). The main limitation of this device, as with any other specular microscope, is to not be absolutely certain that the same area of cornea is being tested (because of the same reasons specified in the paragraph above). The area of testing is limited to the peripheral 3mm from corneal apex, which might be considered to still be too close to corneal apex.

It is still unclear the reason why the DIOP fluctuation in the present sample of treated eyes is higher than those described in the literature. Although the most previous literature is based in Asian ethnicities, it was not possible to explain these differences based on ethnical ocular

differences. There may still be other factors influencing DIOP fluctuation such as age in combination with ethnicity. It is down to future research to further explore this assumption.

It will be interesting in future research to follow these same individuals and corroborate the present findings of a possible association between rate of opening with time and IOP level after the LPI. It would also be interesting to mimic the present study in other ethnicities with PAC/PACS. If statistically significant results are to be found, the rate of opening of the iridotrabecular angle may be predicted with regression models.

However, there is still the problem of not being able to exactly know how 'numerically' open/wide an angle has to be when assessed with the anterior segment OCT to be diagnosed as non occludable by gonioscopy. There have been attempts in the literature to describe a numerical 'cut-off' for occludable/ non-occludable angle while keeping good rates of sensitivity and specificity of the devices. Hong, et al. (2009) described a cut-off for the occludable and unoccludable angles based on the anterior chamber depth and angle. It was shown that the cut-off found with Pentacam for the anterior chamber depth was of 2.27 mm and for the anterior chamber angle 29.5 degrees. They additionally found that the cut-off value for the anterior chamber depth and angle as assessed by the Slit-Lamp OCT was of 2.45 mm and 31.8 degrees respectively.

Therefore, it is possible to find cut-off values to distinguish occludable from non- occludable angles. It is true that the study by Hong, et al. (2007) was only based in the horizontal sections findings (Nasal and Temporal); nevertheless, it is a good starting point. It is possible for future research to use the data that is already available in the present study to allow a correlation between these parameters dimensions and gonioscopy. The gonioscopy performed in this study exactly specifies the structures that were visible at every quadrant and this would enable an examiner to 'match' the dimensions found with the CASIA OCT.

The CASIA OCT has shown a sensitivity of 94.3% (95% CI: 86.2%-97.7%) in diagnosing occludable angles when compared to gonioscopy in dark conditions. This is higher than the sensitivity described by Nolan, et al. (2007) for a two dimensional OCT and higher than the rates described by Hong, et al. (2009) for both, the Pentacam and the Slit-Lamp Anterior Segment OCT. Specificity of diagnosis was not attempted as the entire sample presented occludable angles diagnosed with gonioscopy. Although gonioscopy remains the gold standard, and the specificity of detection of gonioscopically occludable angles by CASIA OCT remains unstudied, this swept source technology

may constitute a step forward towards this goal. A mixed sample of unoccludable and occludable eyes would need to be assessed to understand the specificity of the CASIA OCT.

Although this research was comprehensive in assessing changes in the angle parameters due to LPI and ALPI, there may still be areas to improve in further studies. There are few limitations in the quantifying techniques used in the present study. Only 8 sections of the angle were quantified and 352 other sections remain unexplored. It has been difficult to visually show how the different sections of the angle open at a different rate. This may not be a problem with a three-dimensional (3D) software developed for quantification of changes. The Swept-Source OCT (CASIA OCT) used in this study can build 3D images, but it cannot yet compare dimensions between two 3D images. This would be a great advantage in the study of changes through time due to natural progression of angle closure or to quantify the effect of different surgical/laser procedures. All the information could be build using topographic software similar to that employed to describe the corneal surface.

It would be of interest for a future study to find factors that may predict those angles that do not open after the LPI. As an exploratory first step, the angle parameters found at Visit 1 for those eyes that were unoccludable post-LPI were compared against the ones that ended unoccludable. Those parameters found in the eyes diagnosed as occudable were statistically significantly narrower than those found in the unoccludable eyes at Visit 1. Aside from this finding that narrower pre-laser PI angles are more likely to remain occludable, the influence of other factors such as iris contour and ciliary body position need further investigation. From a clinical perspective it would be useful to define a cut-off in terms of angle dimensions that relates to probability of the finding of a gonioscopically occludable angle post-PI.

The new software for the CASIA OCT permits iris volume to be calculated. The relationship between iris volume and angle parameters is the subject of further research work undertaken by the study team.

The present study constitutes the first part of a longer follow up study that will follow this cohort of narrow angle patients for the next two years of its finalisation. This continuation (Investigating Management of Primary Angle Closure and Treatment study, IMPACT study) aims to assess longer-term effects of the LPI and ALPI in a similar manner as it has been described in this thesis.

Summary of clinical implications of this thesis results

It has already been pointed out the importance of the IOP in glaucoma progression. Higher levels of office IOP are related with progression and onset of the pathology. In this thesis, it has been shown, not only that patients with peripheral anterior synechiae are more likely to have higher levels of diurnal IOP, but that this group of angle closure patients have higher levels of diurnal IOP diuring the mornings than during the afternoons. Therefore, it is recommended that clinicians, who have the choice of assessing these patients either in the morning or afternoon, will do it in the mornings.

The CASIA is a useful diagnostic tool for angle closure. Clinicians should be aware that if a more similar diagnosis as with gonioscopy is to be achieved they should assess only the 4 main angle sections of the iridotracbecular angle with the CASIA OCT (Superior, Inferior, Nasal and Temporal).

It has also been shown that ALPI is an effective method of opening the angle when it remains occludable after LPI. This was the case when the angle was assessed in all treated eyes with both gonioscopy and CASIA OCT. After these results, this method is strongly recommended.

Regarding corneal endothelium, both lasers, LPI and ALPI have revealed themselves as safe. No corneal disturbances were observed at any point of the follow up. Should these patients need another invasive procedure, such as cataract surgery, shortly after these lasers, the risk of corneal decompensation would be as before the lasers were performed.

Future research recommedations

Following the results found in this theis regarding the diurnal IOP trend followed by eyes presenting PAC or PACS it is recommended that these patients are seen in the mornings if their diurnal peaks are to be observed. Additionally, it is important to remark on the DIOP fluctuation present in these eyes. If future research regards the study of change of IOP through time, it is essential that the follow up measurements are performed as close in time to baseline as possible.

The usefulness of adjusting IOP and/or biometric findings in the treated eye for those of the fellow untreated eye has been demonstrated. By doing this, we were able to report that the widening of the anterior chamber angle following the LPI was not as large as one would have found were only the pre- and post-laser measurements of the treated eye to have been measured.

Therefore, the use of the untreated eye to show changes in the treated eye either with time or due to a procedure is recommended.

If a future study involves the investigation of the angle dimensions in relation to other factors (i.e., IOP), it is recommended to analyse at least the 4 main angular sections of the angle (Superior, Nasal, Temporal and Inferior). As shown in this thesis, there are dimensional differences between them both with and without laser procedures (LPI and ALPI) changes in light conditions.

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Appendix 1. Tables

ANOVA	AOD 500 Light							
	S	S-N	N	I-N	I	I-T	T	S-T
Superior	--------	0.0289 p>0.05	0.0994* p<0.001	0.0865* p<0.001	0.415* p=0.021	0.0808* p<0.001	0.0710* p<0.001	0.0185 p>0.05
Nasal	0.0994* p<0.001	0.0704* p<0.001	---------	0.0129 p>0.05	0.0578* p<0.001	0.0185 p>0.05	0.0283 p>0.05	0.0808* p<0.001
	AOD 500 Dark							
Superior	----------	0.0285 p>0.05	0.0897* p<0.001	0.0862* p<0.001	0.0368* p=0.045	0.0686* p<0.001	0.0500* p=0.001	0.0109 p>0.05
Nasal	0.0897* p<0.001	0.0611* p<0.001	----------	0.0035 p>0.05	0.0529* p<0.001	0.0211 p>0.05	0.0397* p=0.020	0.0788* p<0.001

Table 3.4. Differences between the widest angle sector dimension and the rest of the sections and between the narrowest and the rest of the sections for AOD 500 light and dark. S=Superior, S-N= Superior-Nasal, N=Nasal, I-N= Inferior-Nasal, I=Inferior, I-T=Inferior-Temporal, T=Temporal, S-T=Superior-Temporal. The statistically significant values have been flagged with an asterisk.

ANOVA	AOD 750 Light							
	S	S-N	N	I-N	I	I-T	T	S-T
Superior	----------	0.0446 p>0.05	0.1172* p<0.001	0.1253* p<0.001	0.0670* p=0.001	0.1136* p<0.001	0.0926* p<0.001	0.0311 p>0.05
Inf-Nasal	0.1253* p<0.001	0.0807* p<0.001	0.0081 p>0.05	----------	0.0583* p=0.009	0.0117 p>0.05	0.0327 p>0.05	0.0942* p<0.001
	AOD 750 Dark							
Superior	---------	0.0336 p>0.05	0.1089* p<0.001	0.1197* p<0.001	0.0611* p=0.03	0.1037* p<0.001	0.07298* p<0.001	0.0182 p>0.05
Inf-Nasal	0.1197* p<0.001	0.0860* p<0.001	0.0107 p>0.05	---------	0.0585* p=0.06	0.0159 p>0.05	0.0467 p>0.05	0.1014* p<0.001

Table 3.5. Differences between the widest angle sector dimension and the rest of the sections and between the narrowest and the rest of the sections for AOD 750 light and dark. S=Superior, S-N= Superior-Nasal, N=Nasal, I-N= Inferior-Nasal, I=Inferior, I-T=Inferior-Temporal, T=Temporal, S-T=Superior-Temporal. The statistically significant values have been flagged with an asterisk.

ANOVA	ARA 500 Light							
	S	S-N	N	I-N	I	I-T	T	S-T
Superior	----------	0.0196* p=0.021	0.0498* p<0.001	0.0424* p<0.001	0.0103 p>0.05	0.0424* p<0.001	0.0398* p<0.001	0.0101 p>0.05
Nasal	0.0498* p<0.001	0.0301* p<0.001	----------	0.0073 p>0.05	0.0394* p<0.001	0.0073 p>0.05	0.0099 p>0.05	0.0397 p<0.001
	ARA 500 Dark							
Superior	----------	0.0193* p=0.008	0.0481* p<0.001	0.0409* p<0.001	0.0850 p>0.05	0.0372* p<0.001	0.0340* p<0.001	0.0077 p>0.05
Nasal	0.0481* p<0.001	0.2874* p<0.001	----------	0.0071 p>0.05	0.0396* p<0.001	0.0108 p>0.05	0.0140 p>0.05	0.0403* p<0.001

Table 3.6. Differences between the widest angle sector dimension and the rest of the sections and between the narrowest and the rest of the sections for ARA 500 light and dark. S=Superior, S-N= Superior-Nasal, N=Nasal, I-N= Inferior-Nasal, I=Inferior, I-T=Inferior-Temporal, T=Temporal, S-T=Superior-Temporal. The statistically significant values have been flagged with an asterisk.

ANOVA	ARA 750 Light							
	S	S-N	N	I-N	I	I-T	T	S-T
Superior	----------	0.0286* p=0.029	0.0775* p<0.001	0.0710* p<0.001	0.0236 p>0.05	0.0683* p<0.001	0.0612* p<0.001	0.0165 p>0.05
Nasal	0.0775* p<0.001	0.0489* p<0.001	---------	0.0065 p>0.05	0.0539* p<0.001	0.0092 p>0.05	0.0163 p>0.05	0.0610* p<0.001
				ARA 750 Dark				
Superior	----------	0.0306* p=0.04	0.0773* p<0.001	0.0706* p<0.001	0.0223 p>0.05	0.0625* p<0.001	0.0525* p<0.001	0.0141 p>0.05
Nasal	0.0773* p<0.001	0.0467* p<0.001	----------	0.0067 p>0.05	0.0550* p<0.001	0.0148 p>0.05	0.0248* p=0.044	0.0632* p<0.001

Table 3.7. Differences between the widest angle sector dimension and the rest of the sections and between the narrowest and the rest of the sections for ARA 750 light and dark. S=Superior, S-N= Superior-Nasal, N=Nasal, I-N= Inferior-Nasal, I=Inferior, I-T=Inferior-Temporal, T=Temporal, S-T=Superior-Temporal. The statistically significant values have been flagged with an asterisk.

ANOVA	TISA 500 Light							
	S	S-N	N	I-N	I	I-T	T	S-T
Superior	----------	0.0177 p>0.05	0.0426* p<0.001	0.0384* p<0.001	0.0087 p>0.05	0.0383* p<0.001	0.0428* p<0.001	0.0181 p>0.05
Temporal	0.0428* p<0.001	0.2507* p=0.034	0.0002 p>0.05	0.0043 p>0.05	0.0340* p=0.001	0.0044 p>0.05	----------	0.0246* p=0.04
				TISA 500 Dark				
Superior	----------	0.0175* p=0.010	0.0420* p<0.001	0.0380* p<0.001	0.0078 p>0.05	0.0351* p<0.001	0.0310* p<0.001	0.0076 p>0.05
Nasal	0.0420* p<0.001	0.0245* p<0.001	--------	0.0040 p>0.05	0.0342* p<0.001	0.0069 p>0.05	0.0110 p>0.05	0.0344* p<0.001

Table 3.8. Differences between the widest angle sector dimension and the rest of the sections and between the narrowest and the rest of the sections for TISA 500 light and dark. S=Superior, S-N= Superior-Nasal, N=Nasal, I-N= Inferior-Nasal, I=Inferior, I-T=Inferior-Temporal, T=Temporal, S-T=Superior-Temporal. The statistically significant values have been flagged with an asterisk.

ANOVA	TISA 750 Light							
	S	S-N	N	I-N	I	I-T	T	S-T
Superior	----------	0.0374* p=0.005	0.0699* p<0.001	0.0672* p<0.001	0.0220 p>0.05	0.0661* p<0.001	0.0577* p<0.001	0.0158 p>0.05
Nasal	0.0699* p<0.001	0.0325* p=0.024	---------	0.0027 p>0.05	0.0478* p<0.001	0.0038 p>0.05	0.0122 p>0.05	0.0541* p<0.001
				TISA 750 Dark				
Superior	---------	0.0288* p=0.05	0.0713* p<0.001	0.0675* p<0.001	0.0217 p>0.05	0.0615* p<0.001	0.0497* p<0.001	0.0140 p>0.05
Nasal	0.0713* p<0.001	0.0424 p<0.001	---------	0.0038 p>0.05	0.0496* p<0.001	0.0098 p>0.05	0.0216 p>0.05	0.0573* p<0.001

Table 3.9. Differences between the widest angle sector dimension and the rest of the sections and between the narrowest and the rest of the sections for TISA 750 light and dark. S=Superior, S-N= Superior-Nasal, N=Nasal, I-N= Inferior-Nasal, I=Inferior, I-T=Inferior-Temporal, T=Temporal, S-T=Superior-Temporal. The statistically significant values have been flagged with an asterisk.

ANOVA				TIA 500 Light				
	S	S-N	N	I-N	I	I-T	T	S-T
Superior	----------	3.2616	9.4231*	8.4002*	2.8002	8.0574*	7.4531*	2.4016
		p>0.05	p<0.001	p<0.001	p>0.05	p<0.001	p<0.001	p>0.05
Nasal	9.4231*	6.1614*	--------	1.0228	6.6228*	1.3657	1.9700	7.021*
	p<0.001	p<0.001		p>0.05	p<0.001	p>0.05	p>0.05	p<0.001
				TIA 500 Dark				
Superior	----------	3.1558	8.0944*	7.8562*	2.0515	6.8415*	5.2230*	1.7872
		p>0.05	p<0.001	p<0.001	p>0.05	p<0.001	p<0.001	p>0.05
Nasal	8.0944*	4.9385*	----------	0.23814	6.0428*	1.2528	2.8714	6.3071*
	p<0.001	p<0.001		p>0.05	p<0.001	p>0.05	p>0.05	p<0.001

Table 3.10. Differences between the widest angle sector dimension and the rest of the sections and between the narrowest and the rest of the sections for TIA 500 light and dark. S=Superior, S-N= Superior-Nasal, N=Nasal, I-N= Inferior-Nasal, I=Inferior, I-T=Inferior-Temporal, T=Temporal, S-T=Superior-Temporal. The statistically significant values have been flagged with an asterisk.

ANOVA				TIA 750 Light				
	S	S-N	N	I-N	I	I-T	T	S-T
Superior	----------	3.5176*	8.1862*	8.7662*	3.5962*	7.9219*	6.9433*	2.8547
		p=0.012	p<0.001	p<0.001	p=0.009	p<0.001	p<0.001	p>0.05
Inf-Nasal	8.7662*	5.2485*	0.5800	----------	5.170*	0.8442	1.8228	5.9114*
	p<0.001	p<0.001	p>0.05		p<0.001	p>0.05	p>0.05	p<0.001
				TIA 750 Dark				
Superior	----------	2.7516	7.1259*	47.8916*	2.9859*	7.4802*	5.4673*	2.001
		p>0.05	p<0.001	p<0.001	p=0.041	p<0.001	p<0.001	p>0.05
Inf-Nasal	7.8916*	5.1400*	0.7657	----------	4.9057*	0.4114	2.4242	5.8900*
	p<0.001	p<0.001	p>0.05		p<0.001	p>0.05	p>0.05	p<0.001

Table 3.11. Differences between the widest angle sector dimension and the rest of the sections and between the narrowest and the rest of the sections for TIA 750 light and dark. S=Superior, S-N= Superior-Nasal, N=Nasal, I-N= Inferior-Nasal, I=Inferior, I-T=Inferior-Temporal, T=Temporal, S-T=Superior-Temporal. The statistically significant values have been flagged with an asterisk.

ANOVA	Superior Sector		Nasal Sector		Inferior Sector		Temporal Sector	
	Superior-Temp Sector	Superior-Nasal Sector	Superior-Nasal Sector	Inferior-Nasal Sector	Inferior-Nasal Sector	Inferior-Temp Sector	Inferior-Temp Sector	Superior-Temp Sector
AOD 500 (light)	0.018570 p>0.05	0.028998 p>0.05	0.070429* p<0.001	0.012914 p>0.05	0.044929* p=0.007	0.039306* p=0.032	0.009849 p>0.05	0.052471* p<0.001
AOD 750 (light)	0.031104 p>0.05	0.044618 p>0.05	0.072614* p<0.001	0.008143 p>0.05	0.058343* p=0.009	0.046643 p>0.05	0.021043 p>0.05	0.061529* p<0.05
ARA 500 (light)	0.010135 p>0.05	0.019677* p=0.021	0.030157* p<0.001	0.039700* p<0.001	0.032100* p<0.001	0.032129* p<0.001	0.002586 p>0.05	0.029757* p<0.001
ARA 750 (light)	0.016529 p>0.05	0.028615* p=0.029	0.048957* p<0.001	0.006571 p>0.05	0.047386* p>0.05	0.044729* p>0.05	0.007143 p>0.05	0.044671* p<0.001
TISA 500 (light)	0.018175 p>0.05	0.017732 p>0.05	0.024871 p>0.05	0.004186 p>0.05	0.029647* p=0.005	0.029604* p=0.005	0.004429 p>0.05	0.024629 p>0.05
TISA 750 (light)	0.015879 p>0.05	0.037451* p=0.05	0.032529* p=0.012	0.002771 p>0.05	0.045114* p<0.001	0.044071* p<0.001	0.008429 p>0.05	0.041857* p<0.05
TIA 500 (light)	2.401688 p>0.05	3.261688 p>0.05	6.161429* p<0.001	1.022857 p>0.05	5.600000* p<0.001	5.257143* P<0.001	0.604286 p>0.05	5.051429* p<0.001
TIA 750 (light)	2.854790 p>0.05	3.517647* p>0.05	4.668571* p<0.001	0.580000 p>0.05	5.170000* p<0.001	4.325714* p<0.001	0.978571 p>0.05	4.088571* p<0.05
AOD 500 (dark)	0.010945 p>0.05	0.028588 p>0.05	0.061171* p<0.001	0.003529 p>0.05	0.049429* p=0.001	0.031800 p>0.05	0.018557 p>0.05	0.039100* p<0.001
AOD 750 (dark)	0.018253 p>0.05	0.033667 p>0.05	0.075286* p<0.001	0.010757 p>0.05	0.058543* p=0.006	0.042586 p>0.05	0.030771 p>0.05	0.054729* p<0.05
ARA 500 (dark)	0.007748 p>0.05	0.019390* p=0.008	0.028743* p<0.001	0.007186 p>0.05	0.032443* p<0.001	0.028786* p<0.001	0.003243 p>0.05	0.026300* p<0.001
ARA 750 (dark)	0.014139 p>0.05	0.030611* p=0.004	0.046743* p<0.001	0.006714 p>0.05	0.048300* p<0.001	0.040214* p<0.001	0.010029 p>0.05	0.038386* p<0.001
TISA 500 (dark)	0.007661 p>0.05	0.017547* p=0.010	0.024543* p<0.001	0.004043 p>0.05	0.030171* p<0.001	0.027286* p<0.001	0.004071 p>0.05	0.023429* p<0.001
TISA 750 (dark)	0.014027 p>0.05	0.028899* p=0.05	0.042486* p<0.001	0.003829 p>0.05	0.045829* p<0.001	0.039857* p<0.001	0.011871 p>0.05	0.035686* p<0.001
TIA 500 (dark)	1.787288 p>0.05	3.155859 p>0.05	4.938571* p<0.001	0.238143 p>0.05	5.804714* p<0.001	4.790000* p<0.001	1.618571 p>0.05	3.435714 p>0.05
TIA 750 (dark)	2.001681 p>0.05	2.751681 p>0.05	4.374286* p<0.001	0.765714 p>0.05	4.905714* p<0.001	4.494286* p<0.001	2.012857 p>0.05	3.465714* p<0.05

Table 3.12. Comparison between the 4 main sectors (Superior, Nasal, Inferior and Temporal) against their adjacent sectors in light and dark conditions

Differences between Light and Dark in the parameters dimensions (Light dimensions- Dark dimensions)

	Superior		Superior-Nasal		Nasal		Inferior-Nasal		Inferior		Inferior-Temp		Temporal		Superior-Temporal	
	Mean difference (SD)	Significance t test	Mean difference (SD)	Significance t test	Mean difference (SD)	Significance t test	Mean difference (SD)	Significance t test	Mean difference (SD)	Significance t test	Mean difference (SD)	Significance t test	Mean difference (SD)	Significance t test	Mean difference (SD)	Significance t test
AOD 500 (mm)	0.002585 (0.046936)	0.659	0.005114 (0.047846)	0.374	0.014371 (0.044436)	0.009*	0.004986 (0.52716)	0.431	0.009486 (0.062432)	0.208	0.016991 (0.056542)	0.014*	0.025700 (0.042994)	<0.001*	0.012329 (0.037464)	0.008*
AOD 750 (mm)	0.007485 (0.054462)	0.268	0.019157 (0.058623)	0.008*	0.016486 (4.383827)	0.035*	0.013871 (0.077567)	0.139	0.014071 (0.070431)	0.099	0.018129 (0.072053)	0.039*	0.027857 (0.057561)	<0.001*	0.021057 (0.061029)	0.005*
ARA 500 (mm^2)	0.001308 (0.014278)	0.463	0.03014 (0.019289)	0.195	0.004429 (0.023321)	0.117	0.004229 (0.23614)	0.139	0.004571 (0.028795)	0.188	0.007914 (0.026028)	0.013*	0.008571 (0.019719)	0.001*	0.005114 (0.014983)	0.006*
ARA 750 (mm^2)	0.005000 (0.026847)	0.135	0.004871 (0.026558)	0.129	0.007086 (0.031369)	0.063	0.007229 (0.033568)	0.076	0.008143 (0.039547)	0.089	0.012657 (0.037801)	0.039*	0.015543 (0.029533)	<0.001*	0.009257 (0.023720)	0.002*
TISA 500 (mm^2)	0.001797 (0.013427)	0.288	0.03429 (0.017213)	0.100	0.003757 (0.020604)	0.132	0.003614 (0.019816)	0.132	0.003855 (0.023276)	0.173	0.006457 (0.023328)	0.024*	0.014957 (0.055502)	0.027*	0.013757 (0.076874)	0.139
TISA 750 (mm^2)	0.005303 (0.026251)	0.106	0.015729 (0.096335)	0.176	0.005771 (0.030083)	0.113	0.006829 (0.031066)	0.070	0.007543 (0.034421)	0.071	0.011757 (0.036222)	0.008*	0.015200 (0.027062)	<0.001*	0.009029 (0.023035)	0.002*
TIA 500 (°)	0.143077 (3.886755)	0.768	0.411429 (4.570211)	0.454	1.634286 (4.383827)	0.003*	0.849571 (4.845169)	0.147	1.054286 (3.81107)	0.024	1.521429 (4.900928)	0.011*	2.535714 (4.106165)	<0.001*	0.920000 (3.673785)	0.040*
TIA 750 (°)	0.266667 (3.021784)	0.476	1.107143 (3.941026)	0.022*	1.401429 (4.017840)	0.005*	1.215714 (4.886202)	0.041*	0.951429 (3.629179)	0.032	0.782857 (4.265431)	0.129	1.817143 (3.547646)	<0.001*	1.194286 (3.903172)	0.013*

Table 3.13. Differences between light and dark for the angle parameters dimensions in the different 8 sections.

AOD500	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.304	0.076	0.018*	-0.112	0.101	0.094	-0.157	0.009	0.219	0.077	0.074	0.141
Superior-Nasal	-0.360	0.116	0.003*	-0.383			-0.300	0.076	0.016*	-0.291		
Nasal	-0.138	0.003	0.276	0.382			-0.092	-0.008	0.472	0.177		
Inferior-Nasal	-0.310	0.082	0.013*	-0.242			-0.352	0.110	0.004*	-0.318		
Inferior	-0.247	0.046	0.049*	-0.143			-0.217	0.032	0.085	-0.198		
Inferior-Temporal	-0.174	0.015	0.169	0.037			-0.123	-0.001	0.331	0.147		
Temporal	-0.295	0.072	0.018*	-0.127			-0.170	0.013	0.179	-0.024		
Superior-Temporal	-0.239	0.042	0.058	0.171			-0.200	0.025	0.113	0.044		

Table 3.17. Univariate and multivariate regression models over DIOP fluctuation for light and dark conditions with AOD 500 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

AOD750	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.328	0.093	0.009*	0.007	0.249	0.002*	-0.297	0.073	0.018*	-0.165	0.073	0.145
Superior-Nasal	-0.384	0.134	0.002*	-0.436			-0.353	0.111	0.004*	-0.469		
Nasal	-0.208	0.028	0.099	0.242			-0.120	-0.001	0.345	0.225		
Inferior-Nasal	-0.371	0.124	0.003*	-0.373			-0.298	0.074	0.017*	-0.074		
Inferior	-0.314	0.084	0.011*	-0.248			-0.236	0.041	0.060	-0.190		
Inferior-Temporal	-0.155	0.008	0.220	0.356			-0.177	0.016	0.161	0.079		
Temporal	-0.381	0.131	0.002*	-0.338			-0.194	0.022	0.125	0.082		
Superior-Temporal	-0.187	0.020	0.138	0.325			-0.237	0.041	0.060	0.142		

Table 3.18. Univariate and multivariate regression models over DIOP fluctuation for light and dark conditions with AOD 750 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

ARA500	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.254	0.048	0.050*	-0.027	0.131	0.052	-0.193	0.021	0.130	-0.054	0.097	0.091
Superior-Nasal	-0.429	0.171	<0.001*	-0.559			-0.318	0.086	0.011*	-0.327		
Nasal	-0.161	0.010	0.205	0.193			-0.028	-0.015	0.827	0.266		
Inferior-Nasal	-0.216	0.031	0.086	-0.102			-0.348	0.107	0.005*	-0.215		
Inferior	-0.172	0.014	0.174	-0.194			-0.210	0.029	0.096	-0.194		
Inferior-Temporal	0.030	-0.015	0.814	0.166			-0.173	0.014	0.172	0.023		
Temporal	-0.206	0.027	0.103	-0.003			-0.093	-0.007	0.463	-0.02		
Superior-Temporal	-0.182	0.018	0.149	0.146			-0.140	0.004	0.272	0.061		

Table 3.19. Univariate and multivariate regression models over DIOP fluctuation for light and dark conditions with ARA 500 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

ARA750	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.306	0.144	0.016*	-0.020	0.189	0.012*	-0.283	0.065	0.024*	-0.108	0.161	0.023*
Superior-Nasal	-0.438	0.179	<0.001*	-0.526			-0.389	0.138	0.001*	-0.580		
Nasal	-0.189	0.020	0.134	0.284			-0.062	-0.012	0.625	0.365		
Inferior-Nasal	-0.293	0.071	0.019*	-0.203			-0.341	0.102	0.006*	0.016		
Inferior	-0.212	0.030	0.092	-0.253			-0.221	0.034	0.079	-0.292		
Inferior-Temporal	-0.035	-0.015	0.784	0.236			-0.208	0.028	0.099	-0.009		
Temporal	-0.296	0.073	0.018	-0.113			-0.151	0.007	0.234	0.037		
Superior-Temporal	-0.212	0.029	0.093	0.127			-0.178	0.016	0.158	0.120		

Table 3.20. Univariate and multivariate regression models over DIOP fluctuation for light and dark conditions with ARA 750 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

TISA500	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.265	0.054	0.043*	-0.195	0.164	0.029*	-0.184	0.018	0.149	-0.062	0.093	0.098
Superior-Nasal	-0.408	0.153	0.001*	-0.419			-0.325	0.091	0.009*	-0.337		
Nasal	-0.138	0.003	0.270	0.288			-0.038	-0.015	0.766	0.253		
Inferior-Nasal	-0.251	0.048	0.045*	-0.142			-0.349	0.108	0.005*	-0.22		
Inferior	-0.158	0.009	0.215	-0.124			-0.2O1	0.025	0.112	-0.176		
Inferior-Temporal	0.024	-0.016	0.848	0.12			-0.146	0.005	0.251	0.067		
Temporal	0.189	0.020	0.135	-0.092			-0.125	0.000	0.326	-0.057		
Superior-Temporal	0.050	0.018	0.149	0.33			-0.138	0.003	0.277	0.086		

Table 3.21. Univariate and multivariate regression models over DIOP fluctuation for light and dark conditions with TISA 500 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

TISA750	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.335	0.097	0.008*	-0.039	0.253	0.002*	-0.295	0.072	0.018*	-0.197	0.100	0.086
Superior-Nasal	-0.354	0.111	0.004*	-0.407			-0.393	0.141	0.001*	-0.571		
Nasal	-0.195	0.022	0.123	0.389			-0.073	-0.011	0.566	0.189		
Inferior-Nasal	-0.314	0.084	0.011*	-0.422			-0.345	0.105	0.005*	-0.056		
Inferior	-0.267	0.056	0.033*	-0.179			-0.283	0.065	0.023*	-0.180		
Inferior-Temporal	-0.056	0.013	0.662	0.178			-0.173	0.014	0.172	0.201		
Temporal	-0.291	0.070	0.020*	-0.259			-0.174	0.015	0.168	-0.083		
Superior-Temporal	-0.206	0.027	0.102	0.047			-0.177	0.016	0.162	0.032		

Table 3.22. Univariate and multivariate regression models over DIOP fluctuation for light and dark conditions with TISA 750 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

TIA500	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.313	0.084	0.012*	-0.188	0.185	0.012*	-0.236	0.040	0.061	-0.076	0.079	0.126
Superior-Nasal	-0.360	0.115	0.004*	-0.326			-0.314	0.084	0.012*	-0.281		
Nasal	-0.032	-0.015	0.801	0.471			-0.129	0.001	0.308	0.088		
Inferior-Nasal	-0.321	0.088	0.010*	-0.256			-0.348	0.107	0.005*	-0.178		
Inferior	-0.317	0.086	0.011*	-0.282			-0.252	0.049	0.044*	-0.201		
Inferior-Temporal	-0.149	0.007	0.239	0.108			-0.075	-0.010	0.558	0.245		
Temporal	-0.262	0.054	0.037*	-0.200			-0.196	0.023	0.120	-0.070		
Superior-Temporal	-0.229	0.037	0.069	0.158			-0.204	0.026	0.106	0.037		

Table 3.23. Univariate and multivariate regression models over DIOP fluctuation for light and dark conditions with TIA 500 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

TIA750	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.335	0.097	0.008*	-0.039	0.253	0.002*	-0.302	0.076	0.015	-0.008	0.173	0.016*
Superior-Nasal	-0.405	0.151	0.001*	-0.407			-0.371	0.124	0.003*	-0.569		
Nasal	-0.121	-0.01	0.340	0.389			-0.177	0.016	0.161	0.362		
Inferior-Nasal	-0.363	0.118	0.003*	-0.422			-0.312	0.083	0.012*	0.025		
Inferior	-0.267	0.056	0.033*	-0.179			-0.190	0.020	0.134	-0.331		
Inferior-Temporal	-0.169	0.013	0.182	0.178			-0.152	0.007	0.231	0.089		
Temporal	-0.365	0.120	0.003*	-0.259			-0.221	0.034	0.079	-0.083		
Superior-Temporal	-0.188	0.020	0.137	0.260			-0.239	0.042	0.057	0.032		

Table 3.24. Univariate and multivariate regression models over DIOP fluctuation for light and dark conditions with TIA 750 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

AOD500	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.019	-0.016	0.879	0.040	0.086	0.108	-0.068	-0.011	0.583	0.160	-0.026	0.611
Superior-Nasal	-0.151	0.008	0.219	-0.041			0.048	-0.013	0.699	-0.028		
Nasal	-0.103	-0.004	0.402	0.202			-0.018	-0.015	0.884	0.041		
Inferior-Nasal	-0.071	-0.010	0.566	0.131			-0.013	-0.015	0.917	-0.110		
Inferior	-0.367	0.121	0.002*	-0.383			-0.232	-0.040	0.057	-0.312		
Inferior-Temporal	-0.135	0.003	0.271	0.049			0.026	-0.014	0.834	0.104		
Temporal	-0.296	0.074	0.014*	-0.353			-0.016	-0.015	0.895	-0.058		
Superior-Temporal	-0.137	0.004	0.264	0.045			0.071	-0.010	0.567	0.103		

Table 3.25. Univariate and multivariate regression models over Dark room provocation test result (DRPT) for light and dark conditions with AOD 500 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

AOD750	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.100	0.005	0.424	0.235	0.124	0.045*	-0.032	0.015	0.797	0.046	-0.016	0.546
Superior-Nasal	-0.177	0.017	0.149	-0.112			-0.046	-0.013	0.712	-0.045		
Nasal	-0.241	0.044	0.048*	-0.174			-0.152	0.008	0.215	-0.17		
Inferior-Nasal	-0.100	-0.005	0.418	0.225			-0.101	-0.005	0.412	-0.107		
Inferior	-0.382	0.133	0.001*	-0.449			-0.230	0.039	0.059	-0.326		
Inferior-Temporal	-0.248	0.047	0.041*	-0.018			-0.052	-0.012	0.673	0.138		
Temporal	-0.204	0.027	0.095	-0.193			-0.150	0.008	0.222	0.058		
Superior-Temporal	-0.094	-0.006	0.444	0.171			0.022	-0.015	0.861	0.273		

Table 3.26. Univariate and multivariate regression models over Dark room provocation test result (DRPT) for light and dark conditions with AOD 750 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

ARA500	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.013	-0.016	0.920	0.075	0.158	0.023*	0.138	0.004	0.266	0.271	0.042	0.234
Superior-Nasal	-0.151	0.008	0.218	-0.199			0.014	-0.015	0.912	-0.065		
Nasal	-0.167	0.013	0.173	0.124			-0.117	-0.001	0.341	-0.076		
Inferior-Nasal	-0.070	-0.010	0.571	0.147			-0.011	-0.015	0.932	0.006		
Inferior	-0.411	0.156	0.001*	-0.322			-0.187	-0.020	0.126	-0.270		
Inferior-Temporal	-0.141	0.005	0.250	-0.087			-0.069	-0.010	0.574	0.046		
Temporal	-0.307	0.081	0.011*	-0.374			-0.218	0.033	0.074	-0.221		
Superior-Temporal	-0.056	-0.012	0.651	0.233			0.109	-0.003	0.375	0.145		

Table 3.27. Univariate and multivariate regression models over Dark room provocation test result (DRPT) for light and dark conditions with ARA 500 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

ARA750	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.062	-0.012	0.621	0.162	0.161	0.019*	0.025	-0.015	0.841	0.132	0.062	0.166
Superior-Nasal	-0.185	0.020	0.130	-0.280			-0.038	-0.014	0.760	-0.301		
Nasal	-0.180	0.018	0.142	0.211			-0.134	0.003	0.278	-0.030		
Inferior-Nasal	-0.084	-0.008	0.498	0.126			-0.024	-0.015	0.844	0.176		
Inferior	-0.431	0.174	<0.001*	-0.424			-0.114	-0.002	0.355	-0.344		
Inferior-Temporal	-0.190	0.022	0.121	0.019			-0.041	-0.013	0.738	0.094		
Temporal	-0.322	0.090	0.007*	-0.331			-0.225	0.036	0.065	-0.175		
Superior-Temporal	-0.112	-0.002	0.363	0.108			0.108	-0.003	0.380	0.242		

Table 3.28. Univariate and multivariate regression models over Dark room provocation test result (DRPT) for light and dark conditions with ARA 750 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

TISA500	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.035	-0.014	0.774	0.096	0.023	0.315	-0.132	0.003	0.283	0.217	0.012	0.374
Superior-Nasal	-0.145	0.006	0.238	-0.111			0.033	-0.014	0.792	-0.029		
Nasal	-0.169	0.014	0.169	0.115			-0.086	-0.008	0.487	-0.060		
Inferior-Nasal	-0.068	-0.011	0.584	0.153			-0.008	-0.015	0.950	-0.006		
Inferior	-0.253	0.050	0.037*	-0.336			-0.081	-0.008	0.511	-0.260		
Inferior-Temporal	-0.141	0.005	0.251	-0.022			-0.044	-0.013	0.723	0.060		
Temporal	-0.283	0.066	0.019*	-0.330			-0.191	0.022	0.119	-0.219		
Superior-Temporal	0.021	-0.015	0.864	0.131			0.106	-0.004	0.388	0.145		

Table 3.29. Univariate and multivariate regression models over Dark room provocation test result (DRPT) for light and dark conditions with TISA 500 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

TISA750	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.146	0.006	0.235	0.083	0.067	0.144	-0.176	0.016	0.152	0.122	0.002	0.435
Superior-Nasal	-0.269	0.058	0.026*	-0.232			-0.028	-0.014	0.823	-0.298		
Nasal	-0.184	0.019	0.133	0.038			-0.110	-0.003	0.370	-0.009		
Inferior-Nasal	-0.082	-0.008	0.504	0.145			-0.026	-0.014	0.830	0.174		
Inferior	-0.254	0.050	0.037	-0.420			-0.101	-0.005	0.412	-0.349		
Inferior-Temporal	-0.151	0.008	0.218	0.076			-0.046	-0.013	0.708	0.09		
Temporal	-0.307	0.080	0.011*	-0.232			-0.205	0.027	0.094	-0.17		
Superior-Temporal	-0.107	-0.003	0.384	0.034			0.102	-0.005	0.409	0.244		

Table 3.30. Univariate and multivariate regression models over Dark room provocation test result (DRPT) for light and dark conditions with TISA 750 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

TIA500	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.022	-0.015	0.897	0.038	0.099	0.085	0.077	-0.009	0.534	0.131	-0.039	0.700
Superior-Nasal	-0.152	0.008	0.217	-0.093			0.056	-0.012	0.652	-0.059		
Nasal	-0.093	-0.006	0.451	0.198			0.010	-0.015	0.936	0.127		
Inferior-Nasal	-0.078	-0.009	0.528	0.111			-0.030	-0.014	0.809	-0.103		
Inferior	-0.347	0.107	0.004*	-0.419			-0.221	0.035	0.070	-0.267		
Inferior-Temporal	-0.099	-0.005	0.422	0.094			0.030	-0.014	0.806	0.095		
Temporal	-0.300	0.077	0.013*	-0.341			-0.025	-0.015	0.838	-0.099		
Superior-Temporal	-0.125	0.001	0.310	0.072			0.085	-0.008	0.490	0.064		

Table 3.31. Univariate and multivariate regression models over Dark room provocation test result (DRPT) for light and dark conditions with TIA 500 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

TIA750	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.095	0.007	0.450	0.185	0.147	0.026*	-0.051	-0.013	0.686	0.062	-0.034	0.665
Superior-Nasal	-0.181	0.018	0.141	-0.171			-0.032	-0.014	0.793	0.074		
Nasal	-0.223	0.036	0.067	-0.170			-0.151	0.008	0.220	-0.194		
Inferior-Nasal	-0.112	-0.002	0.364	0.232			-0.118	-0.001	0.336	-0.124		
Inferior	-0.386	0.136	0.001*	-0.476			-0.231	0.039	0.058	-0.234		
Inferior-Temporal	-0.228	0.037	0.062	0.051			-0.072	-0.010	0.562	0.092		
Temporal	-0.227	0.037	0.062	-0.246			-0.163	0.012	0.184	-0.007		
Superior-Temporal	-0.087	-0.007	0.480	0.214			-0.001	-0.015	0.995	0.169		

Table 3.32. Univariate and multivariate regression models over Dark room provocation test result (DRPT) for light and dark conditions with TIA 750 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

AOD500	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.100	-0.006	0.431	-0.079	0.039	0.253	-0.029	-0.015	0.818	-0.008	-0.066	0.859
Superior-Nasal	-0.180	0.018	0.141	-0.184			-0.064	-0.011	0.606	-0.040		
Nasal	-0.019	-0.015	0.877	0.090			-0.064	-0.011	0.603	0.015		
Inferior-Nasal	0.089	-0.007	0.468	0.384			0.078	-0.009	0.528	0.257		
Inferior	-0.015	-0.006	0.959	0.181			-0.046	-0.013	0.712	-0.001		
Inferior-Temporal	-0.189	0.021	0.123	-0.295			-0.082	-0.008	0.507	-0.060		
Temporal	-0.081	-0.008	0.511	-0.104			-0.131	0.002	0.285	-0.194		
Superior-Temporal	-0.182	0.018	0.137	-0.135			-0.091	-0.007	0.460	-0.119		

Table 3.33. Univariate and multivariate regression models over the Supine Intraocular Pressure Test Result (SIOP) for light and dark conditions with AOD 500 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

AOD750	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.024	-0.015	0.847	-0.058	-0.074	0.890	0.050	-0.013	0.691	0.016	-0.008	0.498
Superior-Nasal	-0.076	-0.009	0.538	-0.100			-0.015	-0.015	0.901	0.003		
Nasal	-0.035	-0.014	0.774	0.003			-0.089	-0.007	0.470	-0.178		
Inferior-Nasal	0.040	-0.014	0.748	0.117			0.141	0.005	0.250	0.423		
Inferior	0.007	-0.015	0.952	0.034			0.083	-0.008	0.501	0.159		
Inferior-Temporal	-0.032	-0.014	0.796	-0.054			0.014	-0.015	0.911	-0.076		
Temporal	0.033	-0.014	0.789	0.295			-0.017	-0.015	0.892	-0.103		
Superior-Temporal	-0.114	-0.002	0.353	-0.250			-0.059	-0.012	0.630	-0.251		

Table 3.34. Univariate and multivariate regression models over the Supine Intraocular Pressure Test Result (SIOP) for light and dark conditions with AOD 750 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

ARA500	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.085	-0.009	0.506	0.069	-0.026	0.603	-0.080	-0.009	0.521	-0.150	-0.036	0.679
Superior-Nasal	-0.170	0.014	0.165	-0.268			-0.019	-0.015	0.881	0.094		
Nasal	0.037	-0.014	0.767	0.196			-0.026	-0.014	0.832	0.118		
Inferior-Nasal	0.027	-0.014	0.827	0.168			0.094	-0.006	0.448	0.201		
Inferior	-0.016	-0.015	0.898	0.026			-0.088	-0.007	0.473	-0.031		
Inferior-Temporal	-0.136	0.004	0.268	-0.137			-0.166	0.013	0.176	-0.252		
Temporal	-0.099	-0.005	0.422	-0.053			-0.158	0.010	0.198	-0.159		
Superior-Temporal	-0.201	0.026	0.099	-0.142			-0.083	-0.008	0.501	-0.001		

Table 3.35. Univariate and multivariate regression models over the Supine Intraocular Pressure Test Result (SIOP) for light and dark conditions with ARA 500 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

ARA750	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.082	-0.009	0.514	0.001	-0.010	0.510	-0.025	-0.015	0.841	0.132	0.062	0.166
Superior-Nasal	-0.143	0.006	0.244	-0.247			-0.011	-0.015	0.928	-0.301		
Nasal	-0.002	-0.015	0.989	0.186			-0.064	-0.011	0.605	-0.030		
Inferior-Nasal	0.043	-0.013	0.726	0.298			0.103	-0.004	0.403	0.176		
Inferior	-0.008	-0.015	0.951	0.122			-0.243	0.045	0.046*	-0.344		
Inferior-Temporal	-0.135	0.003	0.271	-0.214			-0.103	-0.004	0.402	0.094		
Temporal	-0.100	-0.005	0.418	-0.174			-0.135	0.003	0.274	-0.175		
Superior-Temporal	-0.170	0.014	0.166	-0.101			-0.112	-0.002	0.361	0.242		

Table 3.36. Univariate and multivariate regression models over The Supine Intraocular Pressure Test Result (SIOP) for light and dark conditions with ARA 750 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

TISA500	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.094	-0.007	0.465	0.034	-0.035	0.653	-0.067	-0.011	0.589	-0.126	-0.051	0.773
Superior-Nasal	-0.191	0.022	0.120	-0.294			-0.040	0.014	0.744	0.094		
Nasal	0.000	-0.015	0.998	0.161			-0.055	-0.012	0.657	0.079		
Inferior-Nasal	0.005	-0.015	0.969	0.176			0.058	-0.012	0.636	0.159		
Inferior	-0.026	-0.015	0.832	0.074			-0.066	-0.011	0.594	-0.002		
Inferior-Temporal	-0.164	0.012	0.181	-0.223			-0.167	0.013	0.174	-0.216		
Temporal	-0.123	0.000	0.319	-0.129			-0.192	0.022	0.116	-0.195		
Superior-Temporal	-0.094	-0.006	0.448	0.027			-0.087	-0.007	0.481	0.009		

Table 3.37. Univariate and multivariate regression models over the Supine Intraocular Pressure Test Result (SIOP) for light and dark conditions with TISA 500 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

TISA750	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.081	-0.009	0.518	-0.065	-0.015	0.541	-0.020	-0.015	0.873	0.033	-0.018	0.561
Superior-Nasal	0.067	-0.011	0.587	0.100			-0.029	-0.014	0.814	0.122		
Nasal	-0.028	-0.014	0.821	0.042			-0.089	-0.007	0.472	-0.037		
Inferior-Nasal	0.030	-0.014	0.810	0.253			0.082	-0.008	0.506	0.247		
Inferior	-0.011	-0.015	0.931	0.163			-0.002	-0.015	0.988	0.118		
Inferior-Temporal	-0.173	0.015	0.159	-0.239			-0.128	0.001	0.299	-0.178		
Temporal	-0.115	-0.002	0.351	-0.213			-0.157	0.010	0.201	-0.241		
Superior-Temporal	-0.174	0.016	0.155	-0.127			-0.119	-0.001	0.334	-0.156		

Table 3.38. Univariate and multivariate regression models over the Supine Intraocular Pressure Test Result (SIOP) for light and dark conditions with TISA 750 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

TIA500	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.145	0.005	0.253	-0.097	0.014	0.371	-0.035	-0.014	0.777	0.025	-0.046	0.741
Superior-Nasal	-0.220	0.034	0.072	-0.197			-0.111	-0.003	0.368	-0.082		
Nasal	-0.053	-0.012	0.665	0.045			-0.110	-0.003	0.371	-0.045		
Inferior-Nasal	0.041	-0.013	0.738	0.308			0.052	-0.012	0.674	0.239		
Inferior	-0.016	-0.015	0.898	0.077			-0.023	-0.015	0.855	0.024		
Inferior-Temporal	-0.208	0.029	0.089	-0.23			-0.124	0.000	0.315	-0.092		
Temporal	-0.117	-0.001	0.340	-0.051			-0.174	0.015	0.157	-0.207		
Superior-Temporal	-0.192	0.022	0.117	-0.103			-0.103	-0.004	0.405	-0.067		

Table 3.39. Univariate and multivariate regression models over The Supine Intraocular Pressure Test Result (SIOP) for light and dark conditions with TIA 500 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

TIA750	LIGHT						DARK					
	Single Predictor			Multiple Predictor			Single Predictor			Multiple Predictor		
	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value	Standardised Coefficients	Adj. R^2	Significance P Value
Superior	-0.081	-0.009	0.519	-0.114	-0.091	0.954	0.065	-0.011	0.606	0.017	-0.006	0.480
Superior-Nasal	-0.095	-0.006	0.439	-0.092			-0.058	-0.012	0.638	-0.050		
Nasal	-0.069	-0.010	0.575	0.007			-0.143	0.006	0.245	-0.257		
Inferior-Nasal	-0.019	-0.015	0.876	0.042			0.114	-0.002	0.353	0.428		
Inferior	-0.003	-0.015	0.979	0.054			0.072	-0.010	0.561	0.111		
Inferior-Temporal	-0.058	-0.012	0.638	-0.079			0.009	-0.015	0.943	-0.008		
Temporal	0.007	-0.015	0.954	0.271			-0.060	-0.012	0.630	-0.140		
Superior-Temporal	-0.107	-0.004	0.385	-0.143			-0.035	-0.014	0.778	-0.130		

Table 3.40. Univariate and multivariate regression models over The Supine Intraocular Pressure Test Result (SIOP) for light and dark conditions with TIA 750 adjusted for the 8 different sections. Statistically significant p values have been flagged with an asterisk.

		VISIT 1		VISIT 4		VISIT 5		VISIT 6		VISIT 11	
		TR	UNTR	TR	UNTR	TR	UNTR	TR	UNTR	TR	UNTR
	IOP	16.3	16.3	18.7	18.3	18.5	18.6	18.1	18.7	16.5	17.092
		(4.058)	(3.695)	(3.805)	(4.032)	(3.378)	(3.927)	(3.543)	(4.136)	(3.604)	(4.139)
SUPERIOR	AOD500	0.056	0.031	0.047	0.040	0.050	0.042	0.057	0.041	0.063	0.046
		(0.056)	(0.037)	(0.062)	(0.054)	(0.063)	(0.050)	(0.065)	(0.049)	(0.078)	(0.055)
	ARA500	0.023	0.011	0.013	0.014	0.015	0.011	0.016	0.012	0.022	0.013
		0.023)	(0.025)	(0.022)	(0.025)	(0.022)	(0.022)	(0.027)	(0.021)	(0.029)	(0.020)
	TISA500	0.021	0.010	0.012	0.012	0.015	0.010	0.015	0.011	0.022	0.013
		0.021)	(0.022)	(0.021)	(0.022)	(0.022)	(0.021)	(0.026)	(0.019)	(0.028)	(0.020)
	TIA500	4.247	2.435	3.829	3.013	4.049	3.379	4.226	3.074	4.734	3.821
		(4.247)	(2.815)	(5.226)	(4.155)	(5.190)	(4.196)	(4.671)	(3.619)	(5.671)	(4.629)
	AOD750	0.074	0.071	0.101	0.078	0.101	0.079	0.121	0.075	0.137	0.092
		(0.074)	(0.082)	(0.095)	(0.081)	(0.091)	(0.067)	(0.095)	(0.063)	(0.107)	(0.085)
	ARA750	0.036	0.022	0.033	0.031	0.034	0.029	0.040	0.029	0.050	0.033
		(0.036)	(0.030)	(0.040)	(0.039)	(0.037)	(0.034)	(0.045)	(0.032)	(0.052)	(0.036)
	TISA750	0.034	0.021	0.032	0.029	0.034	0.028	0.039	0.028	0.049	0.032
		(0.034)	(0.029)	(0.039)	(0.037)	(0.037)	(0.033)	(0.043)	(0.030)	(0.051)	(0.036)
	TIA750	4.079	3.906	5.897	4.328	5.759	4.468	6.713	4.305	7.360	5.400
		(4.079)	(4.094)	(5.498)	(4.405)	(5.065)	(3.826)	(4.887)	(3.468)	(5.535)	(4.898)
INFERIOR	AOD500	0.079	0.067	0.076	0.054	0.081	0.066	0.079	0.055	0.078	0.067
		(0.079)	(0.068)	(0.067)	(0.068)	(0.070)	(0.076)	(0.076)	(0.065)	(0.072)	(0.074)
	ARA500	0.027	0.019	0.024	0.016	0.025	0.022	0.022	0.017	0.020	0.021
		(0.027)	(0.032)	(0.033)	(0.023)	(0.029)	(0.033)	(0.031)	(0.025)	(0.023)	(0.031)
	TISA500	0.026	0.017	0.022	0.015	0.024	0.022	0.020	0.016	0.019	0.019
		(0.026)	(0.028)	(0.028)	(0.021)	(0.027)	(0.030)	(0.028)	(0.024)	(0.022)	(0.027)
	TIA500	5.110	4.829	5.374	3.495	5.523	4.395	5.656	3.782	5.476	4.718
		(5.110)	(5.163)	(4.492)	(4.371)	(4.775)	(4.681)	(5.698)	(4.287)	(5.079)	(4.864)
	AOD750	0.103	0.132	0.150	0.116	0.146	0.131	0.163	0.121	0.159	0.121
		(0.103)	(0.106)	(0.086)	(0.102)	(0.103)	(0.108)	(0.099)	(0.108)	(0.093)	(0.108)
	ARA750	0.046	0.045	0.056	0.038	0.055	0.048	0.054	0.042	0.051	0.046
		(0.046)	(0.045)	(0.048)	(0.041)	(0.047)	(0.051)	(0.049)	(0.042)	(0.042)	(0.050)
	TISA750	0.045	0.043	0.053	0.037	0.055	0.047	0.052	0.040	0.052	0.044
		(0.045)	(0.043)	(0.043)	(0.041)	(0.045)	(0.049)	(0.047)	(0.041)	(0.041)	(0.046)
	TIA750	5.315	6.977	7.958	5.862	7.533	6.721	8.759	6.287	8.511	6.489
		(5.315)	(5.303)	(4.195)	(4.828)	(5.105)	(5.007)	(5.311)	(5.355)	(4.709)	(5.392)
SUPERIOR-NASAL	AOD500	0.061	0.075	0.080	0.076	0.077	0.076	0.077	0.091	0.085	0.083
		(0.061)	(0.067)	(0.074)	(0.075)	(0.072)	(0.068)	(0.071)	(0.075)	(0.075)	(0.066)
	ARA500	0.028	0.036	0.042	0.039	0.038	0.036	0.038	0.040	0.042	0.037
		(0.028)	(0.033)	(0.033)	(0.035)	(0.032)	(0.035)	(0.033)	(0.033)	(0.037)	(0.034)
	TISA500	0.026	0.032	0.038	0.036	0.034	0.033	0.034	0.037	0.039	0.034
		(0.026)	(0.030)	(0.030)	(0.031)	(0.029)	(0.031)	(0.030)	(0.030)	(0.033)	(0.031)
	TIA500	6.124	6.666	7.058	6.413	6.451	6.663	5.913	7.519	7.150	6.864
		(6.124)	(6.312)	(6.815)	(6.521)	(6.189)	(6.157)	(5.245)	(6.475)	(6.049)	(5.614)
	AOD750	0.093	0.108	0.142	0.124	0.129	0.123	0.140	0.127	0.148	0.123
		(0.093)	(0.080)	(0.094)	(0.094)	(0.094)	(0.081)	(0.096)	(0.083)	(0.093)	(0.084)
	ARA750	0.045	0.062	0.074	0.067	0.067	0.065	0.068	0.070	0.074	0.065
		(0.045)	(0.049)	(0.050)	(0.053)	(0.050)	(0.049)	(0.051)	(0.049)	(0.055)	(0.050)
	TISA750	0.043	0.059	0.069	0.064	0.063	0.061	0.064	0.067	0.070	0.062
		(0.043)	(0.046)	(0.048)	(0.050)	(0.047)	(0.046)	(0.048)	(0.047)	(0.051)	(0.047)
	TIA750	6.354	6.877	8.939	7.434	7.795	7.726	7.930	7.585	9.021	7.322
		(6.354)	(5.190)	(5.966)	(5.616)	(5.753)	(5.181)	(5.055)	(4.667)	(5.339)	(4.828)
INFERIOR-TEMPORAL	AOD500	0.086	0.101	0.150	0.109	0.143	0.121	0.157	0.111	0.162	0.122
		(0.086)	(0.067)	(0.093)	(0.066)	(0.098)	(0.078)	(0.086)	(0.077)	(0.095)	(0.074)
	ARA500	0.032	0.048	0.065	0.051	0.068	0.057	0.071	0.053	0.074	0.053
		(0.032)	(0.030)	(0.041)	(0.031)	(0.041)	(0.032)	(0.045)	(0.031)	(0.042)	(0.032)
	TISA500	0.031	0.045	0.059	0.046	0.060	0.053	0.063	0.047	0.067	0.048
		(0.031)	(0.028)	(0.037)	(0.027)	(0.036)	(0.030)	(0.038)	(0.028)	(0.038)	(0.029)
	TIA500	8.575	8.903	12.739	8.695	10.638	10.532	12.321	8.423	13.339	9.918
		(8.575)	(5.814)	(8.163)	(5.637)	(7.343)	(7.215)	(6.682)	(5.763)	(7.945)	(5.998)
	AOD750	0.101	0.180	0.249	0.184	0.242	0.197	0.253	0.202	0.265	0.194
		(0.101)	(0.088)	(0.117)	(0.094)	(0.120)	(0.103)	(0.108)	(0.096)	(0.124)	(0.101)
	ARA750	0.046	0.087	0.119	0.091	0.122	0.099	0.127	0.095	0.132	0.095
		(0.046)	(0.045)	(0.065)	(0.047)	(0.067)	(0.049)	(0.065)	(0.049)	(0.066)	(0.049)
	TISA750	0.048	0.084	0.113	0.086	0.115	0.095	0.119	0.090	0.125	0.090
		(0.048)	(0.043)	(0.061)	(0.044)	(0.063)	(0.049)	(0.060)	(0.046)	(0.062)	(0.046)
	TIA750	6.165	11.146	15.061	10.542	13.364	12.069	14.456	11.324	15.705	11.374
		(6.165)	(5.344)	(6.971)	(5.375)	(6.628)	(6.527)	(6.072)	(5.138)	(7.739)	(5.745)

Continuation table 4.1.

		VISIT 1		VISIT 4		VISIT 5		VISIT 6		VISIT 11	
		TR	UNTR	TR	UNTR	TR	UNTR	TR	UNTR	TR	UNTR
NASAL	AOD500	0.075 (0.075)	0.125 (0.092)	0.148 (0.076)	0.140 (0.091	0.145 (0.074)	0.139 (0.091)	0.150 (0.075)	0.144 (0.092)	0.164 (0.079)	0.147 (0.092)
	ARA500	0.040 (0.040)	0.058 (0.044)	0.068 (0.038)	0.072 (0.053)	0.067 (0.038)	0.067 (0.048)	0.069 (0.036)	0.070 (0.052)	0.070 (0.038)	0.070 (0.050)
	TISA500	0.036 (0.036)	0.051 (0.038)	0.061 (0.034)	0.063 (0.044)	0.059 (0.034)	0.059 (0.040)	0.061 (0.032)	0.062 (0.046)	0.062 (0.033)	0.062 (0.041)
	TIA500	6.387 (6.387)	10.491 (7.601)	12.853 (7.253)	11.597 (7.673)	11.592 (6.605)	11.351 (7.603)	12.356 (6.774)	11.503 (7.320)	12.961 (6.637)	11.086 (6.394)
	AOD750	0.091 (0.091)	0.178 (0.109)	0.234 (0.092)	0.189 (0.110)	0.214 (0.105)	0.205 (0.112)	0.236 (0.106)	0.196 (0.114)	0.246 (0.098)	0.212 (0.121)
	ARA750	0.053 (0.053)	0.100 (0.065)	0.121 (0.051)	0.116 (0.073)	0.115 (0.056)	0.113 (0.068)	0.121 (0.054)	0.113 (0.074)	0.126 (0.055)	0.116 (0.072)
	TISA750	0.049 (0.049)	0.093 (0.060)	0.114 (0.047)	0.110 (0.063)	0.107 (0.052)	0.105 (0.061)	0.113 (0.050)	0.105 (0.068)	0.118 (0.051)	0.108 (0.063)
	TIA750	4.926 (4.926)	10.851 (6.423)	14.324 (5.821)	11.274 (6.344)	12.469 (6.613)	12.011 (6.421)	13.921 (6.660)	11.433 (6.314)	14.211 (5.510)	11.857 (5.906)
TEMPORAL	AOD500	0.057 (0.057)	0.087 (0.066)	0.115 (0.066)	0.102 (0.069)	0.114 (0.072)	0.110 (0.057)	0.113 (0.074)	0.106 (0.062)	0.128 (0.072)	0.114 (0.070)
	ARA500	0.024 (0.024)	0.047 (0.033)	0.053 (0.028)	0.050 (0.033)	0.053 (0.032)	0.049 (0.029)	0.054 (0.032)	0.055 (0.031)	0.061 (0.036)	0.056 (0.033)
	TISA500	0.023 (0.023)	0.042 (0.029)	0.048 (0.026)	0.045 (0.030)	0.047 (0.027)	0.045 (0.027)	0.050 (0.029)	0.052 (0.028)	0.055 (0.030)	0.050 (0.029)
	TIA500	5.180 (5.180)	8.046 (6.417)	9.911 (5.386)	8.868 (6.048)	9.461 (6.570)	9.300 (5.255)	9.382 (5.998)	9.421 (5.555)	10.786 (5.736)	9.886 (6.077)
	AOD750	0.080 (0.080)	0.145 (0.086)	0.178 (0.081)	0.157 (0.085)	0.178 (0.086)	0.169 (0.083)	0.188 (0.095)	0.175 (0.094)	0.192 (0.093)	0.172 (0.109)
	ARA750	0.035 (0.035)	0.076 (0.047)	0.093 (0.041)	0.085 (0.048)	0.092 (0.047)	0.088 (0.041)	0.094 (0.048)	0.092 (0.047)	0.102 (0.050)	0.091 (0.053)
	TISA750	0.034 (0.034)	0.072 (0.044)	0.089 (0.039)	0.081 (0.045)	0.086 (0.042)	0.083 (0.039)	0.089 (0.047)	0.088 (0.044)	0.096 (0.045)	0.086 (0.049)
	TIA750	5.125 (5.125)	9.543 (5.819)	11.111 (4.942)	9.758 (5.266)	10.805 (5.273)	10.290 (5.181)	11.295 (5.303)	11.118 (5.967)	11.855 (5.615)	10.616 (6.362)
INFERIOR-NASAL	AOD500	0.084 (0.084)	0.123 (0.100)	0.144 (0.090)	0.119 (0.097)	0.138 (0.106)	0.137 (0.108)	0.151 (0.080)	0.121 (0.101)	0.166 (0.085)	0.132 (0.096)
	ARA500	0.037 (0.037)	0.051 (0.043)	0.058 (0.036)	0.057 (0.046)	0.060 (0.048)	0.061 (0.056)	0.066 (0.046)	0.054 (0.047)	0.066 (0.042)	0.058 (0.049)
	TISA500	0.035 (0.035)	0.047 (0.039)	0.053 (0.033)	0.052 (0.041)	0.053 (0.042)	0.053 (0.046)	0.058 (0.037)	0.048 (0.042)	0.060 (0.037)	0.052 (0.042)
	TIA500	7.557 (7.557)	10.383 (8.858)	12.276 (7.673)	9.616 (8.242)	10.828 (8.425)	10.579 (8.575)	11.403 (6.360)	9.649 (8.385)	13.432 (7.614)	10.695 (7.774)
	AOD750	0.107 (0.107)	0.188 (0.127)	0.223 (0.115)	0.196 (0.119)	0.222 (0.119)	0.204 (0.132)	0.252 (0.105)	0.193 (0.126)	0.252 (0.116)	0.216 (0.136)
	ARA750	0.059 (0.059)	0.093 (0.070)	0.108 (0.056)	0.101 (0.071)	0.108 (0.074)	0.105 (0.084)	0.120 (0.064)	0.096 (0.073)	0.120 (0.061)	0.104 (0.074)
	TISA750	0.058 (0.058)	0.088 (0.067)	0.103 (0.055)	0.097 (0.066)	0.102 (0.068)	0.098 (0.075)	0.112 (0.057)	0.091 (0.069)	0.114 (0.057)	0.098 (0.068)
	TIA750	6.790 (6.790)	11.334 (7.729)	13.574 (6.999)	11.449 (7.238)	12.679 (6.696)	11.774 (7.639)	14.153 (5.654)	11.359 (7.639)	14.821 (7.329)	12.578 (7.655)
SUPERIOR-TEMPORAL	AOD500	0.060 (0.060)	0.042 (0.046)	0.083 (0.075)	0.061 (0.066)	0.085 (0.073)	0.049 (0.056)	0.071 (0.067)	0.054 (0.057)	0.078 (0.072)	0.055 (0.065)
	ARA500	0.024 (0.024)	0.019 (0.022)	0.032 (0.035)	0.031 (0.033)	0.033 (0.028)	0.024 (0.030)	0.027 (0.028)	0.023 (0.026)	0.028 (0.029)	0.022 (0.027)
	TISA500	0.024 (0.024)	0.018 (0.021)	0.029 (0.031)	0.028 (0.030)	0.031 (0.028)	0.022 (0.028)	0.026 (0.027)	0.022 (0.024)	0.027 (0.028)	0.020 (0.025)
	TIA500	6.189 (6.189)	3.897 (4.306)	7.026 (6.205)	5.042 (5.796)	6.686 (5.537)	4.489 (5.444)	5.751 (5.416)	4.818 (5.453)	6.584 (6.365)	4.333 (5.110)
	AOD750	0.074 (0.074)	0.089 (0.087)	0.141 (0.103)	0.116 (0.099)	0.138 (0.089)	0.096 (0.086)	0.133 (0.091)	0.101 (0.090)	0.144 (0.085)	0.099 (0.095)
	ARA750	0.038 (0.038)	0.037 (0.036)	0.063 (0.054)	0.061 (0.052)	0.062 (0.046)	0.046 (0.045)	0.054 (0.044)	0.043 (0.039)	0.059 (0.045)	0.043 (0.046)
	TISA750	0.038 (0.038)	0.035 (0.035)	0.061 (0.051)	0.056 (0.050)	0.060 (0.045)	0.044 (0.043)	0.055 (0.044)	0.044 (0.041)	0.058 (0.044)	0.042 (0.044)
	TIA750	5.168 (5.168)	5.717 (5.485)	8.663 (6.062)	6.753 (6.143)	7.966 (4.529)	6.092 (5.610)	7.813 (5.020)	6.258 (5.666)	8.789 (5.115)	5.825 (5.442)

Table 4.1. Mean values for every parameter (treated eyes with LPI only and fellow untreated eyes) in dark for visits 1, 4, 5, 6 and 11 together with their standard deviation within brackets.

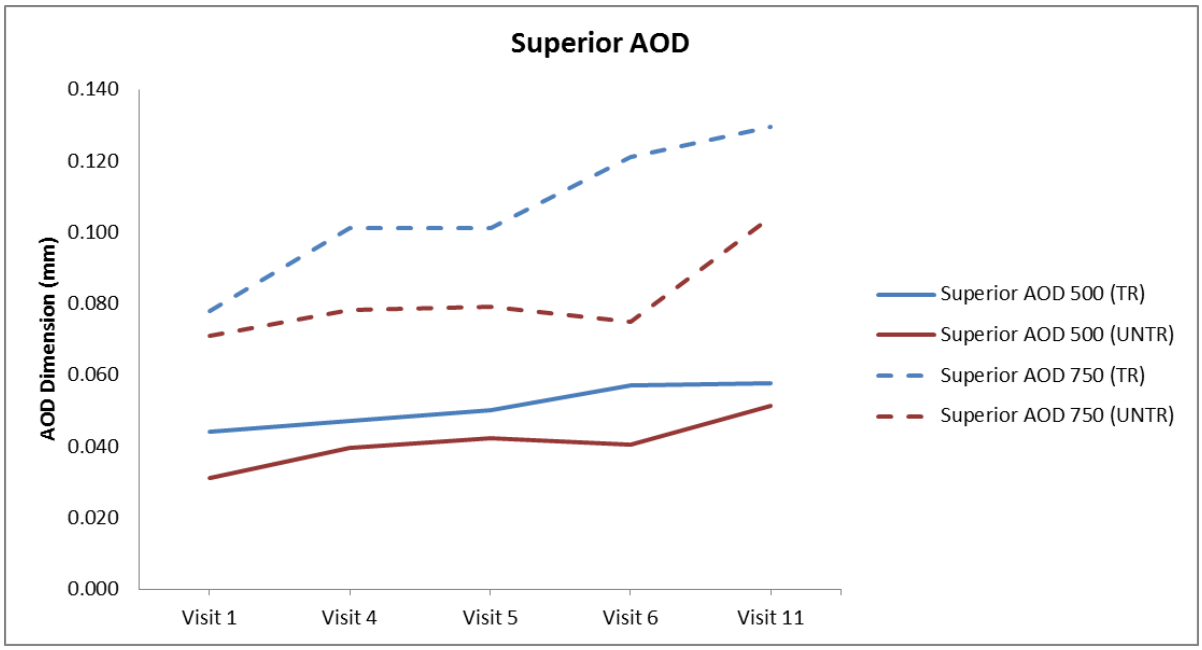


Figure 4.2 AOD 500 and 750µm in the Superior section for LPI Treated and Untreated eyes through Visits 1,4 ,5 ,6 and 11

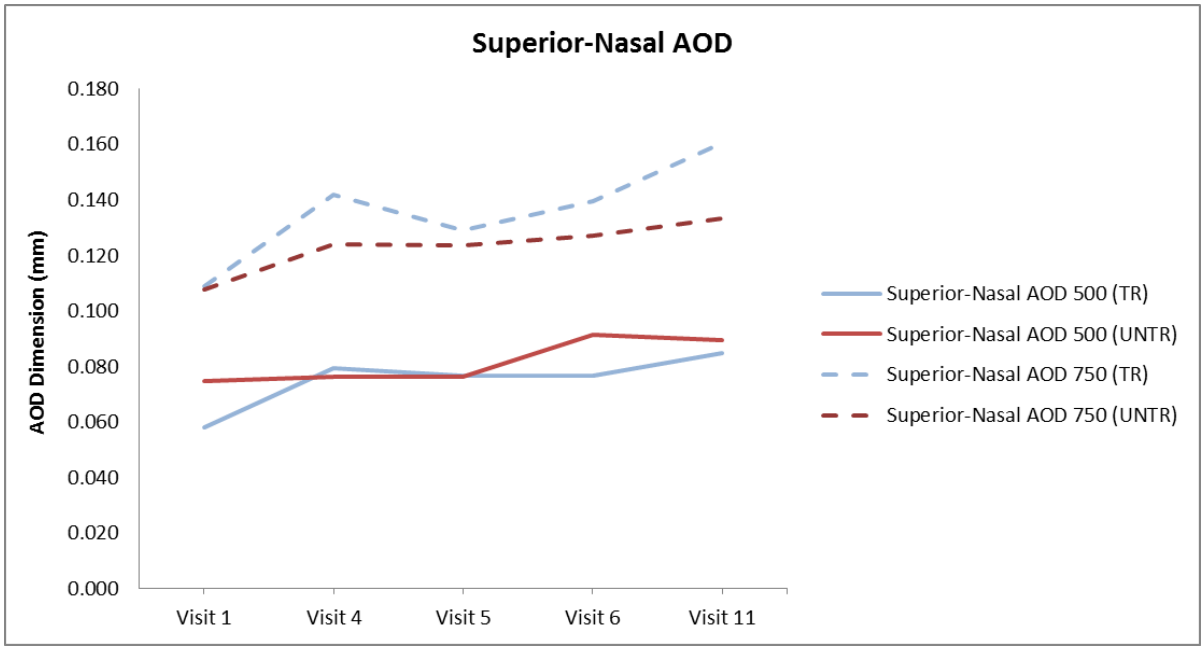


Figure 4.3 AOD 500 and 750µm in the Superior-Nasal section for LPI Treated and Untreated eyes through Visits 1,4 ,5 ,6 and 11.

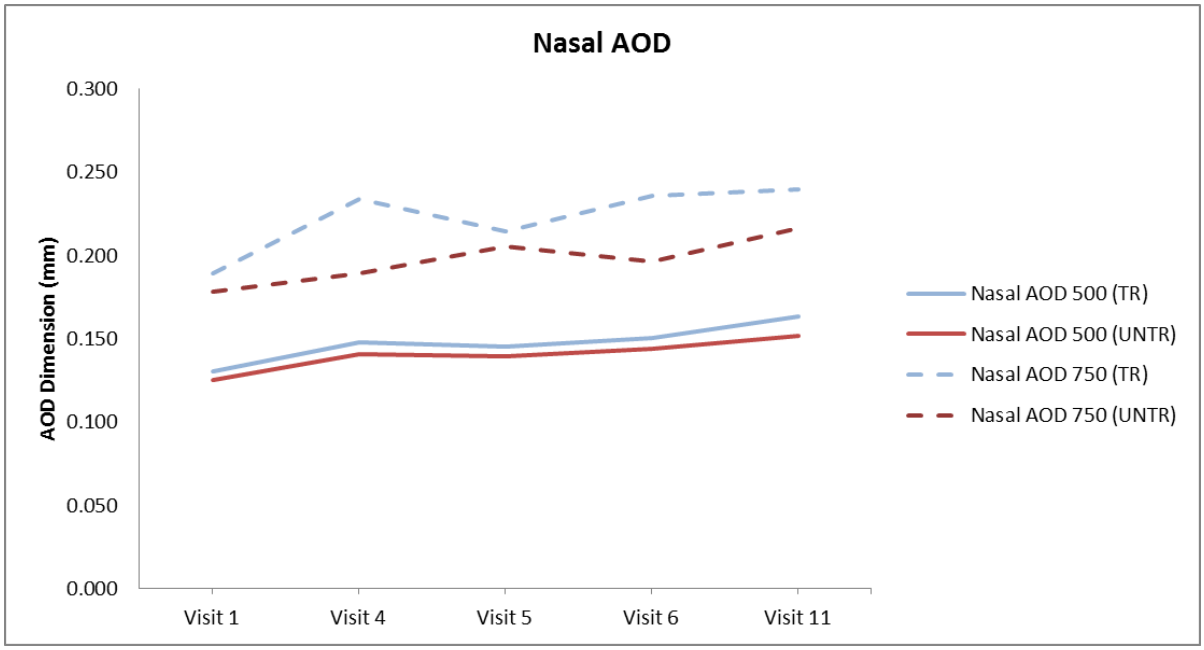


Figure 4.4 AOD 500 and 750µm in the Nasal section for LPI Treated and Untreated eyes through Visits 1,4 ,5 ,6 and 11.

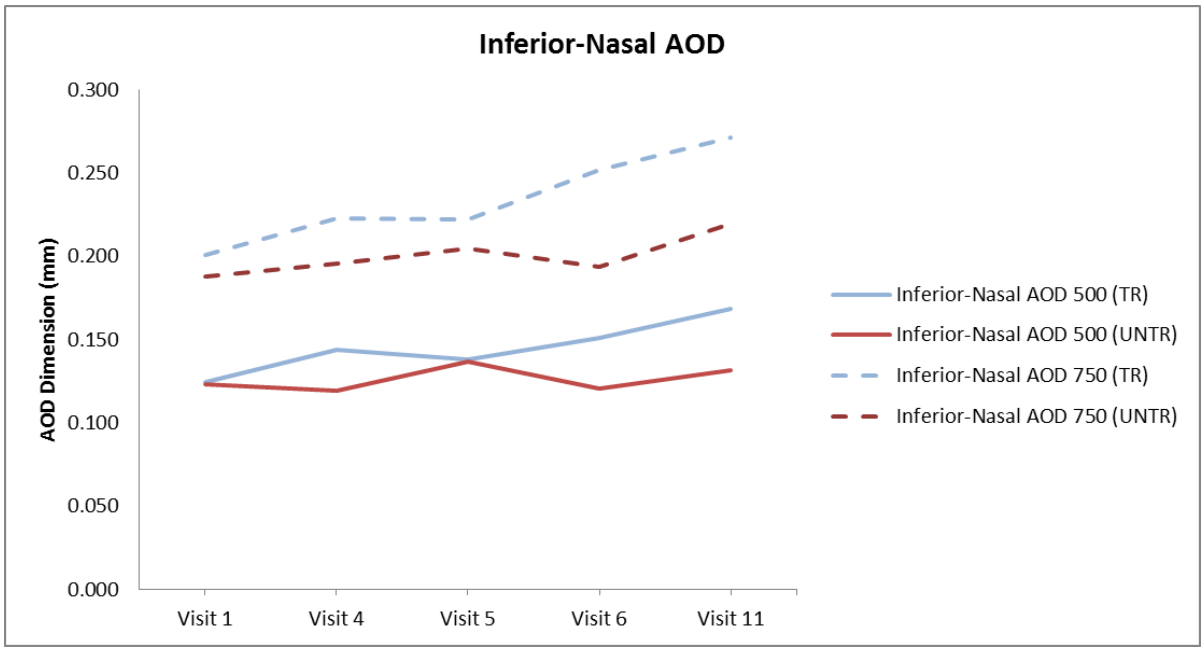


Figure 4.5 AOD 500 and 750µm in the Inferior-Nasal section for LPI Treated and Untreated eyes through Visits 1,4 ,5 ,6 and 11.

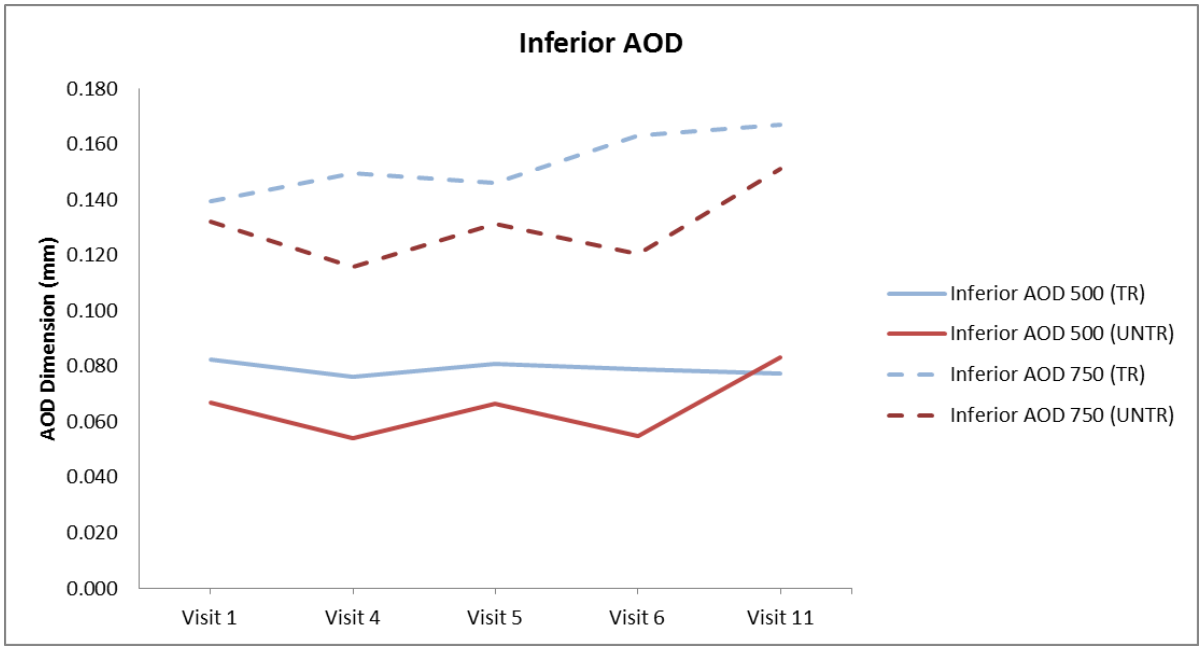


Figure 4.6 AOD 500 and 750µm in the Inferior section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

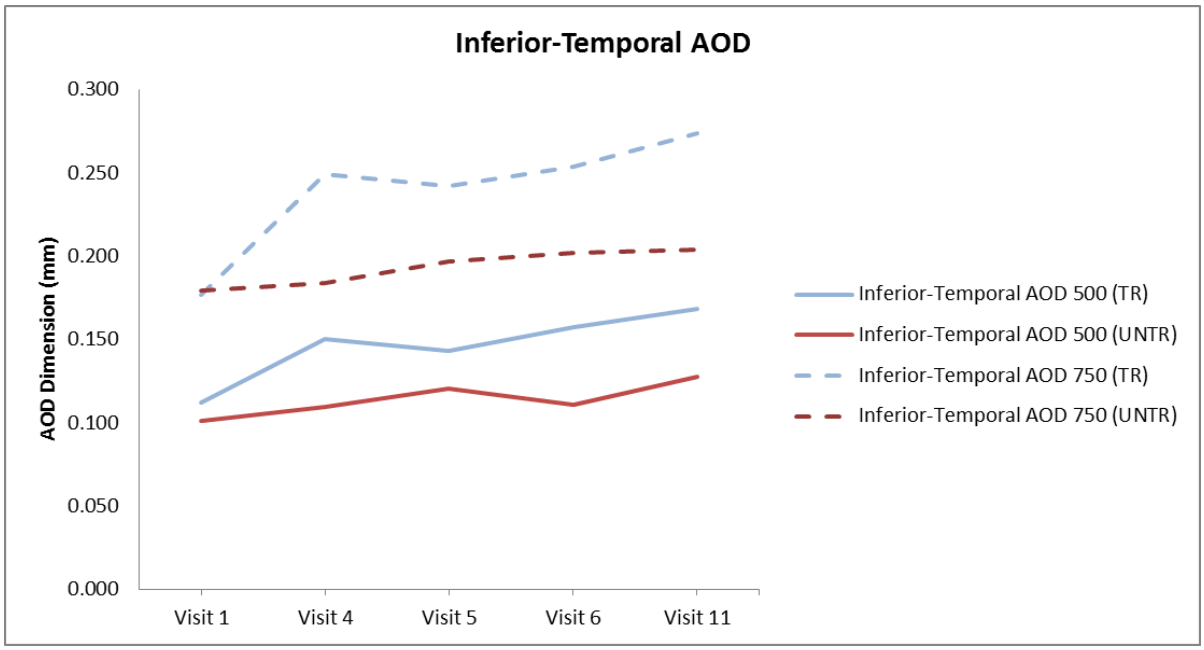


Figure 4.7 AOD 500 and 750µm in the Inferior –Temporal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

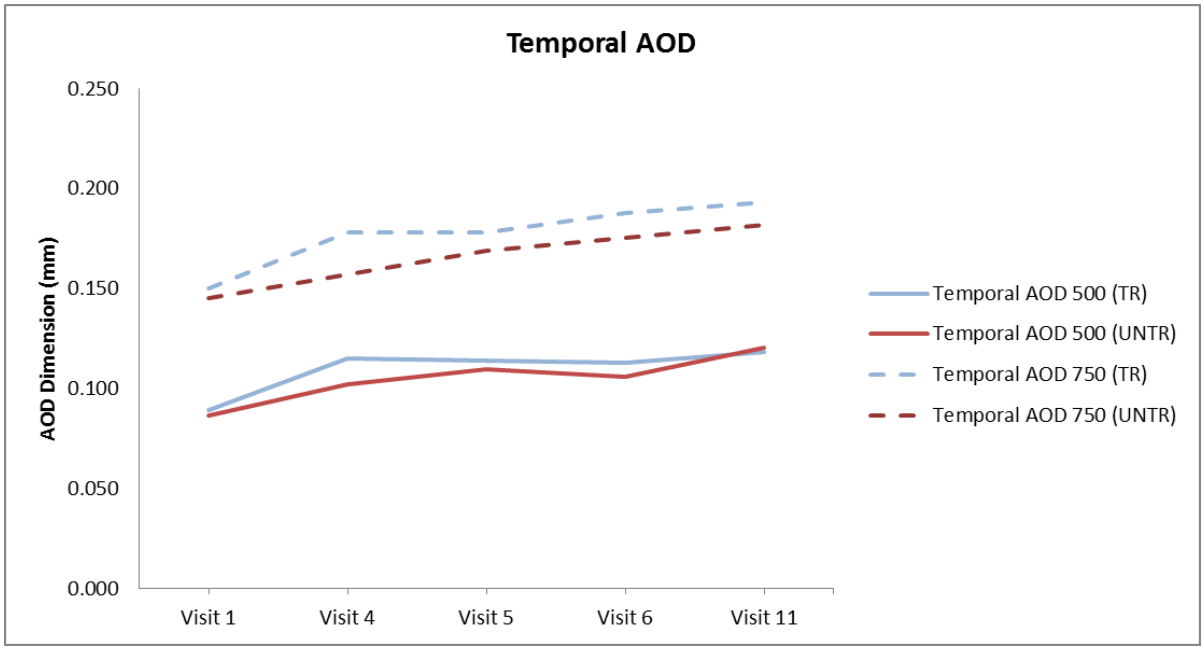


Figure 4.8 AOD 500 and 750µm in the Temporal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

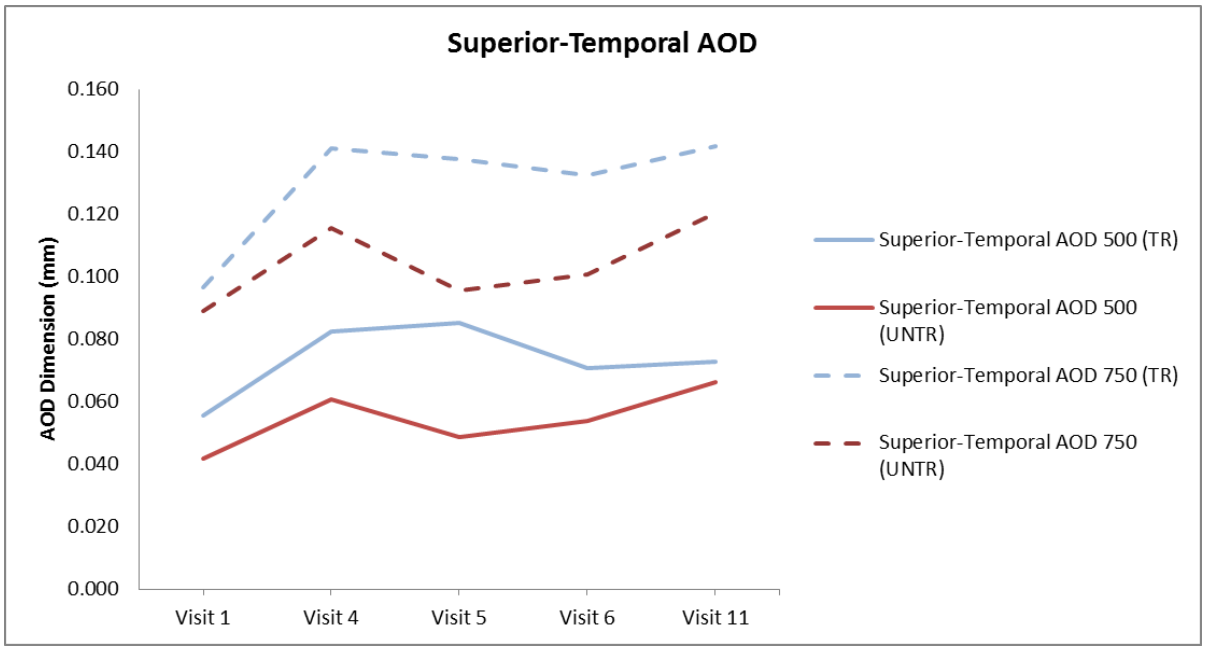


Figure 4.9 AOD 500 and 750µm in the Superior-Temporal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

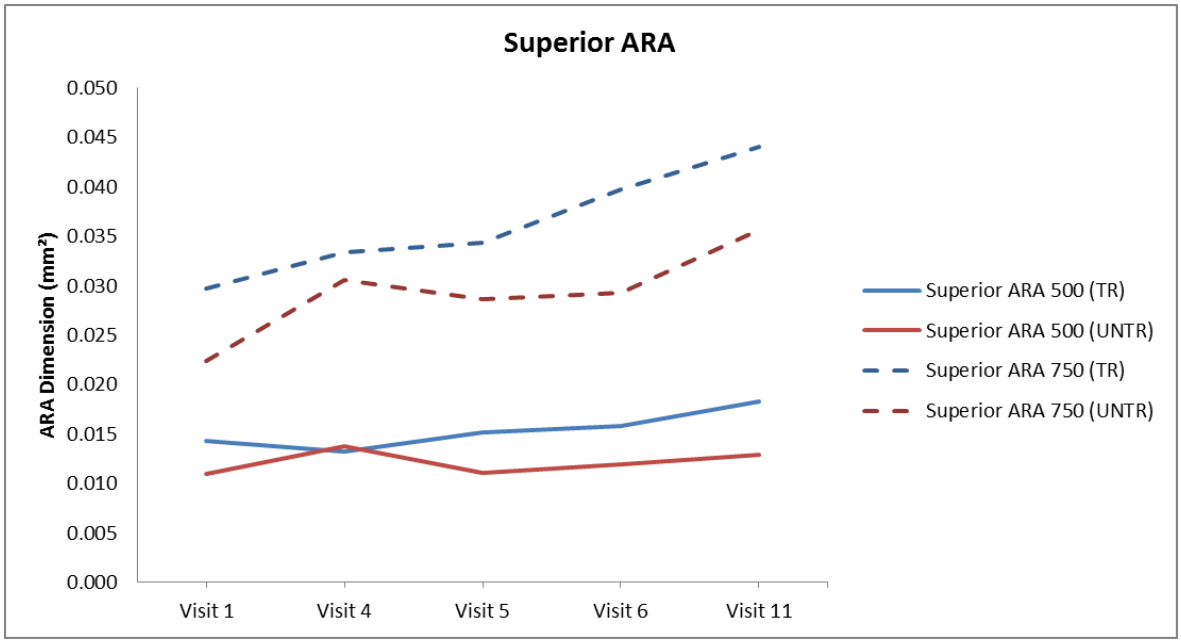


Figure 4.10 ARA 500 and 750µm in the Superior section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

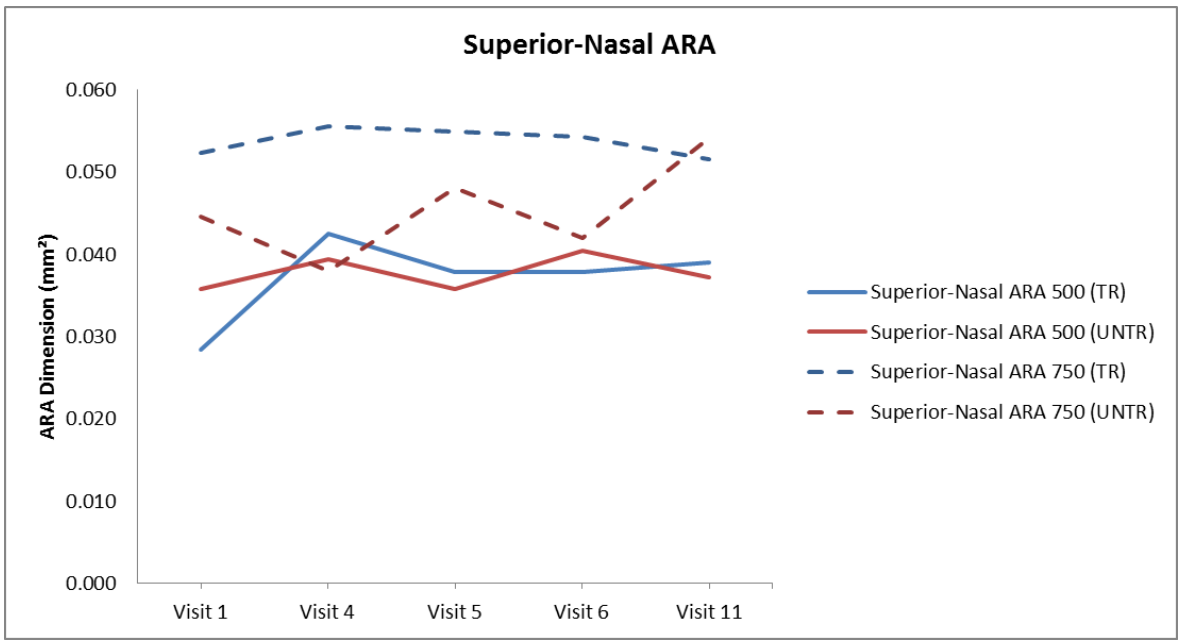


Figure 4.11 ARA 500 and 750µm in the Superior-Nasal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

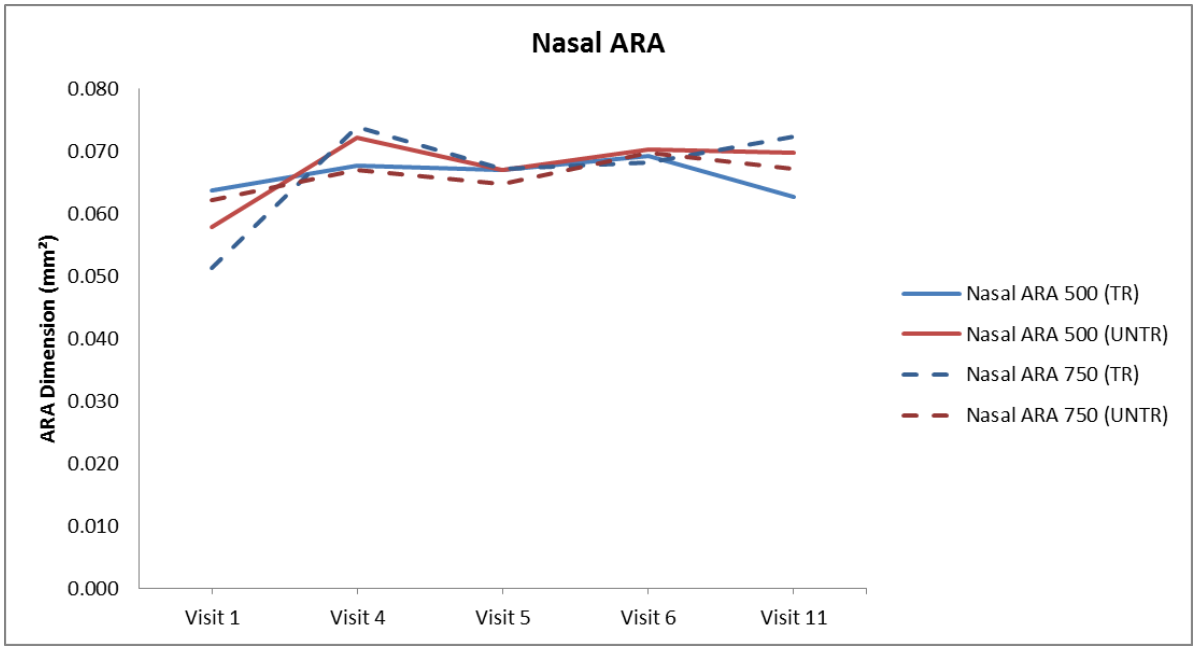


Figure 4.12 ARA 500 and 750µm in the Nasal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

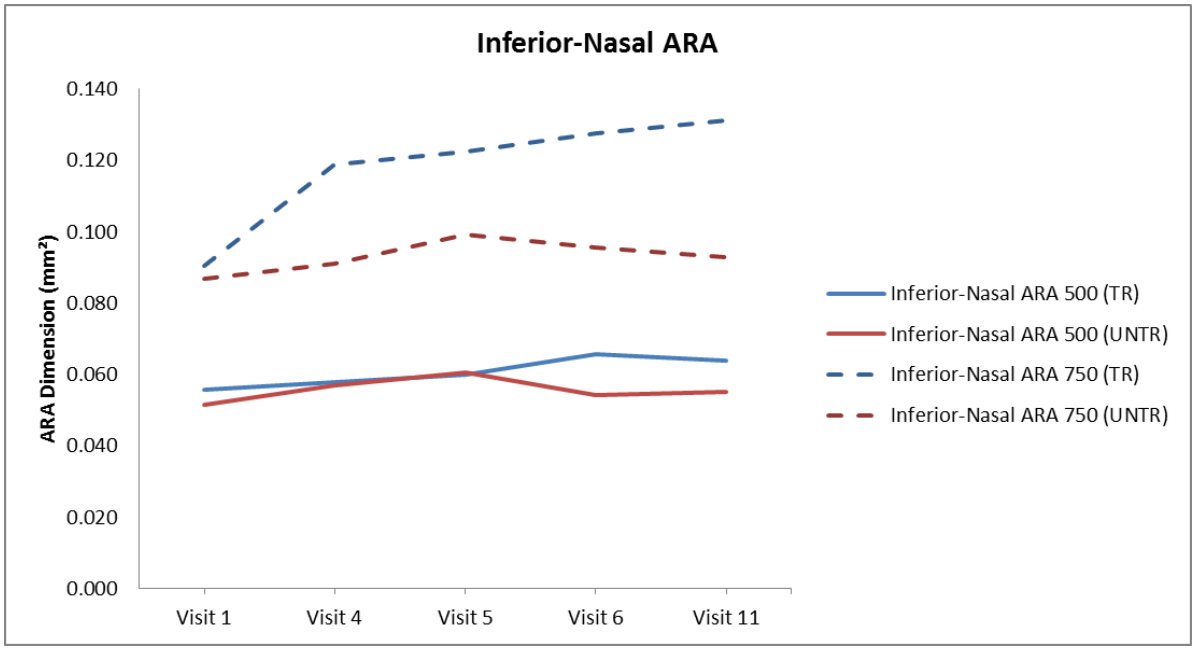


Figure 4.13 ARA 500 and 750µm in the Inferior-Nasal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

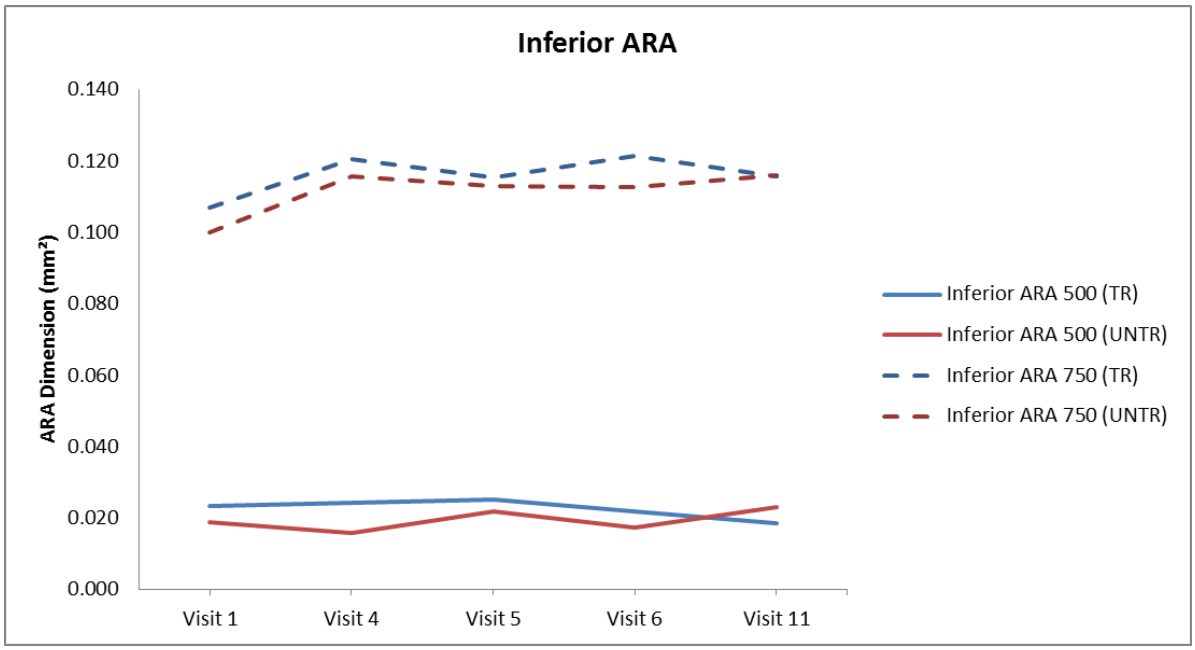


Figure 4.14 ARA 500 and 750µm in the Inferior section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

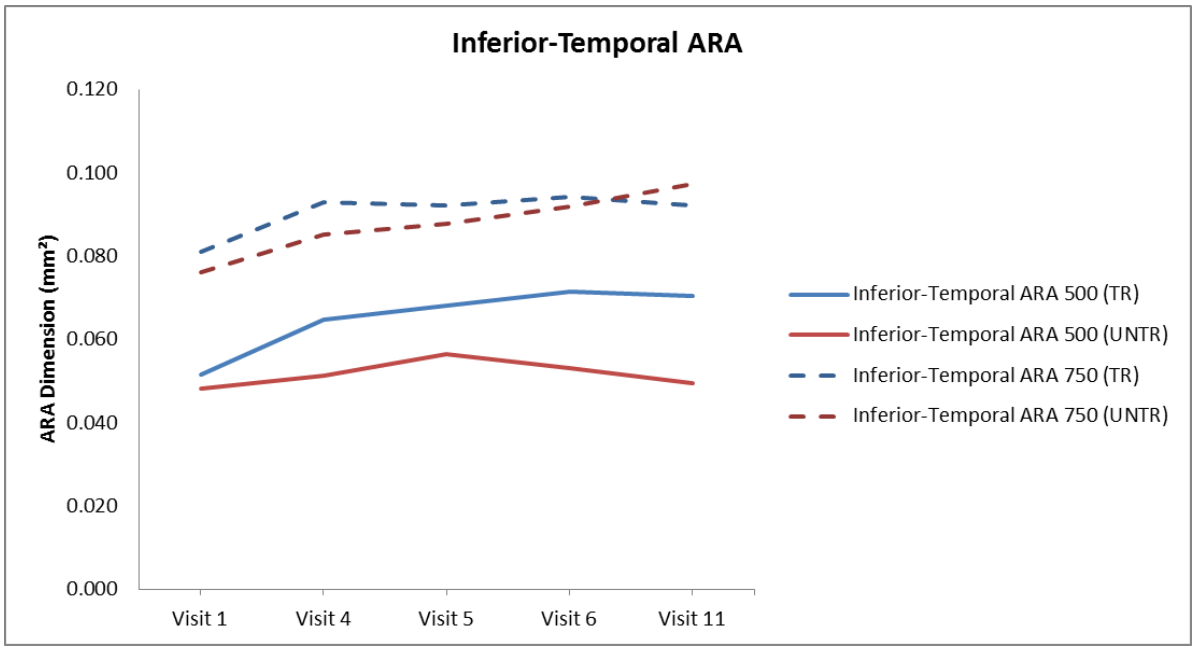


Figure 4.15 ARA 500 and 750µm in the Inferior-Temporal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

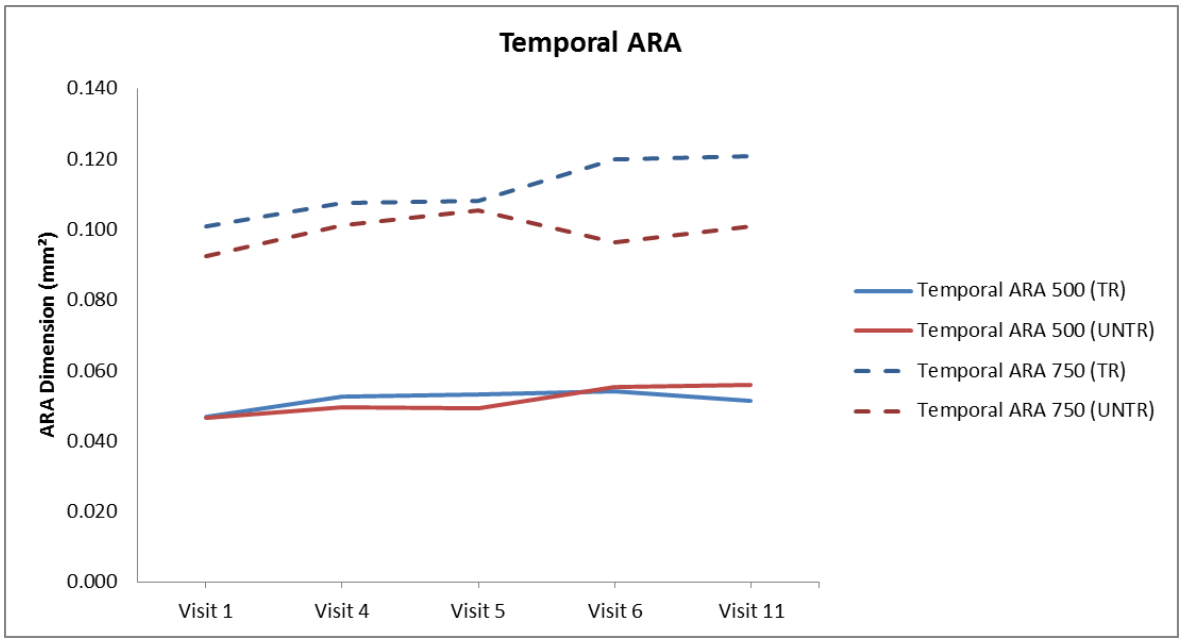


Figure 4.16 ARA 500 and 750µm in the Temporal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

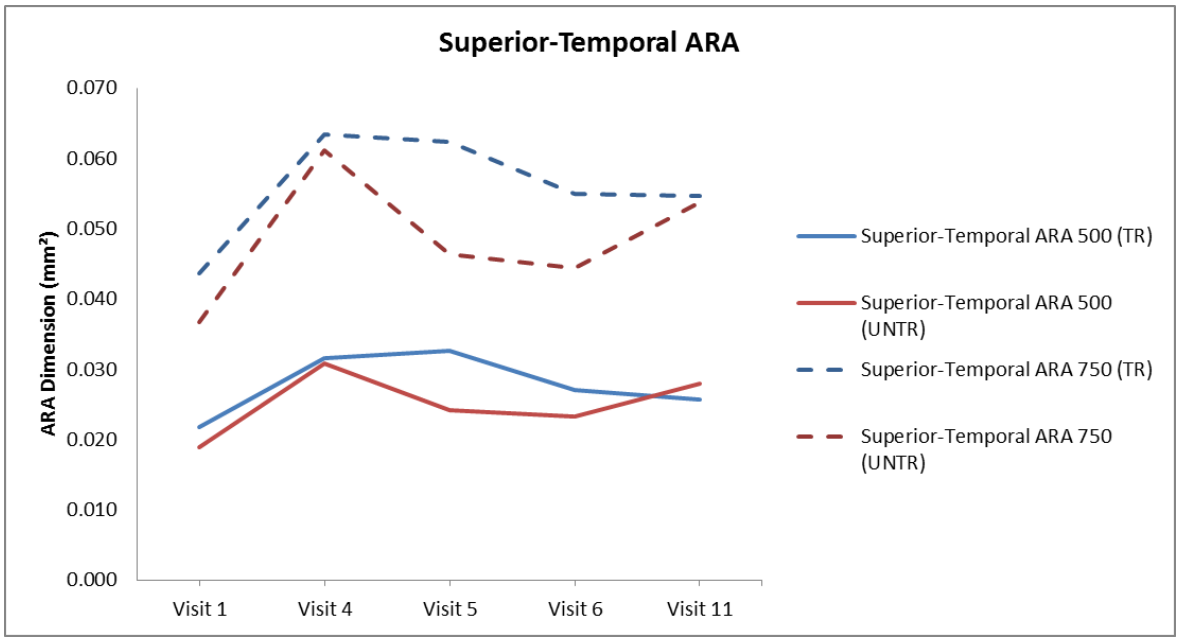


Figure 4.17 ARA 500 and 750µm in the Superior-Temporal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

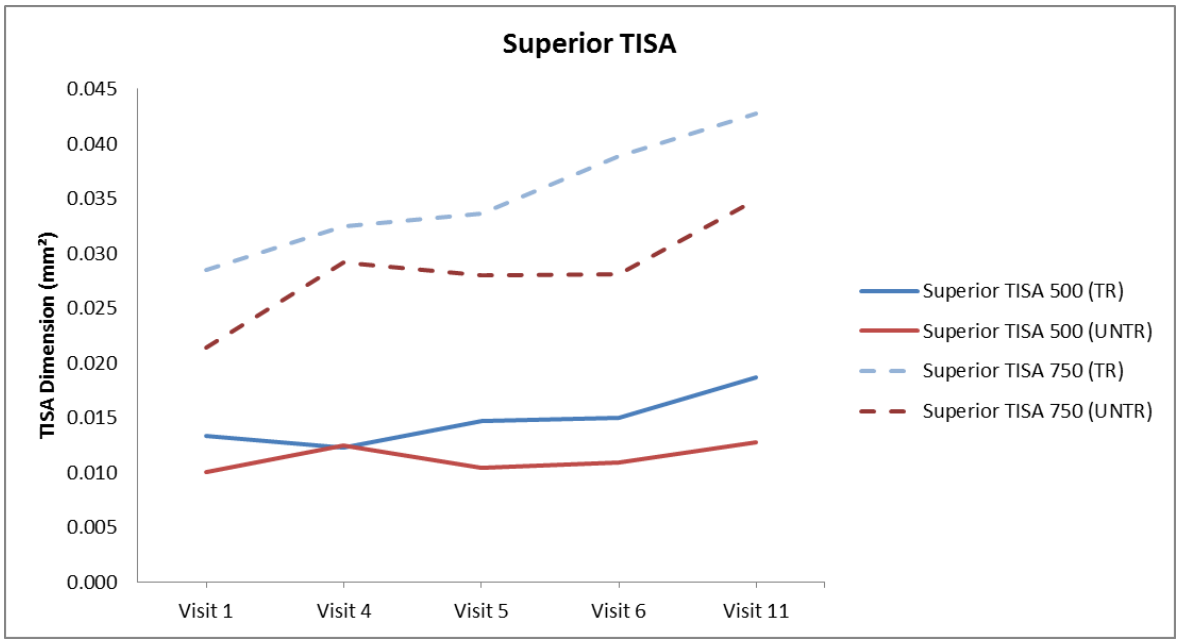


Figure 4.18 TISA 500 and 750µm in the Superior section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

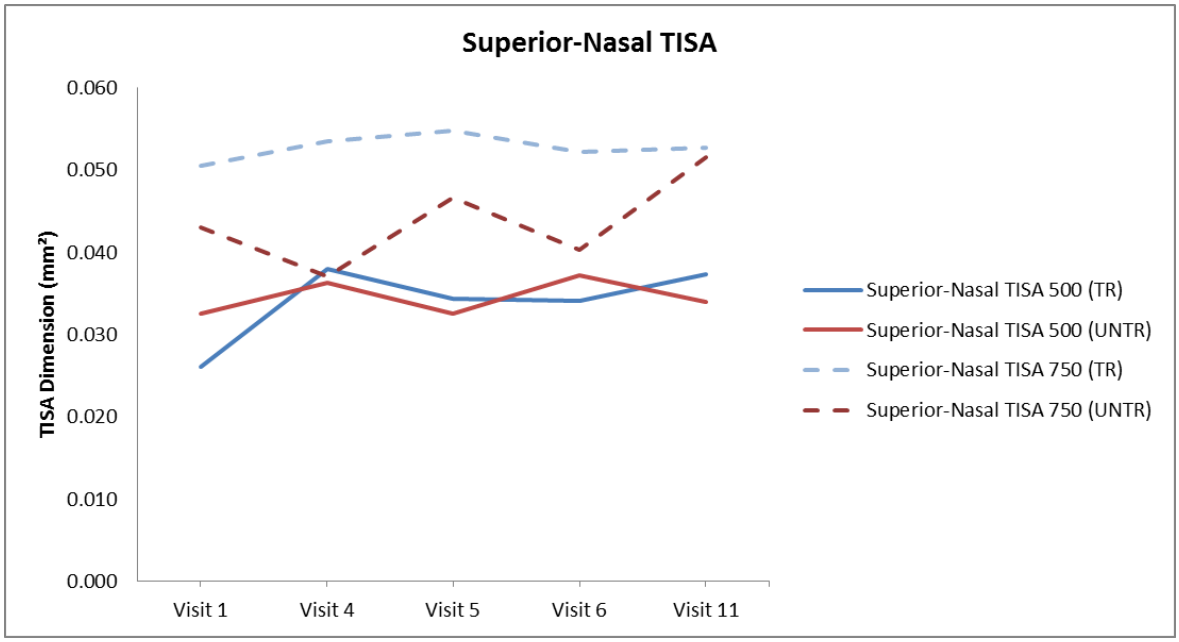


Figure 4.19 TISA 500 and 750µm in the Superior-Nasal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

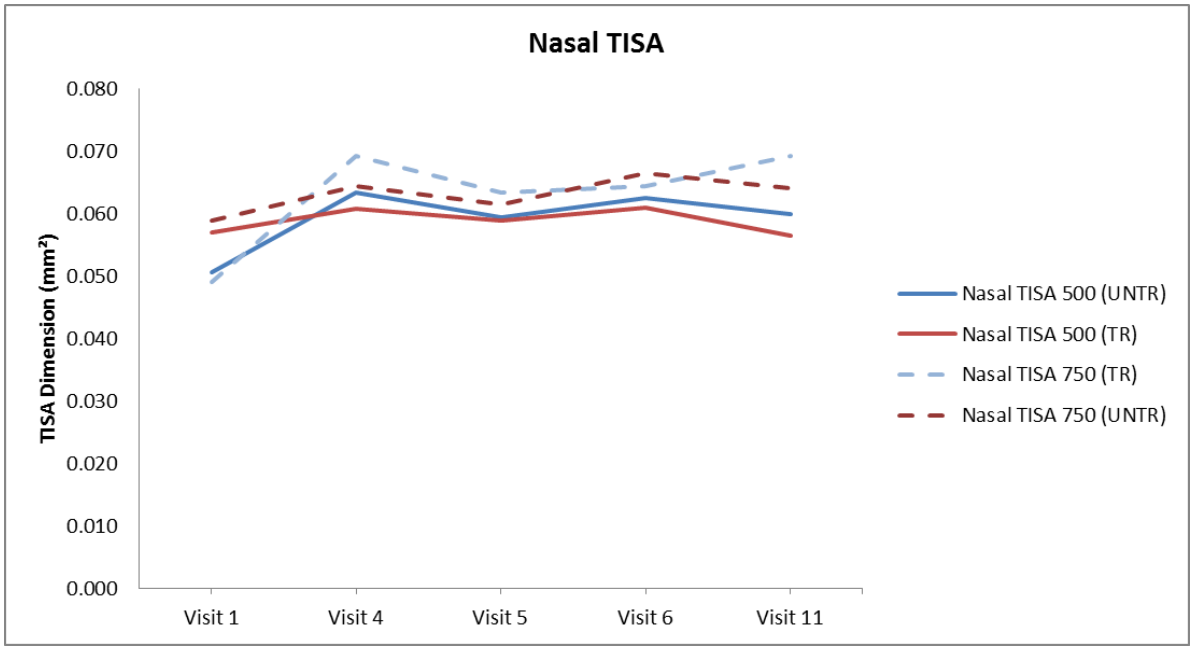


Figure 4.20 TISA 500 and 750µm in the Nasal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

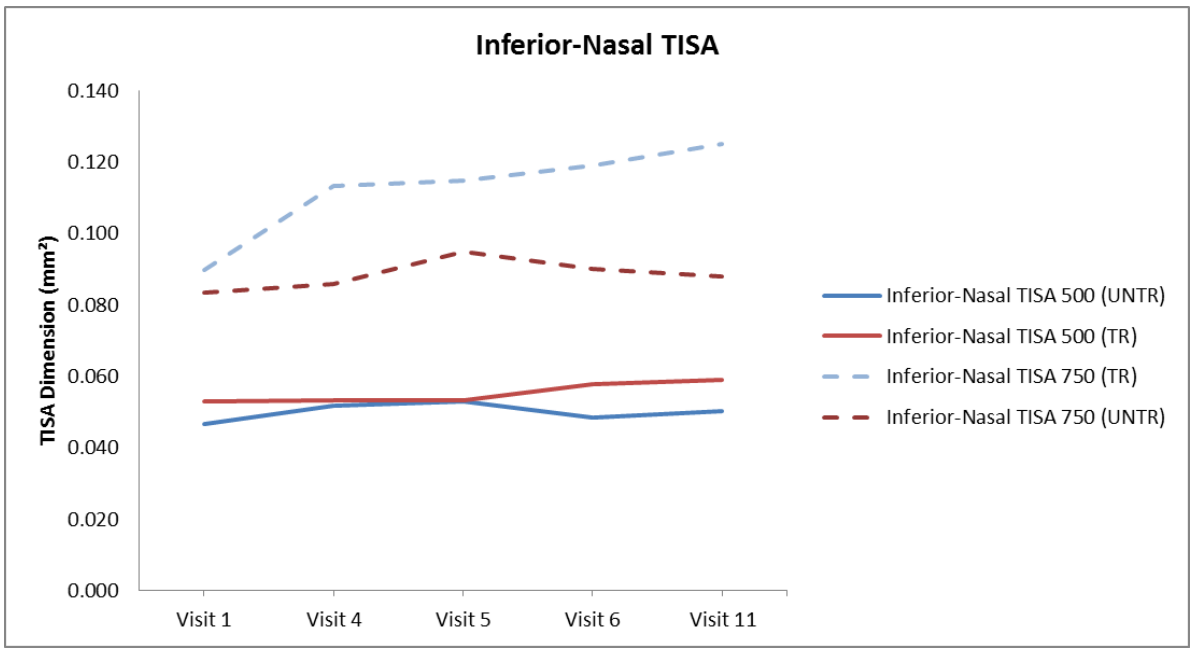


Figure 4.21 TISA 500 and 750µm in the Inferior-Nasal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

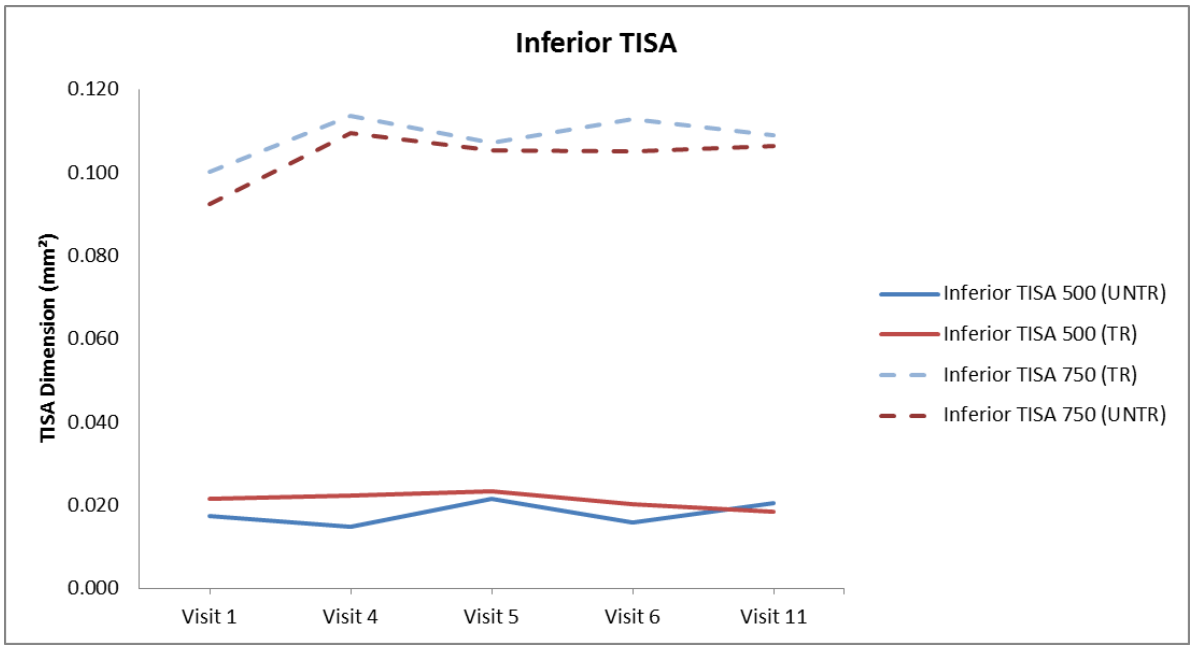


Figure 4.22 TISA 500 and 750µm in the Inferior section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

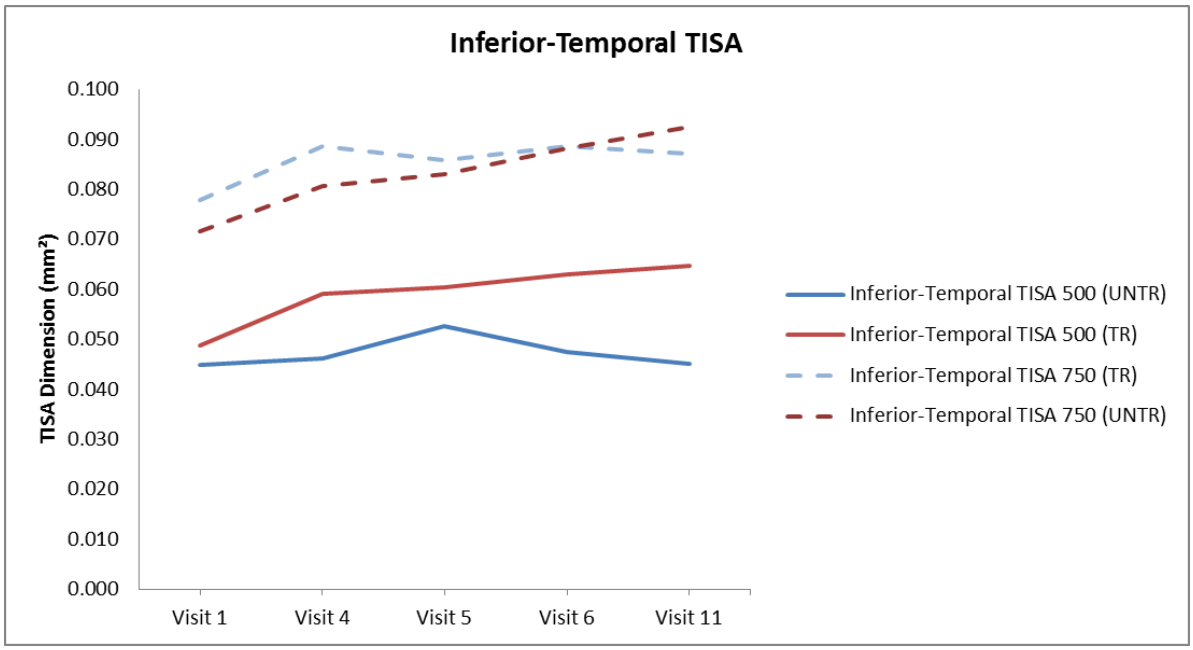


Figure 4.23 TISA 500 and 750µm in the Inferior-Temporal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

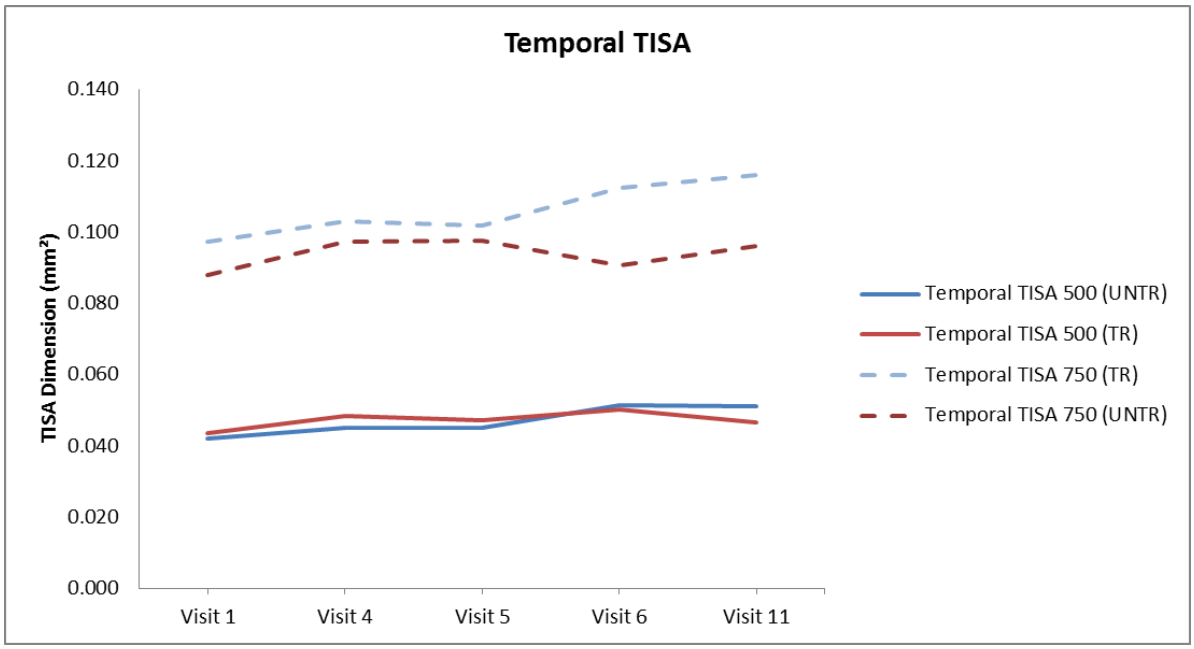


Figure 4.24 TISA 500 and 750µm in the Temporal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

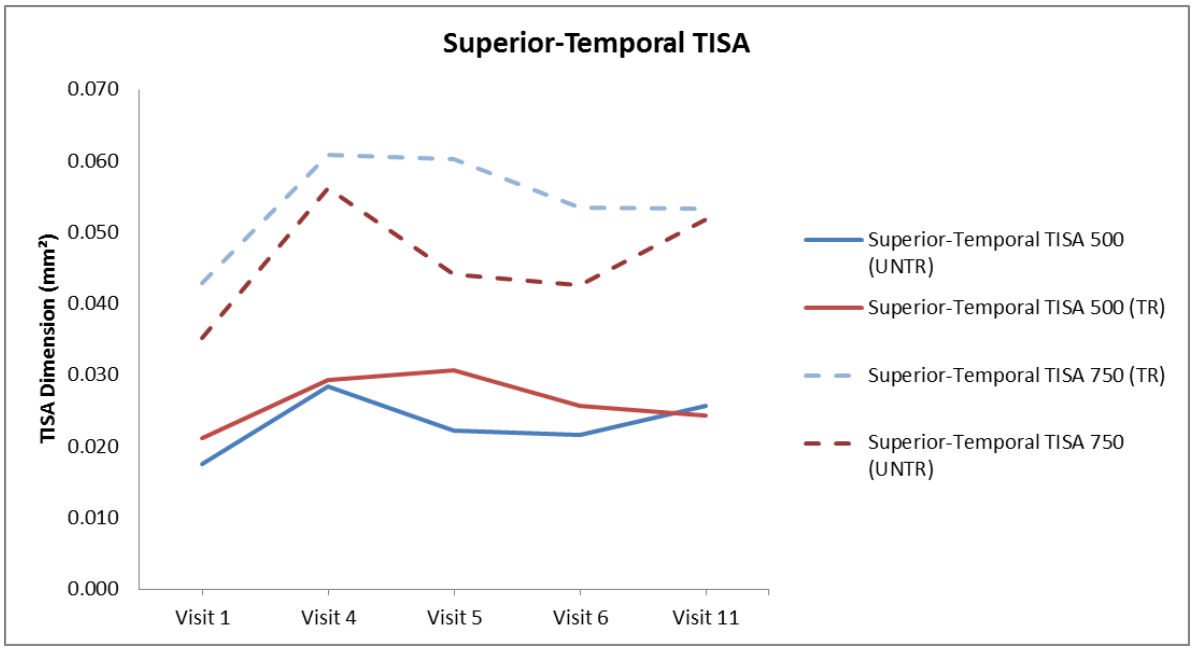


Figure 4.25 TISA 500 and 750µm in the Superior-Temporal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

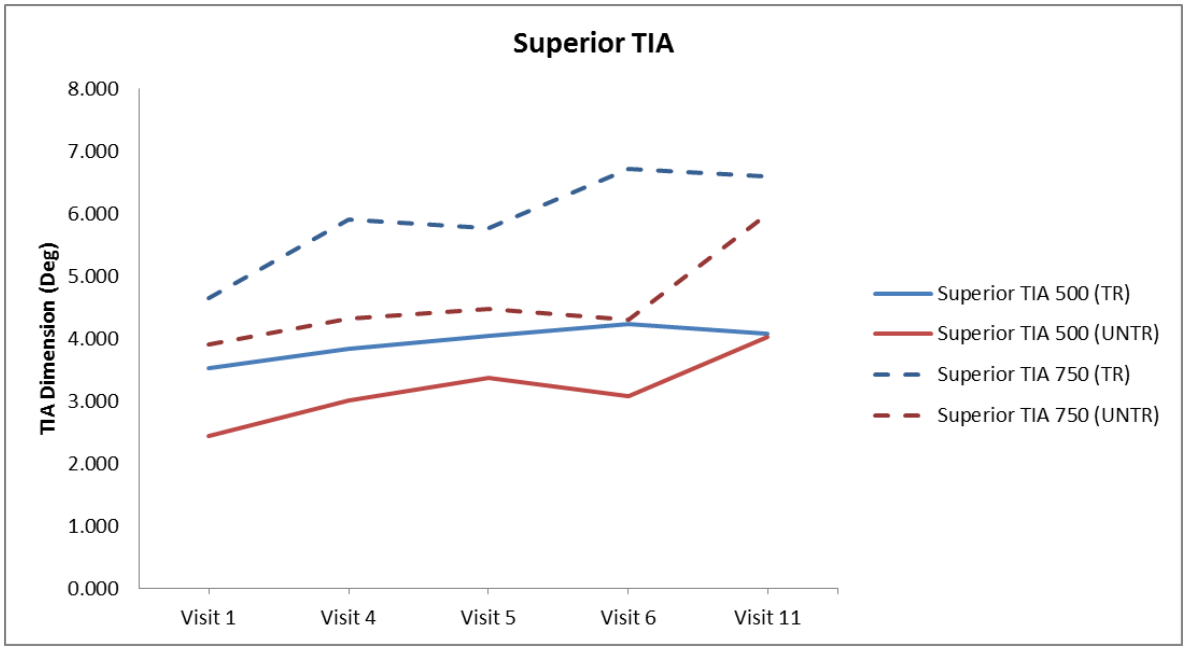


Figure 4.26 TSA 500 and 750µm in the Superior section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

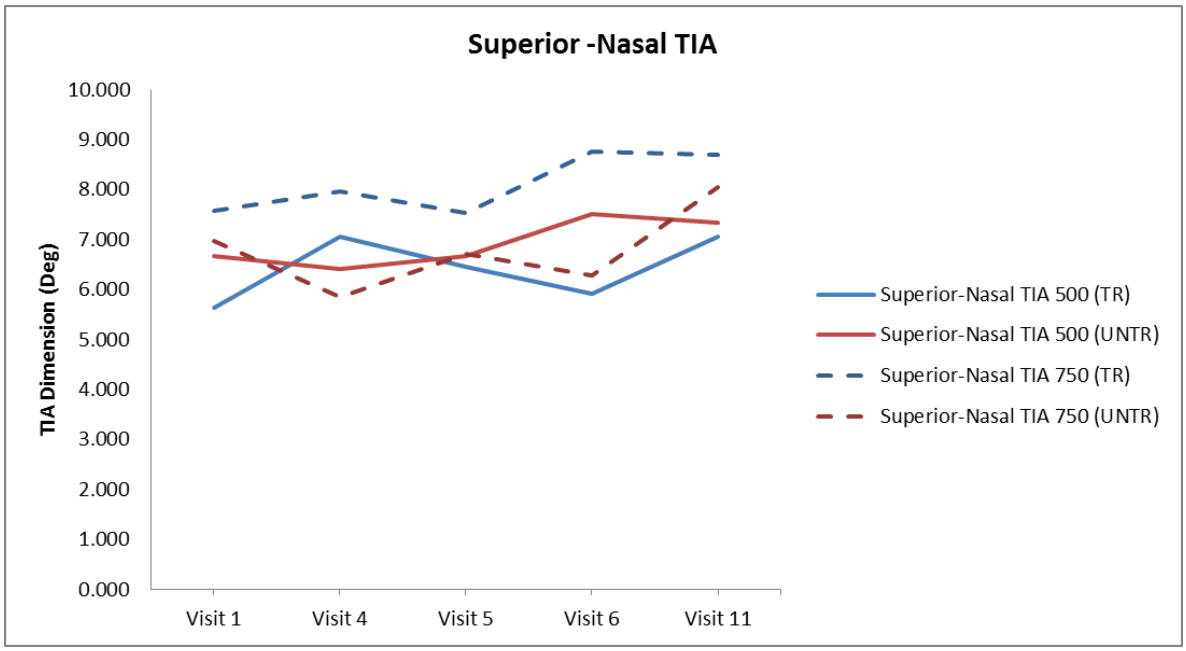


Figure 4.27 TIA 500 and 750µm in the Superior-Nasal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

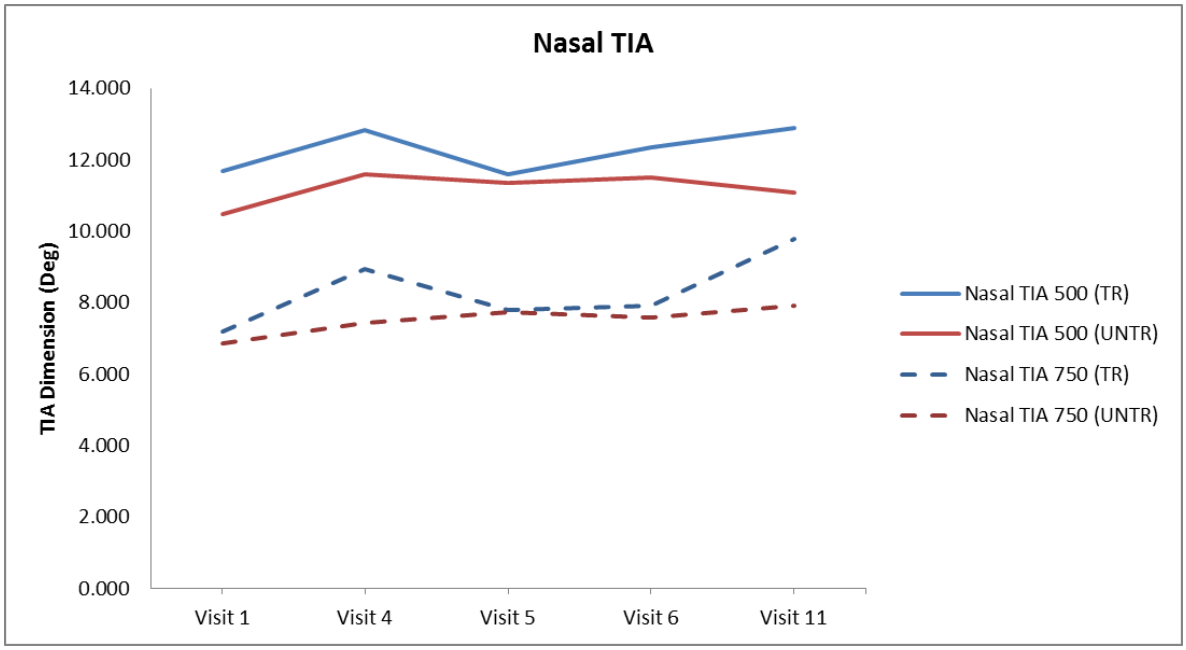


Figure 4.28 TIA 500 and 750µm in the Nasal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

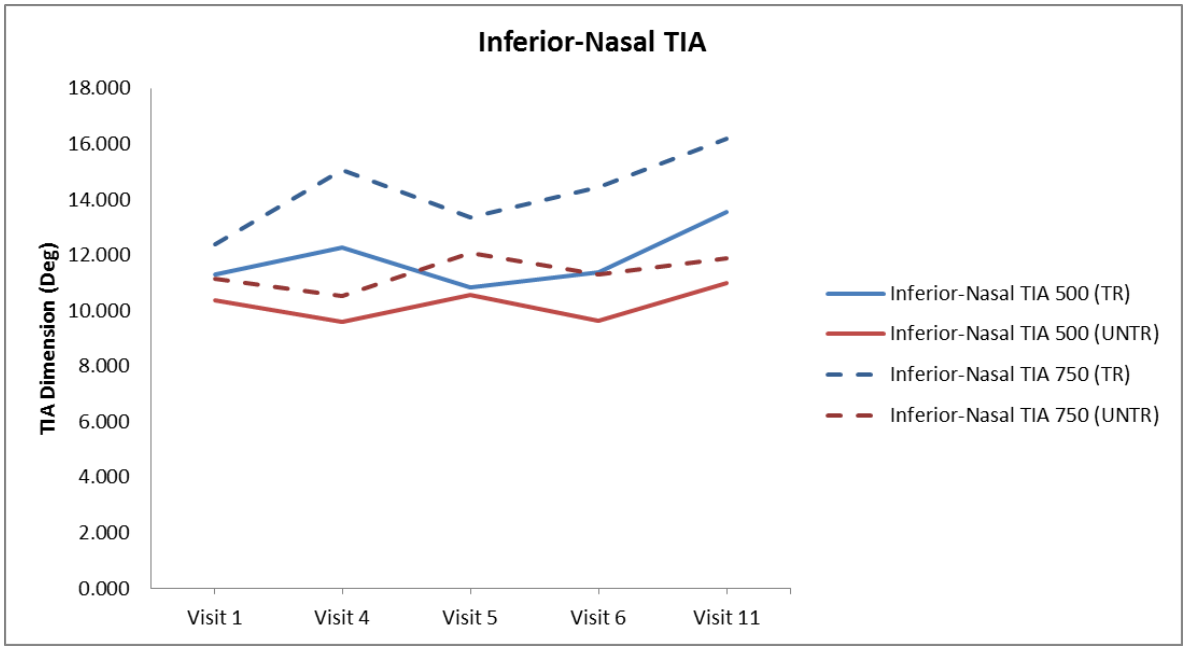


Figure 4.29 TIA 500 and 750µm in the Inferior-Nasal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

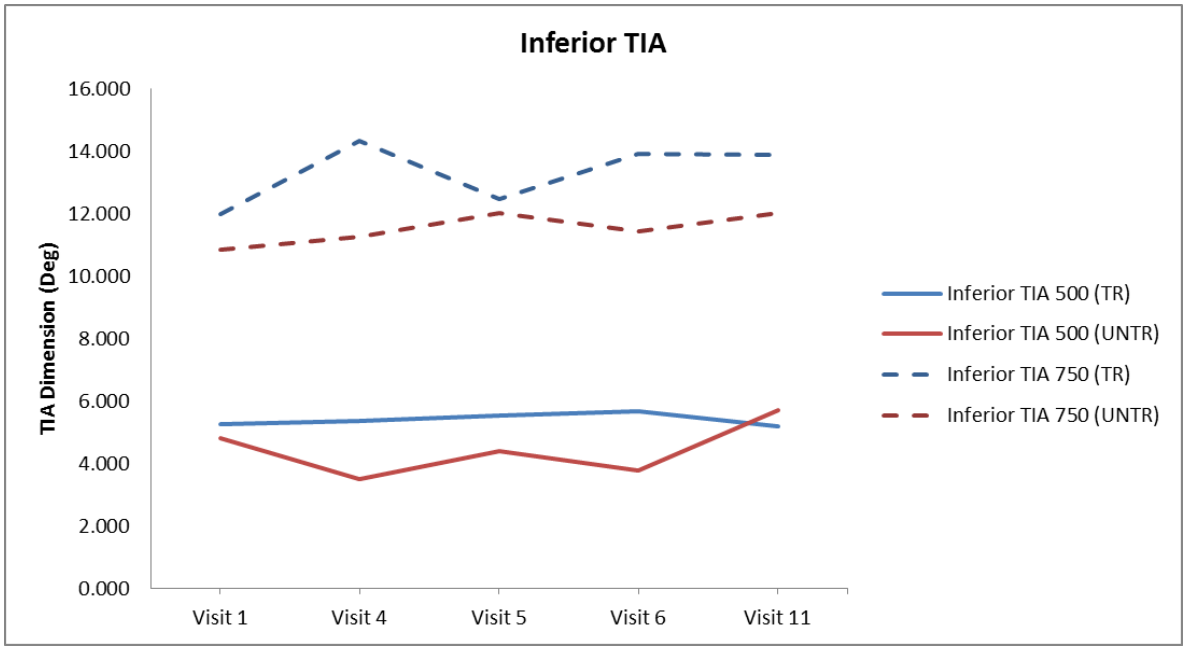


Figure 4.30 TIA 500 and 750µm in the Inferior section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

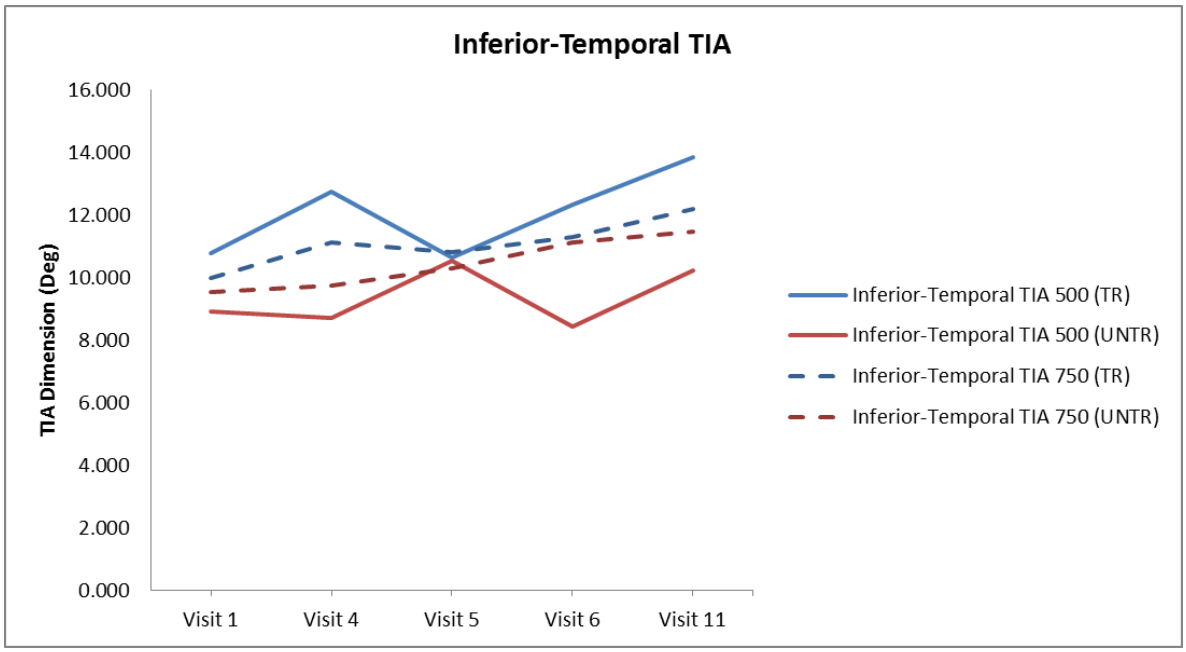


Figure 4.31 TIA 500 and 750µm in the Inferior-Temporal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

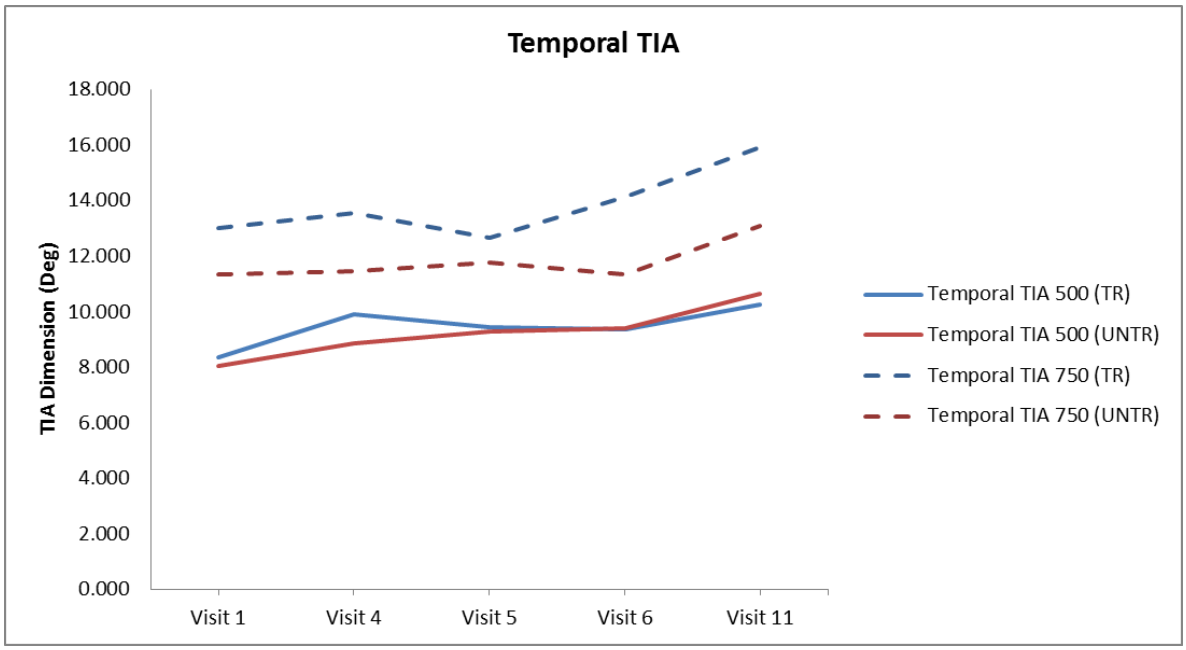


Figure 4.32 TIA 500 and 750µm in the Temporal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

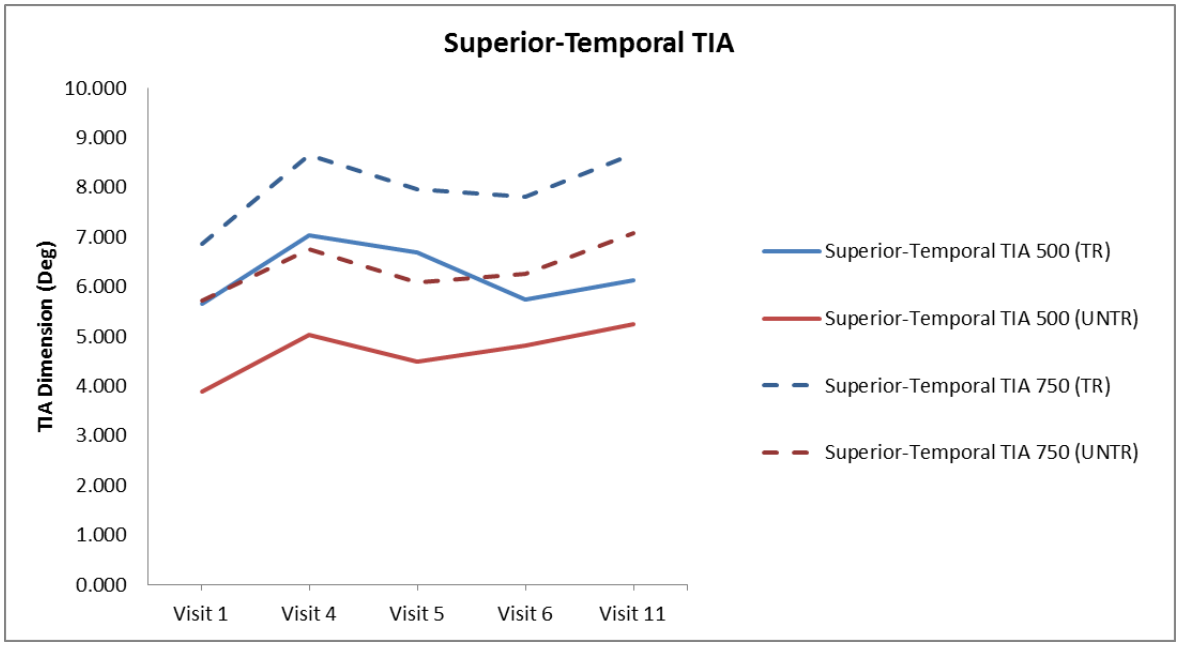


Figure 4.33 TIA 500 and 750µm in the Superior-Temporal section for LPI Treated and Untreated eyes through Visits 1, 4, 5, 6 and 11.

		VISIT 6		VISIT 8		VISIT 9		VISIT 10		VISIT 11	
		TR	UNTR	TR	UNTR	TR	UNTR	TR	UNTR	TR	UNTR
	IOP	18.3 (3.4)	18.7 (2.8)	15.0 (3.2)	NA	17.4 (3.2)	NA	18.4 (2.3)	NA	15.8 (2.7)	17.2 (3.2)
SUPERIOR	AOD 500	0.052 (0.073)	0.020 (0.036)	0.109 (0.118)	NA	0.106 (0.134)	NA	0.084 (0.099)	NA	0.075 (0.080)	0.017 (0.026)
	ARA500	0.018 (0.038)	0.007 (0.016)	0.046 (0.046)	NA	0.043 (0.058)	NA	0.042 (0.049)	NA	0.031 (0.032)	0.006 (0.015)
	TISA500	0.017 (0.037)	0.006 (0.015)	0.045 (0.046)	NA	0.039 (0.053)	NA	0.039 (0.046)	NA	0.030 (0.032)	0.006 (0.015)
	TIA500	4.150 (6.265)	1.690 (3.078)	10.282 (10.960)	NA	8.682 (10.973)	NA	6.936 (7.881)	NA	6.355 (7.108)	1.311 (1.877)
	AOD750	0.103 (0.100)	0.078 (0.063)	0.180 (0.147)	NA	0.159 (0.169)	NA	0.125 (0.111)	NA	0.160 (0.110)	0.071 (0.059)
	ARA750	0.038 (0.057)	0.022 (0.029)	0.086 (0.076)	NA	0.082 (0.092)	NA	0.070 (0.071)	NA	0.068 (0.054)	0.019 (0.026)
	TISA750	0.037 (0.055)	0.022 (0.028)	0.085 (0.076)	NA	0.078 (0.089)	NA	0.067 (0.068)	NA	0.066 (0.054)	0.019 (0.026)
	TIA750	5.970 (5.890)	4.540 (3.660)	11.645 (9.566)	NA	9.464 (10.148)	NA	7.582 (6.449)	NA	9.556 (6.440)	4.000 (3.216)
INFERIOR	AOD500	0.049 (0.074)	0.051 (0.064)	0.181 (0.106)	NA	0.165 (0.134)	NA	0.127 (0.086)	NA	0.079 (0.069)	0.031 (0.049)
	ARA500	0.020 (0.037)	0.013 (0.023)	0.069 (0.043)	NA	0.066 (0.049)	NA	0.050 (0.043)	NA	0.022 (0.024)	0.007 (0.010)
	TISA500	0.019 (0.035)	0.012 (0.023)	0.065 (0.039)	NA	0.061 (0.045)	NA	0.046 (0.040)	NA	0.021 (0.023)	0.007 (0.010)
	TIA500	4.018 (6.249)	3.820 (4.914)	14.600 (8.735)	NA	11.955 (8.972)	NA	10.520 (7.355)	NA	6.218 (5.550)	2.011 (2.732)
	AOD750	0.108 (0.100)	0.144 (0.099)	0.285 (0.140)	NA	0.274 (0.190)	NA	0.197 (0.126)	NA	0.138 (0.096)	0.140 (0.111)
	ARA750	0.041 (0.057)	0.040 (0.042)	0.133 (0.071)	NA	0.124 (0.086)	NA	0.089 (0.066)	NA	0.051 (0.043)	0.032 (0.031)
	TISA750	0.040 (0.055)	0.039 (0.041)	0.128 (0.068)	NA	0.119 (0.083)	NA	0.086 (0.064)	NA	0.049 (0.042)	0.035 (0.031)
	TIA750	6.400 (6.003)	7.660 (5.497)	16.955 (8.766)	NA	14.382 (8.716)	NA	11.755 (7.777)	NA	8.036 (5.651)	7.389 (5.454)
SUPERIOR-NASAL	AOD500	0.058 (0.072)	0.051 (0.044)	0.157 (0.081)	NA	0.129 (0.135)	NA	0.080 (0.081)	NA	0.087 (0.074)	0.047 (0.054)
	ARA500	0.033 (0.041)	0.029 (0.027)	0.063 (0.038)	NA	0.042 (0.041)	NA	0.043 (0.040)	NA	0.048 (0.049)	0.026 (0.025)
	TISA500	0.031 (0.038)	0.025 (0.023)	0.060 (0.036)	NA	0.040 (0.039)	NA	0.039 (0.035)	NA	0.043 (0.041)	0.029 (0.024)
	TIA500	5.191 (6.697)	4.170 (3.633)	13.982 (6.525)	NA	8.564 (8.746)	NA	6.591 (6.394)	NA	7.355 (6.137)	4.000 (4.222)
	AOD750	0.095 (0.070)	0.098 (0.076)	0.217 (0.121)	NA	0.166 (0.132)	NA	0.136 (0.098)	NA	0.118 (0.092)	0.132 (0.087)
	ARA750	0.053 (0.056)	0.051 (0.041)	0.113 (0.062)	NA	0.071 (0.071)	NA	0.075 (0.058)	NA	0.076 (0.068)	0.052 (0.040)
	TISA750	0.050 (0.054)	0.047 (0.037)	0.110 (0.060)	NA	0.069 (0.070)	NA	0.071 (0.052)	NA	0.071 (0.059)	0.051 (0.040)
	TIA750	5.944 (4.553)	5.750 (4.215)	13.682 (7.191)	NA	10.527 (8.161)	NA	7.973 (5.176)	NA	7.136 (4.832)	8.056 (4.843)
INFERIOR-TEMPORAL	AOD500	0.104 (0.058)	0.120 (0.052)	0.234 (0.113)	NA	0.183 (0.124)	NA	0.173 (0.092)	NA	0.147 (0.080)	0.092 (0.072)
	ARA500	0.059 (0.034)	0.055 (0.049)	0.097 (0.055)	NA	0.078 (0.061)	NA	0.086 (0.057)	NA	0.081 (0.043)	0.038 (0.034)
	TISA500	0.053 (0.033)	0.046 (0.036)	0.093 (0.048)	NA	0.073 (0.051)	NA	0.076 (0.046)	NA	0.073 (0.037)	0.035 (0.028)
	TIA500	9.027 (6.089)	9.510 (4.631)	20.891 (9.408)	NA	14.800 (8.575)	NA	13.609 (5.337)	NA	12.127 (6.613)	7.011 (5.645)
	AOD750	0.199 (0.086)	0.208 (0.073)	0.301 (0.183)	NA	0.279 (0.185)	NA	0.238 (0.125)	NA	0.243 (0.104)	0.180 (0.095)
	ARA750	0.101 (0.046)	0.100 (0.060)	0.168 (0.090)	NA	0.141 (0.096)	NA	0.138 (0.079)	NA	0.133 (0.060)	0.075 (0.050)
	TISA750	0.095 (0.045)	0.090 (0.048)	0.164 (0.084)	NA	0.135 (0.086)	NA	0.128 (0.067)	NA	0.125 (0.054)	0.071 (0.046)
	TIA750	11.755 (5.293)	12.020 (4.684)	18.718 (10.561)	NA	16.518 (9.929)	NA	13.836 (6.015)	NA	14.509 (6.352)	9.911 (4.595)

Continues in next page

Continuation Table 5.4

		VISIT 6		VISIT 8		VISIT 9		VISIT 10		VISIT 11	
		TR	UNTR	TR	UNTR	TR	UNTR	TR	UNTR	TR	UNTR
NASAL	AOD500	0.136 (0.081)	0.129 (0.062)	0.245 (0.108)	NA	0.202 (0.113)	NA	0.185 (0.106)	NA	0.166 (0.097)	0.133 (0.062)
	ARA500	0.072 (0.042)	0.057 (0.037)	(0.108 (0.053)	NA	0.091 (0.049)	NA	0.084 (0.053)	NA	0.086 (0.049)	0.057 (0.035)
	TISA500	0.063 (0.037)	0.050 (0.031)	0.097 (0.042)	NA	0.080 (0.041)	NA	0.074 (0.045)	NA	0.076 (0.040)	0.050 (0.030)
	TIA500	10.573 (6.215)	9.940 (6.207)	21.491 (9.872)	NA	16.945 (9.886)	NA	14.309 (8.213)	NA	13.145 (8.029)	9.867 (5.433)
	AOD750	0.194 (0.111)	0.210 (0.100)	0.302 (0.153)	NA	0.256 (0.159)	NA	0.234 (0.157)	NA	0.264 (0.128)	0.207 (0.080)
	ARA750	0.116 (0.064)	0.105 (0.052)	0.180 (0.079)	NA	0.150 (0.073)	NA	0.140 (0.081)	NA	0.153 (0.067)	0.103 (0.048)
	TISA750	0.107 (0.058)	0.097 (0.047)	0.170 (0.070)	NA	0.139 (0.066)	NA	0.129 (0.073)	NA	0.142 (0.059)	0.096 (0.043)
	TIA500	10.973 (5.308)	11.610 (6.174)	18.827 (9.703)	NA	15.464 (9.705)	NA	13.064 (7.933)	NA	15.110 (6.920)	11.544 (4.714)
TEMPORAL	AOD500	0.093 (0.077)	0.096 (0.062)	0.198 (0.107)	NA	0.148 (0.113)	NA	0.154 (0.089)	NA	0.149 (0.089)	0.102 (0.052)
	ARA500	0.055 (0.042)	0.047 (0.035)	0.090 (0.051)	NA	0.073 (0.044)	NA	0.078 (0.043)	NA	0.084 (0.047)	0.054 (0.032)
	TISA500	0.054 (0.038)	0.042 (0.030)	0.083 (0.043)	NA	0.069 (0.043)	NA	0.071 (0.036)	NA	0.074 (0.037)	0.050 (0.030)
	TIA500	8.218 (6.749)	8.778 (5.718)	18.064 (8.752)	NA	14.627 (12.045)	NA	13.609 (7.397)	NA	11.991 (6.894)	9.413 (5.040)
	AOD750	0.148 (0.077)	0.140 (0.081)	0.257 (0.140)	NA	0.226 (0.172)	NA	0.218 (0.098)	NA	0.187 (0.102)	0.140 (0.098)
	ARA750	0.088 (0.057)	0.078 (0.047)	0.150 (0.079)	NA	0.121 (0.077)	NA	0.127 (0.060)	NA	0.127 (0.064)	0.083 (0.047)
	TISA750	0.081 (0.055)	0.072 (0.043)	0.144 (0.071)	NA	0.117 (0.077)	NA	0.119 (0.054)	NA	0.116 (0.055)	0.078 (0.046)
	TIA 750	9.118 (4.764)	8.960 (4.978)	16.609 (8.356)	NA	15.173 (11.796)	NA	13.845 (5.968)	NA	11.018 (5.408)	9.122 (6.337)
INFERIOR-NASAL	AOD500	0.103 (0.090)	0.134 (0.070)	0.232 (0.082)	NA	0.197 (0.125)	NA	0.158 (0.080)	NA	0.160 (0.105)	0.135 (0.084)
	ARA500	0.052 (0.041)	0.058 (0.052)	0.088 (0.040)	NA	0.081 (0.056)	NA	0.077 (0.054)	NA	0.071 (0.042)	0.055 (0.051)
	TISA500	0.046 (0.036)	0.051 (0.043)	0.083 (0.037)	NA	0.071 (0.050)	NA	0.067 (0.042)	NA	0.063 (0.037)	0.048 (0.040)
	TIA500	7.855 (7.674)	10.350 (5.627)	20.455 (8.069)	NA	15.291 (9.356)	NA	11.218 (4.589)	NA	13.164 (9.500)	10.789 (6.605)
	AOD750	0.188 (0.116)	0.221 (0.087)	0.326 (0.151)	NA	0.252 (0.190)	NA	0.222 ((0.148)	NA	0.203 (0.139)	0.213 (0.075)
	ARA750	0.091 (0.063)	0.105 (0.067)	0.163 (0.061)	NA	0.140 (0.090)	NA	0.129 (0.074)	NA	0.118 (0.064)	0.101 (0.073)
	TISA750	0.085 (0.059)	0.098 (0.059)	0.158 (0.060)	NA	0.131 (0.086)	NA	0.118 (0.063)	NA	0.110 (0.061)	0.093 (0.061)
	TIA750	10.770 (5.931)	12.610 (5.235)	20.200 (9.273)	NA	14.382 (10.592)	NA	11.855 (7.114)	NA	12.073 (8.516)	12.511 (4.153)
SUPERIOR-TEMPORA	AOD500	0.060 (0.088)	0.048 (0.043)	0.138 (0.123)	NA	0.116 (0.091)	NA	0.095 (0.090)	NA	0.090 (0.095)	0.042 (0.050)
	ARA500	0.028 (0.042)	0.023 (0.021)	0.055 (0.050)	NA	0.043 (0.040)	NA	0.034 (0.038)	NA	0.034 (0.038)	0.017 (0.021)
	TISA500	0.027 (0.041)	0.021 (0.020)	0.052 (0.046)	NA	0.042 (0.038)	NA	0.031 (0.035)	NA	0.032 (0.037)	0.016 (0.020)
	TIA500	5.255 (8.190)	4.510 (4.057)	11.109 (9.286)	NA	10.491 (8.105)	NA	7.345 (6.519)	NA	7.673 (8.667)	3.725 (4.560)
	AOD750	0.094 (0.096)	0.089 (0.066)	0.210 (0.153)	NA	0.174 (0.128)	NA	0.167 (0.133)	NA	0.149 (0.094)	0.091 (0.068)
	ARA750	0.050 (0.062)	0.040 (0.032)	0.101 (0.081)	NA	0.083 (0.063)	NA	0.070 (0.056)	NA	0.070 (0.059)	0.037 (0.032)
	TISA750	0.052 (0.064)	0.042 (0.033)	0.098 (0.077)	NA	0.082 (0.061)	NA	0.068 (0.054)	NA	0.068 (0.058)	0.035 (0.031)
	TIA750	5.691 (5.590)	5.860 (4.529)	12.255 (8.211)	NA	10.982 (7.963)	NA	9.400 (7.203)	NA	9.064 (5.634)	5.789 (4.217)

Table 5.4. Mean values for every parameter (treated eyes with ALPI and occludable eyes left untreated) in dark for visits 6, 8, 9, 10 and 11 together with their standard deviation within brackets. TR= ALPI Treated. UNTR= Post PI Occludable, but not treated with ALPI. NA= Not applicable.

CENTRAL POSITION LPI Treated Eyes and Fellows Descriptive Statistics		Visit 1 Mean (SD)	Visit 2 Mean (SD)	Visit 3 Mean (SD)	Visit 4 Mean (SD)	Visit 5 Mean (SD)	Visit 6 Mean (SD)	Visit 11 Mean (SD)
Density	Treated eye	2436.065 (247.543)	2353.636 (336.982)	2420.914 (299.817)	2381.314 (341.859)	2404.649 (300.126)	2405.590 (331.241)	2430.565 (250.658)
	Untreated eye	2434.125 (255.205)	2403.677 (351.032)	2467.167 (339.975)	2406.750 (405.572)	2458.973 (370.328)	2416.200 (355.480)	2402.364 (282.834)
Average Cell Size	Treated eye	414.548 (41.462)	437.030 (92.524)	421.086 (69.635)	430.057 (75.858)	422.892 (59.850)	425.718 (78.085)	415.913 (45.622)
	Untreated eye	415.250 (43.961)	431.441 (117.250)	417.333 (95.478)	434.500 (128.814)	420.081 (98.710)	428.625 (112.098)	422.909 (60.795)
Percentage of Hexagonal Cells	Treated eye	49.323 (07.799)	46.625 (12.760)	50.971 (06.798)	48.882 (07.690)	47.865 (10.122)	43.757 (12.205)	47.409 (07.799)
	Untreated eye	46.774 (9.482)	48.515 (9.484)	49.583 (9.912)	48.314 (7.959)	49.579 (7.800)	41.737 (15.425)	50.000 (8.950)
Corneal Thickness	Treated eye	536.000 (40.127)	534.781 (39.761)	547.849 (34.978)	545.343 (35.991)	543.162 (36.892)	533.030 (34.312)	540.818 (33.768)
	Untreated eye	532.000 (38.796)	539.242 (43.661)	539.457 (34.781)	542.235 (38.296)	542.784 (37.665)	552.933 (36.067)	535.905 (34.106)

Table 6.1. Descriptive statistics for the LPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the CENTRAL area of cornea. SD= Standard Deviation.

SUPERIOR-NASAL POSITION LPI Treated Eyes and Fellows Descriptive Statistics		Visit 1 Mean (SD)	Visit 2 Mean (SD)	Visit 3 Mean (SD)	Visit 4 Mean (SD)	Visit 5 Mean (SD)	Visit 6 Mean (SD)	Visit 11 Mean (SD)
Density	Treated eye	173.000 (47.516)	174.188 (69.209)	191.171 (61.856)	183.306 (57.545)	184.622 (58.141)	174.875 (68.658)	180.348 (59.161)
	Untreated eye	171.697 (51.027)	176.212 (63.476)	184.200 (66.773)	177.028 (49.345)	187.405 (51.428)	180.632 (52.863)	181.546 (56.768)
Average Cell Size	Treated eye	408.813 (60.049)	407.933 (71.101)	408.314 (71.431)	408.056 (63.950)	405.946 (59.463)	402.436 (63.018)	403.091 (53.768)
	Untreated eye	411.091 (62.479)	423.849 (133.988)	408.088 (96.467)	419.667 (106.217)	413.054 (98.726)	403.053 (62.080)	407.046 (55.370)
Percentage of Hexagonal Cells	Treated eye	49.938 (8.743)	48.867 (8.012)	52.800 (10.448)	49.371 (7.021)	47.405 (8.694)	41.026 (13.602)	42.909 (15.632)
	Untreated eye	49.849 (6.681)	49.656 (7.934)	51.000 (5.852)	46.444 (8.337)	48.333 (8.698)	45.763 (11.098)	40.546 (14.289)

Table 6.2. Descriptive statistics for the LPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size and percentage of hexagonal cells for the SUPERIOR-NASAL area of cornea. SD= Standard Deviation.

INFERIOR-NASAL POSITION LPI Treated Eyes and Fellows Descriptive Statistics		Visit Mean (SD)	Visit 2 Mean (SD)	Visit 3 Mean (SD)	Visit 4 Mean (SD)	Visit 5 Mean (SD)	Visit 6 Mean (SD)	Visit 11 Mean (SD)
Density	Treated eye	2459.742 (358.862)	2487.807 (339.826)	2501.743 (353.398)	2486.886 (382.925)	2519.286 (402.753)	2552.250 (356.341)	2510.381 (328.113)
	Untreated eye	2478.273 (321.884)	2538.906 (402.858)	2531.086 (394.798)	2477.059 (423.937)	2569.657 (408.513)	2539.564 (406.787)	2468.546 (356.520)
Average Cell Size	Treated eye	415.258 (63.943)	410.516 (65.914)	408.571 (66.508)	412.686 (73.100)	409.829 (87.060)	400.125 (62.441)	405.381 (57.761)
	Untreated eye	410.849 (60.229)	406.625 (87.069)	412.457 (127.372)	421.677 (117.356)	403.343 (99.260)	408.769 (104.689)	415.455 (77.635)
Percentage of Hexagonal Cells	Treated eye	48.871 (8.253)	49.933 (8.658)	52.618 (7.766)	48.794 (7.260)	51.743 (9.030)	50.550 (7.699)	37.905 (15.336)
	Untreated eye	50.219 (8.194)	51.300 (5.472)	53.029 (10.815)	52.353 (11.023)	50.971 (5.512)	50.154 (6.900)	43.476 (15.677)

Table 6.3. Descriptive statistics for the LPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size and percentage of hexagonal cells for the INFERIOR-NASAL area of cornea. SD= Standard Deviation.

INFERIOR POSITION LPI Treated Eyes and Fellows Descriptive Statistics		Visit 1 Mean (SD)	Visit 2 Mean (SD)	Visit 3 Mean (SD)	Visit 4 Mean (SD)	Visit 5 Mean (SD)	Visit 6 Mean (SD)	Visit 11 Mean (SD)
Density	Treated eye	2426.936 (320.485)	2441.333 (341.352)	2479.147 (386.573)	2434.139 (375.919)	2475.973 (362.859)	2457.575 (359.506)	2450.957 (315.945)
	Untreated eye	2432.485 (283.451)	2510.219 (379.473)	2460.971 (397.334)	2477.667 (441.196)	2473.973 (431.898)	2436.564 (411.892)	2466.000 (279.882)
Average Cell Size	Treated eye	419.581 (60.495)	418.121 (63.877)	416.029 (88.287)	422.167 (78.219)	413.189 (66.582)	416.375 (68.439)	414.913 (57.641)
	Untreated eye	417.000 (52.451)	411.531 (95.117)	420.853 (99.111)	424.694 (134.881)	426.027 (146.238)	427.410 (112.231)	410.381 (45.614)
Percentage of Hexagonal Cells	Treated eye	49.800 (8.826)	49.500 (8.016)	51.235 (6.120)	49.306 (9.844)	49.730 (8.352)	46.692 (9.825)	47.783 (9.075)
	Untreated eye	45.455 (8.768)	52.781 (12.122)	49.939 (11.792)	49.000 (8.441)	48.865 (7.056)	47.947 (7.939)	48.000 (11.238)

Table 6.4. Descriptive statistics for the LPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size and percentage of hexagonal cells for the INFERIOR area of cornea. SD= Standard Deviation.

INFERIOR-TEMPORAL POSITION LPI Treated Eyes and Fellows Descriptive Statistics		Visit 1 Mean (SD)	Visit 2 Mean (SD)	Visit 3 Mean (SD)	Visit 4 Mean (SD)	Visit 5 Mean (SD)	Visit 6 Mean (SD)	Visit 11 Mean (SD)
Density	Treated eye	2433.290 (312.000)	2455.406 (358.123)	2480.029 (343.401)	2451.444 (346.259)	2481.778 (330.545)	2500.075 (366.850)	2495.826 (277.928)
	Untreated eye	2403.969 (328.698)	2466.667 (430.222)	2441.394 (448.658)	2473.265 (406.444)	2464.297 (405.835)	2444.447 (429.503)	2428.909 (308.614)
Average Cell Size	Treated eye	418.161 (59.041)	417.188 (70.948)	411.912 (66.273)	416.556 (63.978)	411.056 (63.865)	410.075 (72.313)	405.478 (44.903)
	Untreated eye	424.500 (64.931)	421.400 (99.293)	431.212 (131.536)	422.294 (123.416)	426.892 (146.387)	429.947 (130.402)	418.546 (58.114)
Percentage of Hexagonal Cells	Treated eye	46.032 (8.701)	46.419 (10.318)	51.091 (6.979)	47.528 (8.052)	49.472 (9.204)	48.385 (8.400)	49.696 (7.570)
	Untreated eye	46.200 (8.339)	46.448 (11.236)	50.182 (13.563)	49.971 (12.518)	48.757 (7.879)	47.083 (9.123)	49.409 (6.299)

Table 6.5. Descriptive statistics for the LPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size and percentage of hexagonal cells for the INFERIOR-TEMPORAL area of cornea. SD= Standard Deviation.

SUPERIOR-TEMPORAL POSITION LPI Treated Eyes and Fellows Descriptive Statistics		Visit 1 Mean (SD)	Visit 2 Mean (SD)	Visit 3 Mean (SD)	Visit 4 Mean (SD)	Visit 5 Mean (SD)	Visit 6 Mean (SD)	Visit 11 Mean (SD)
Density	Treated eye	2466.031 (299.244)	2499.156 (344.312)	2507.514 (372.323)	2514.441 (354.363)	2520.270 (344.132)	2522.974 (357.095)	2511.739 (351.878)
	Untreated eye	2476.061 (312.830)	2436.355 (473.741)	2518.286 (376.967)	2506.286 (433.156)	2497.270 (393.849)	2467.282 (417.233)	2508.364 (325.309)
Average Cell Size	Treated eye	411.938 (55.383)	408.750 (66.097)	410.686 (86.633)	406.794 (68.711)	403.405 (60.299)	405.795 (69.842)	406.870 (67.065)
	Untreated eye	410.576 (56.148)	435.871 (151.727)	407.171 (72.468)	412.229 (81.113)	414.865 (101.611)	421.744 (108.751)	404.682 (49.656)
Percentage of Hexagonal Cells	Treated eye	45.813 (9.630)	47.710 (8.478)	47.486 (10.362)	48.029 (9.134)	50.378 (9.190)	48.949 (7.643)	50.348 (7.145)
	Untreated eye	47.406 (8.032)	49.129 (7.424)	50.794 (8.545)	49.824 (7.082)	48.757 (9.194)	46.821 (7.887)	47.273 (9.346)

Table 6.6. Descriptive statistics for the LPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size and percentage of hexagonal cells for the SUPERIOR-TEMPORAL area of cornea. SD= Standard Deviation.

SUPERIOR POSITION LPI Treated Eyes and Fellows Descriptive Statistics		Visit 1 Mean (SD)	Visit 2 Mean (SD)	Visit 3 Mean (SD)	Visit 4 Mean (SD)	Visit 5 Mean (SD)	Visit 6 Mean (SD)	Visit 11 Mean (SD)
Density	Treated eye	184.438 (46.362)	186.000 (64.077)	212.171 (59.301)	192.444 (62.192)	199.027 (61.461)	178.949 (62.873)	183.130 (75.977)
	Untreated eye	179.303 (57.713)	180.794 (75.231)	199.917 (66.328)	192.611 (67.967)	205.368 (57.924)	181.975 (59.604)	193.773 (65.642)
Average Cell Size	Treated eye	394.844 (60.845)	392.094 (73.666)	390.914 (80.626)	392.086 (66.610)	379.972 (55.204)	410.205 (85.836)	399.333 (73.746)
	Untreated eye	389.182 (60.826)	378.933 (60.678)	388.514 (75.273)	406.944 (140.052)	390.351 (93.593)	403.775 (109.514)	382.286 (67.875)
Percentage of Hexagonal Cells	Treated eye	48.531 (8.651)	51.813 (7.639)	50.324 (7.474)	51.000 (8.582)	49.417 (7.721)	46.410 (11.396)	48.286 (8.719)
	Untreated eye	48.849 (7.918)	51.600 (7.147)	49.382 (7.177)	49.853 (7.003)	49.722 (6.864)	42.513 (13.062)	49.000 (6.693)

Table 6.7. Descriptive statistics for the LPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size and percentage of hexagonal cells for the SUPERIOR area of cornea. SD= Standard Deviation.

CENTRAL POSITION LPI Effect Paired Sample T-test		Visit 2-Visit 1 Mean Diff (SD); P Value	Visit 3- Visit 1 Mean Diff (SD); P Value	Visit 4- Visit 1 Mean Diff (SD); P Value	Visit 5- Visit 1 Mean Diff (SD); P Value	Visit 6- Visit 1 Mean Diff (SD); P Value	Visit 11- Visit 1 Mean Diff (SD); P Value
Density	Treated eye	54.036 (147.544); P=0.063	10.172 (88.055); P=0.539	22.074 (99.352); P=0.259	24.690 (139.607); P=0.349	-6.467 (132.256); P=0.791	4.895 (147.245); P=0.886
	Untreated eye	3.667 (143.755); P=0.890	-31.600 (148.536); P=0.253	8.621 (125.408); P=0.714	-14.033 (135.005); P=0.574	1.938 (143.622); P=0.940	28.947 (143.398); P=0.390
Average Cell Size	Treated eye	-8.536 (21.920); P=0.049*	-2.000 (14.360); P=0.460	-4.370 (17.625); P=0.209	-5.000 (24.527); P=0.282	1.000 (22.455); P=0.809	-0.316 (24.543); P=0.956
	Untreated eye	0.200 (24.646); P=0.965	5.367 (24.657); P=0.243	-2.517 (22.534); P=0.552	1.667 (22.196); P=0.684	-0.031 (25.440); P=0.995	-3.842 (25.065); P=0.513
Percentage of Hexagonal Cells	Treated eye	4.036 (11.475); P=0.074	-2.483 (8.249); P=0.116	-0.296 (9.318); P=0.870	0.000 (12.230); P=1.000	4.172 (13.486); P=0.107	1.211 (9.578); P=0.588
	Untreated eye	-1.207 (9.652); P=0.506	-3.172 (11.285); P=0.141	-0.929 (10.579); P=0.646	-4.200 (10.908); P=0.044*	5.167 (15.232); P=0.073	-2.389 (14.641); P=0.498
Corneal Thickness	Treated eye	-0.320 (9.118); P=0.862	-13.769 (12.206); P<0.001*	-5.840 (10.246); P=0.009*	-4.852 (10.654); P=0.026*	-2.045 (11.652); P=0.420	-0.389 (7.586); P=0.830
	Untreated eye	-0.500 (10.567); P=0.804	-9.000 (7.897); P<0.001*	-3.200 (8.874); P=0.084	-3.138 (8.101); P=0.046*	-1.909 (7.752); P=0.261	-0.353 (8.631); P=0.868

Table 6.8. Paired Samples t test for the LPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the CENTRAL area of cornea. Statistically significant results (P≤0.05) are flagged with an asterisk. Mean Diff= Mean Difference; SD= Standard Deviation

SUPERIOR-NASAL POSITION LPI Effect Paired Sample T-test		Visit 2-Visit 1 Mean Diff (SD); P Value	Visit 3- Visit 1 Mean Diff (SD); P Value	Visit 4- Visit 1 Mean Diff (SD); P Value	Visit 5- Visit 1 Mean Diff (SD); P Value	Visit 6- Visit 1 Mean Diff (SD); P Value	Visit 11- Visit 1 Mean Diff (SD); P Value
Density	Treated eye	2.966 (44.680); P=0.723	-16.533 (43.168); P=0.045	-12.000 (37.925); P=0.099	-17.138 (40.428); P=0.030*	-7.625 (34.308); P=0.218	-5.650 (47.490); P=0.601
	Untreated eye	-5.367 (43.879); P=0.508	-14.935 (43.337); P=0.065	-12.533 (35.938); P=0.066	-24.533 (40.737); P=0.003*	-11.875 (38.308); P=0.089	-7.850 (41.476); P=0.408
Average Cell Size	Treated eye	-3.815 (27.673); P=0.480	-2.433 (25.569); P=0.606	-1.000 (27.087); P=0.844	-5.931 (33.845); P=0.353	-2.031 (18.234); P=0.533	0.105 (22.038); P=0.984
	Untreated eye	0.200 (29.421); P=0.971	3.000 (23.134); P=0.483	5.167 (22.240); P=0.213	1.800 (20.997); P=0.642	4.906 (22.801); P=0.233	-3.900 (21.662); P=0.431
Percentage of Hexagonal Cells	Treated eye	2.741 (6.976); P=0.051	-1.200 (8.413); P=0.441	-0.345 (9.367); P=0.844	1.379 (7.552); P=0.334	9.125 (14.983); P=0.002*	5.368 (16.697); P=0.178
	Untreated eye	0.200 (10.274); P=0.916	-1.000 (8.749); P=0.536	2.033 (9.342); P=0.243	0.733 (9.892); P=0.688	3.875 (12.613); P=0.092	11.000 (18.313); P=0.015*

Table 6.9. Paired Samples t test for the LPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the SUPERIOR-NASAL area of cornea. Statistically significant results (P≤0.05) are flagged with an asterisk. Mean Diff= Mean Difference; SD= Standard Deviation.

INFERIOR-NASAL POSITION LPI Effect Paired Sample T-test		Visit 2-Visit 1 Mean Diff (SD); P Value	Visit 3- Visit 1 Mean Diff (SD); P Value	Visit 4- Visit 1 Mean Diff (SD); P Value	Visit 5- Visit 1 Mean Diff (SD); P Value	Visit 6- Visit 1 Mean Diff (SD); P Value	Visit 11- Visit 1 Mean Diff (SD); P Value
Density	Treated eye	-19.269 (162.291); P=0.550	-10.000 (128.420); P=0.678	-1.704 (161.784); P=0.957	-34.481 (120.674); P=0.150	-65.677 (174.924); P=0.045*	19.684 (176.691); P=0.633
	Untreated eye	-67.414(149.709); P=0.022*	-42.710 (195.540); P=0.233	-14.964 (169.586); P=0.644	-58.464 (169.274); P=0.079	-69.719 (149.911); P=0.013*	60.700 (196.400); P=0.183
Average Cell Size	Treated eye	3.769 (29.347); P=0.519	3.138 (21.891); P=0.447	1.593 (32.086); P=0.799	5.926 (21.532); P=0.165	12.387 (30.827); P=0.033*	-2.421 (31.081); P=0.738
	Untreated eye	12.034 (24.860); P=0.014*	9.742 (40.105); P=0.186	2.857 (36.765); P=0.684	7.464 (27.811); P=0.167	12.156 (24.073); P=0.008*	-13.800 (37.815); P=0.119
Percentage of Hexagonal Cells	Treated eye	-1.120 (9.409); P=0.557	-3.143 (11.971); P=0.176	-0.231 (8.449); P=0.890	-3.333 (9.747); P=0.087	-2.548 (8.895); P=0.121	11.053 (16.748); P=0.010*
	Untreated eye	-2.444 (7.192); P=0.089	-1.200 (10.723); P=0.545	-2.667 (9.207); P=0.144	-2.519 (9.870); P=0.196	0.129 (10.317); P=0.945	7.000 (16.145); P=0.075

Table 6.10. Paired Samples t test for the LPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the INFERIOR-NASAL area of cornea. Statistically significant results (P≤0.05) are flagged with an asterisk. Mean Diff= Mean Difference; SD= Standard Deviation.

INFERIOR POSITION LPI Effect Paired Sample T-test		Visit 2-Visit 1 Mean Diff (SD); P Value	Visit 3- Visit 1 Mean Diff (SD); P Value	Visit 4- Visit 1 Mean Diff (SD); P Value	Visit 5- Visit 1 Mean Diff (SD); P Value	Visit 6- Visit 1 Mean Diff (SD); P Value	Visit 11- Visit 1 Mean Diff (SD); P Value
Density	Treated eye	-1.179 (166.877); P=0.970	-17.643 (202.329); P=0.648	3.821 (206.487); P=0.923	-40.036 (170.679); P=0.225	-23.677 (181.445); P=0.473	45.684 (175.170); P=0.271
	Untreated eye	-83.724(177.608); P=0.017*	-37.667 (185.548); P=0.275	-47.033 (177.842); P=0.158	-40.500 (202.869); P=0.283	-15.406 (158.764); P=0.587	-26.842 (146.757); P=0.436
Average Cell Size	Treated eye	0.857 (26.393); P=0.865	-1.214 (42.150); P=0.880	-0.607 (32.318); P=0.922	4.571 (27.676); P=0.390	2.226 (30.532); P=0.688	-8.579 (27.637); P=0.193
	Untreated eye	14.379 (33.476); P=0.028*	4.133 (35.030); P=0.523	5.167 (32.486); P=0.391	4.533 (35.936); P=0.495	0.781 (30.059); P=0.884	5.474 (26.966); P=0.388
Percentage of Hexagonal Cells	Treated eye	0.333 (8.138); P=0.833	-1.963 (8.506); P=0.241	-0.429 (10.772); P=0.835	-2.185 (8.629); P=0.200	1.241 (11.398); P=0.562	1.889 (10.943); P=0.474
	Untreated eye	-7.034 (15.424); P=0.021*	-4.933 (14.105); P=0.065	-2.933 (10.998); P=0.155	-3.700 (9.904); P=0.050	-2.563 (9.476); P=0.136	-2.211 (12.354); P=0.446

Table 6.11. Paired Samples t test for the LPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the INFERIOR area of cornea. Statistically significant results (P≤0.05) are flagged with an asterisk. Mean Diff= Mean Difference; SD= Standard Deviation.

INFERIOR-TEMPORAL POSITION LPI Effect Paired Sample T-test		Visit 2-Visit 1 Mean Diff (SD); P Value	Visit 3- Visit 1 Mean Diff (SD); P Value	Visit 4- Visit 1 Mean Diff (SD); P Value	Visit 5- Visit 1 Mean Diff (SD); P Value	Visit 6- Visit 1 Mean Diff (SD); P Value	Visit 11- Visit 1 Mean Diff (SD); P Value
Density	Treated eye	-30.179 (99.715); P=0.121	-47.036 (135.148); P=0.077	1.750 (136.552); P=0.946	-46.259 (130.459); P=0.077	-54.645 (125.169); P=0.021*	-50.684 (136.515); P=0.123
	Untreated eye	-74.192 (199.952); P=0.070	-32.483 (171.370); P=0.316	-74.714(159.628); P=0.020*	-51.862 (201.515); P=0.177	-55.032 (213.091); P=0.161	22.450 (140.914); P=0.485
Average Cell Size	Treated eye	3.893 (16.952); P=0.235	7.964 (24.976); P=0.103	-1.071 (22.737); P=0.805	5.704 (23.229); P=0.213	7.742 (21.085); P=0.050*	10.105 (27.799); P=0.130
	Untreated eye	12.692 (40.010); P=0.118	3.552 (40.891); P=0.644	15.714 (32.844); P=0.017*	10.552 (40.037); P=0.167	6.516 (54.089); P=0.508	-5.150 (28.251); P=0.425
Percentage of Hexagonal Cells	Treated eye	-1.250 (9.717); P=0.502	-3.667 (7.071); P=0.012*	-3.143 (9.156); P=0.080	-3.926 (11.770); P=0.095	-1.800 (8.660); P=0.264	-6.053 (10.685); P=0.024*
	Untreated eye	0.391 (12.773); P=0.885	-4.593 (14.872); P=0.121	-5.889 (14.734); P=0.048*	-3.333 (8.367); P=0.049*	-0.857 (8.927); P=0.616	-2.263 (10.697); P=0.369

Table 6.12. Paired Samples t test for the LPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the INFERIOR-TEMPORAL area of cornea. Statistically significant results (P≤0.05) are flagged with an asterisk. Mean Diff= Mean Difference; SD= Standard Deviation.

SUPERIOR-TEMPORAL POSITION LPI Effect Paired Sample T-test		Visit 2-Visit 1 Mean Diff (SD); P Value	Visit 3- Visit 1 Mean Diff (SD); P Value	Visit 4- Visit 1 Mean Diff (SD); P Value	Visit 5- Visit 1 Mean Diff (SD); P Value	Visit 6- Visit 1 Mean Diff (SD); P Value	Visit 11- Visit 1 Mean Diff (SD); P Value
Density	Treated eye	-34.621 (135.521); P=0.180	-35.500 (129.056); P=0.143	-21.893 (140.963); P=0.418	-30.586 (131.978); P=0.222	-43.774 (144.632); P=0.102	20.150 (133.704); P=0.508
	Untreated eye	49.107 (261.768); P=0.330	-15.903 (146.199); P=0.549	-11.433 (154.527); P=0.688	-1.267 (243.111); P=0.977	34.500 (137.819); P=0.167	-0.400 (193.258); P=0.993
Average Cell Size	Treated eye	5.241 (22.532); P=0.221	5.300 (19.679); P=0.151	4.036 (22.499); P=0.351	4.379 (19.505); P=0.237	6.548 (21.903); P=0.106	-7.350 (29.810); P=0.284
	Untreated eye	-8.964 (40.093); P=0.247	2.645 (24.656); P=0.555	-1.967 (27.163); P=0.695	0.767 (37.476); P=0.912	-6.000 (21.418); P=0.123	-0.900 (29.727); P=0.894
Percentage of Hexagonal Cells	Treated eye	-2.448 (9.653); P=0.183	-2.300 (13.641); P=0.363	-1.679 (11.595); P=0.450	-5.966 (10.752); P=0.006*	-4.194 (10.663); P=0.036*	-3.200 (11.176); P=0.216
	Untreated eye	0.107 (9.964); P=0.955	-2.903 (9.361); P=0.094	-2.200 (10.437); P=0.258	-3.069 (8.689); P=0.067	1.094 (9.296); P=0.511	0.650 (12.642); P=0.821

Table 6.13. Paired Samples t test for the LPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the SUPERIOR-TEMPORAL area of cornea. Statistically significant results (P≤0.05) are flagged with an asterisk. Mean Diff= Mean Difference; SD= Standard Deviation.

SUPERIOR POSITION LPI Effect Paired Sample T-test		Visit 2-Visit 1 Mean Diff (SD); P Value	Visit 3- Visit 1 Mean Diff (SD); P Value	Visit 4- Visit 1 Mean Diff (SD); P Value	Visit 5- Visit 1 Mean Diff (SD); P Value	Visit 6- Visit 1 Mean Diff (SD); P Value	Visit 11- Visit 1 Mean Diff (SD); P Value
Density	Treated eye	-2.966 (46.904); P=0.736	-32.333 (48.849); P=0.001*	-17.414 (36.327); P=0.015*	-20.103 (38.934); P=0.010*	-2.742 (39.330); P=0.701	1.850 (63.554); P=0.898
	Untreated eye	-2.258 (67.581); P=0.854	-28.290 (42.095); P=0.001*	-21.133 (49.042); P=0.025*	-28.613 (49.328); P=0.003*	-6.364 (45.026); P=0.423	-16.550 (80.026); P=0.367
Average Cell Size	Treated eye	-3.517 (23.928); P=0.435	0.467 (23.301); P=0.913	-1.552 (23.496); P=0.725	3.862 (18.322); P=0.266	-12.806 (40.279); P=0.087	-11.389 (56.200); P=0.402
	Untreated eye	1.929 (27.936); P=0.718	-1.194 (28.074); P=0.814	-0.100 (29.866); P=0.985	-0.133 (32.841); P=0.982	-9.727 (35.136); P=0.122	6.789 (53.689); P=0.588
Percentage of Hexagonal Cells	Treated eye	-2.862 (7.044); P=0.037*	-1.133 (7.807); P=0.433	-2.310 (6.929); P=0.083	-1.310 (6.257); P=0.269	-2.031 (11.010); P=0.305	-0.333 (10.261); P=0.892
	Untreated eye	-3.250 (7.127); P=0.023*	-0.484 (9.563); P=0.780	-1.069 (10.559); P=0.590	-1.533 (10.702); P=0.439	7.030 (14.152); P=0.008*	-0.316 (08.583); P=0.874

Table 6.14. Paired Samples t test for the LPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the SUPERIOR area of cornea. Statistically significant results ($P \leq 0.05$) are flagged with an asterisk. Mean Diff= Mean Difference; SD= Standard Deviation.

CENTRAL POSITION Effect of LPI Analysis of Covariance	Visit 2 Mean Diff (SE); P Value	Visit 3 Mean Diff (SE); P Value	Visit 4 Mean Diff (SE); P Value	Visit 5 Mean Diff (SE); P Value	Visit 6 Mean Diff (SE); P Value	Visit 11 Mean Diff (SE); P Value
Density	51.258 (34.031); P=0.138	41.252 (31.116); P=0.190	13.520 (30.657); P=0.661	39.004 (35.752); P=0.280	-8.738 (33.742); P=0.797	-25.371 (41.034); P=0.540
Average Cell Size	-8.867 (5.598); P=0.119	-7.224 (5.177); P=0.168	-1.855 (5.485); P=0.737	-6.683 (6.121); P=0.280	1.132 (5.860); P=0.848	3.883 (6.955); P=0.580
Percentage of Hexagonal Cells	3.534 (2.181); P=0.111	-1.098 (1.843); P=0.554	-1.003 (2.071); P=0.630	2.125 (2.050); P=0.304	-2.543 (3.492); P=0.470	0.935 (2.729); P=0.734
Corneal Thickness	0.193 (2.746); P=0.944	-5.012 (2.685); P=0.068	-3.351 (2.444); P=0.177	-2.084 (2.266); P=0.362	1.100 (3.116); P=0.726	-0.016 (2.792); P=0.995

Table 6.15. Analysis of Covariance where the response variable has been adjusted using the Visit 1 data for the Central area of endothelium. (Diff=difference; SE= Standard Error)

SUPERIOR-NASAL POSITION Effect of LPI Analysis of Covariance	Visit 2 Mean Diff (SE); P Value	Visit 3 Mean Diff (SE); P Value	Visit 4 Mean Diff (SE); P Value	Visit 5 Mean Diff (SE); P Value	Visit 6 Mean Diff (SE); P Value	Visit 11 Mean Diff (SE); P Value
Density	8.379 (11.540); P=0.471	-1.207 (10.704); P=0.911	-0.727 (8.782); P=0.934	6.718 (10.023); P=0.505	4.139 (8.961); P=0.646	2.336 (13.676); P=0.865
Average Cell Size	-4.182 (7.512); P=0.580	-5.645 (6.216); P=0.368	-5.696 (6.251); P=0.366	-7.573 (7.317); P=0.305	-6.885 (5.198); P=0.190	3.870 (6.951); P=0.581
Percentage of Hexagonal Cells	1.644 (2.012); P=0.418	-0.539 (1.573); P=0.733	-2.145 (1.912); P=0.267	0.152 (2.143); P=0.944	5.080 (3.226); P=0.121	-3.363 (5.047); P=0.509

Table 6.16. Analysis of Covariance where the response variable has been adjusted using the Visit 1 data for the Superior-Nasal area of endothelium. (Diff=difference; SE= Standard Error)

INFERIOR-NASAL POSITION Effect of LPI Analysis of Covariance	Visit 2 Mean Diff (SE); P Value	Visit 3 Mean Diff (SE); P Value	Visit 4 Mean Diff (SE); P Value	Visit 5 Mean Diff (SE); P Value	Visit 6 Mean Diff (SE); P Value	Visit 11 Mean Diff (SE); P Value
Density	51.478 (39.356); P=0.197	36.559 (37.246); P=0.330	10.904 (42.354); P=0.798	26.564 (39.900); P=0.508	7.263 (38.698); P=0.852	-40.420 (59.064); P=0.498
Average Cell Size	-8.779 (7.016); P=0.216	-7.786 (6.674); P=0.248	-1.229 (8.746); P=0.889	-2.030 (6.784); P=0.766	-0.675 (6.161); P=0.913	11.433 (11.260); P=0.317
Percentage of Hexagonal Cells	1.635 (1.893); P=0.392	-0.317 (2.039); P=0.877	3.398 (2.353); P=0.155	0.370 (1.746); P=0.833	-1.302 (1.850); P=0.484	5.433 (5.031); P=0.288

Table 6.17. Analysis of Covariance where the response variable has been adjusted using the Visit 1 data for the Inferior-Nasal area of endothelium. (Diff=difference; SE= Standard Error)

INFERIOR POSITION Effect of LPI Analysis of Covariance	Visit 2 Mean Diff (SE); P Value	Visit 3 Mean Diff (SE); P Value	Visit 4 Mean Diff (SE); P Value	Visit 5 Mean Diff (SE); P Value	Visit 6 Mean Diff (SE); P Value	Visit 11 Mean Diff (SE); P Value
Density	84.720 (43.060); P=0.054	19.604 (51.412); P=0.704	51.528 (50.612); P=0.313	0.175 (49.929); P=0.997	-8.311 (43.231); P=0.848	72.544 (50.324); P=0.158
Average Cell Size	-14.182 (7.573); P=0.067	-5.877 (10.104); P=0.563	-6.023 (8.533); P=0.483	-0.055 (8.556); P=0.995	1.463 (7.695); P=0.850	-13.799 (8.478); P=0.112
Percentage of Hexagonal Cells	4.734 (2.800); P=0.097	0.156 (2.612); P=0.952	-0.258 (2.326); P=0.912	-0.587 (2.040); P=0.775	0.767 (2.097); P=0.716	0.017 (3.298); P=0.996

Table 6.18. Analysis of Covariance where the response variable has been adjusted using the Visit 1 data for the Inferior area of endothelium. (Diff=difference; SE= Standard Error)

INFERIOR-TEMPORAL POSITION Effect of LPI Analysis of Covariance	Visit 2 Mean Diff (SE); P Value	Visit 3 Mean Diff (SE); P Value	Visit 4 Mean Diff (SE); P Value	Visit 5 Mean Diff (SE); P Value	Visit 6 Mean Diff (SE); P Value	Visit 11 Mean Diff (SE); P Value
Density	41.965(42.652); P=0.330	-15.722 (41.186); P=0.704	72.881 (38.416); P=0.063	2.740 (44.614); P=0.951	-1.802 (44.774); P=0.968	-74.079 (43.644); P=0.098
Average Cell Size	-8.158 (8.238); P=0.327	4.830 (9.039); P=0.595	-15.617 (6.948); P=0.029	-4.056 (8.632); P=0.640	1.130 (10.546); P=0.915	15.358 (8.687); P=0.086
Percentage of Hexagonal Cells	-1.351 (2.974); P=0.652	1.488 (2.816); P=0.599	3.199 (2.650); P=0.233	-0.695 (2.258); P=0.760	-1.156 (2.047); P=0.575	-2.391 (2.175); P=0.279

Table 6.19. Analysis of Covariance where the response variable has been adjusted using the Visit 1 data for the Inferior-Temporal area of endothelium. (Diff=difference; SE= Standard Error)

SUPERIOR-TEMPORAL POSITION Effect of LPI Analysis of Covariance	Visit 2 Mean Diff (SE); P Value	Visit 3 Mean Diff (SE); P Value	Visit 4 Mean Diff (SE); P Value	Visit 5 Mean Diff (SE); P Value	Visit 6 Mean Diff (SE); P Value	Visit 11 Mean Diff (SE); P Value
Density	-80.417(53.326);P=0.137	-18.581(34.990); P=0.597	-10.226 (39.241); P=0.795	-26.837 (48.854); P=0.585	-77.284 (35.336); P=0.033	20.838 (53.102); P=0.697
Average Cell Size	14.002 (8.531); P=0.107	2.577 (5.685); P=0.652	5.872 (6.603); P=0.378	3.393 (7.527); P=0.654	12.475 (5.469); P=0.026	-6.529 (9.388); P=0.491
Percentage of Hexagonal Cells	-0.016 (2.097); P=0.994	1.438 (2.435); P=0.557	1.480 (2.205); P=0.505	-1.460 (1.725); P=0.401	-4.010 (1.821); P=0.031	-2.653 (2.801); P=0.350

Table 6.20. Analysis of Covariance where the response variable has been adjusted using the Visit 1 data for the Superior-Temporal area of endothelium. (Diff=difference; SE= Standard Error)

SUPERIOR POSITION Effect of LPI Analysis of Covariance	Visit 2 Mean Diff; SE (p Value)	Visit 3 Mean Diff; SE (p Value)	Visit 4 Mean Diff; SE (p Value)	Visit 5 Mean Diff; SE (p Value)	Visit 6 Mean Diff; SE (p Value)	Visit 11 Mean Diff; SE (p Value)
Density	-1.255 (14.833); P=0.933	-5.656 (10.831); P=0.603	2.889 (11.047); P=0.795	6.427 (11.086); P=0.564	2.722 (10.248); P=0.791	14.391 (21.520); P=0.508
Average Cell Size	-5.414 (6.960); P=0.440	1.780 (6.676); P=0.791	-1.309 (7.070); P=0.854	4.100 (7.005); P=0.561	-2.077 (9.233); P=0.823	-18.848 (18.016); P=0.303
Percentage of Hexagonal Cells	0.197 (1.679); P=0.907	-0.631 (1.774); P=0.723	-1.040 (1.881); P=0.583	0.339 (1.881); P=0.858	-4.863 (3.051); P=0.116	0.527 (2.412); P=0.828

Table 6.21. Analysis of Covariance where the response variable has been adjusted using the Visit 1 data for the Superior area of endothelium. (Diff=difference; SE= Standard Error)

CENTRAL POSITION ALPI Treated and Fellow Eyes Descriptive Statistics		Visit 6 Mean (SD)	Visit 7 Mean (SD)	Visit 8 Mean (SD)	Visit 9 Mean (SD)	Visit 10 Mean (SD)	Visit 11 Mean (SD)
Density	Treated eye	2377.000 (417.212)	2345.273 (411.047)	2384.546 (462.114)	2269.500 (375.167)	2389.111 (375.384)	2465.889 (338.453)
	Untreated eye	2482.000 (275.809)	N/A	N/A	N/A	N/A	2513.833 (247.022)
Average Cell Size	Treated eye	434.500 (90.440)	441.273 (94.974)	437.000 (103.183)	455.200 (99.609)	429.333 (78.580)	412.222 (56.242)
	Untreated eye	407.800 (49.924)	N/A	N/A	N/A	N/A	400.833 (37.494)
Percentage of Hexagonal Cells	Treated eye	45.100 (12.270)	45.182 (13.826)	48.727 (8.344)	48.800 (11.003)	50.222 (6.099)	50.444 (6.366)
	Untreated eye	43.500 (13.697)	N/A	N/A	N/A	N/A	44.000 (6.663)
Corneal Thickness	Treated eye	525.889 (35.385)	543.727 (43.614)	552.800 (40.041)	551.222 (43.791)	540.625 (53.711)	539.778 (52.664)
	Untreated eye	534.222 (48.823)	N/A	N/A	N/A	N/A	528.400 (50.841)

Table 6.22. Descriptive statistics for the ALPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the CENTRAL area of cornea. SD= Standard Deviation.

SUPERIOR-NASAL POSITION ALPI Treated and Fellow Eyes Descriptive Statistics		Visit 6 Mean (SD)	Visit 7 Mean (SD)	Visit 8 Mean (SD)	Visit 9 Mean (SD)	Visit 10 Mean (SD)	Visit 11 Mean (SD)
Density	Treated eye	162.727 (63.525)	161.909 (60.970)	185.727 (66.192)	181.700 (53.922)	176.889 (71.822)	176.222 (52.141)
	Untreated eye	182.900 (86.288)	N/A	N/A	N/A	N/A	152.667 (48.430)
Average Cell Size	Treated eye	409.500 (58.849)	399.500 (58.935)	405.900 (59.752)	446.700 (110.044)	396.250 (67.502)	402.778 (63.675)
	Untreated eye	399.200 (79.465)	N/A	N/A	N/A	N/A	422.167 (33.145)
Percentage of Hexagonal Cells	Treated eye	41.500 (15.869)	47.300 (9.141)	48.400 (8.566)	49.667 (9.798)	51.500 (8.669)	38.333 (15.182)
	Untreated eye	40.800 (11.821)	N/A	N/A	N/A	N/A	38.500 (17.410)

Table 6.23. Descriptive statistics for the ALPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the SUPERIOR-NASAL area of cornea. SD= Standard Deviation.

INFERIOR-NASAL POSITION ALPI Treated and Fellow Eyes Descriptive Statistics		Visit 6 Mean (SD)	Visit 7 Mean (SD)	Visit 8 Mean (SD)	Visit 9 Mean (SD)	Visit 10 Mean (SD)	Visit 11 Mean (SD)
Density	Treated eye	2456.636 (408.211)	2482.700 (330.250)	2467.818 (401.756)	2382.200 (381.063)	2475.444 (371.545)	2445.000 (357.317)
	Untreated eye	2565.400 (417.621)	N/A	N/A	N/A	N/A	2494.000 (384.094)
Average Cell Size	Treated eye	419.546 (83.981)	410.100 (60.929)	416.727 (79.514)	432.400 (87.285)	413.444 (71.514)	418.000 (71.791)
	Untreated eye	399.700 (67.802)	N/A	N/A	N/A	N/A	408.833 (62.952)
Percentage of Hexagonal Cells	Treated eye	50.364 (7.632)	51.100 (6.999)	52.182 (6.524)	52.100 (10.148)	48.333 (15.580)	44.000 (14.392)
	Untreated eye	51.700 (7.196)	N/A	N/A	N/A	N/A	36.167 (16.167)

Table 6.24. Descriptive statistics for the ALPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for INFERIOR-NASAL area of cornea. SD= Standard Deviation.

INFERIOR POSITION ALPI Treated and Fellow Eyes Descriptive Statistics		Visit 6 Mean (SD)	Visit 7 Mean (SD)	Visit 8 Mean (SD)	Visit 9 Mean (SD)	Visit 10 Mean (SD)	Visit 11 Mean (SD)
Density	Treated eye	2413.818 (424.498)	2388.182 (488.528)	2440.727 (454.219)	2334.000 (433.945)	2487.111 (465.163)	2577.556 (415.413)
	Untreated eye	2516.000 (368.745)	N/A	N/A	N/A	N/A	2410.667 (263.879)
Average Cell Size	Treated eye	426.727 (79.284)	439.091 (113.390)	424.546 (89.342)	445.100 (101.231)	415.444 (82.219)	397.889 (70.458)
	Untreated eye	405.400 (63.186)	N/A	N/A	N/A	N/A	419.000 (46.109)
Percentage of Hexagonal Cells	Treated eye	43.182 (13.906)	46.455 (8.768)	46.727 (9.519)	51.600 (6.328)	46.667 (13.360)	50.667 (8.093)
	Untreated eye	49.444 (4.065)	N/A	N/A	N/A	N/A	50.000 (10.752)

Table 6.25. Descriptive statistics for the ALPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for INFERIOR area of cornea. SD= Standard Deviation.

INFERIOR-TEMPORAL POSITION ALPI Treated and Fellow Eyes Descriptive Statistics		Visit 6 Mean (SD)	Visit 7 Mean (SD)	Visit 8 Mean (SD)	Visit 9 Mean (SD)	Visit 10 Mean (SD)	Visit 11 Mean (SD)
Density	Treated eye	2461.727 (459.098)	2468.546 (468.813)	2429.182 (457.767)	2388.800 (414.529)	2522.556 (461.612)	2564.375 (343.854)
	Untreated eye	2541.100 (359.250)	N/A	N/A	N/A	N/A	2444.333 (223.838)
Average Cell Size	Treated eye	423.091 (100.930)	422.818 (103.923)	427.273 (93.596)	432.800 (92.394)	409.778 (83.997)	397.125 (60.737)
	Untreated eye	401.900 (65.336)	N/A	N/A	N/A	N/A	412.000 (37.731)
Percentage of Hexagonal Cells	Treated eye	47.727 (7.525)	49.091 (11.597)	47.727 (8.956)	48.300 (7.775)	47.111 (8.418)	43.375 (6.760)
	Untreated eye	48.200 (9.259)	N/A	N/A	N/A	N/A	50.000 (4.472)

Table 6.26. Descriptive statistics for the ALPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the INFERIOR-TEMPORAL area of cornea. SD= Standard Deviation.

SUPERIOR-TEMPORAL POSITION ALPI Treated and Fellow Eyes Descriptive Statistics		Visit 10 Mean (SD)	Visit 7 Mean (SD)	Visit 8 Mean (SD)	Visit 9 Mean (SD)	Visit 10 Mean (SD)	Visit 11 Mean (SD)
Density	Treated eye	2433.500 (441.932)	2435.546 (419.404)	2445.600 (294.566)	2387.600 (411.234)	2447.667 (410.151)	2511.111 (326.532)
	Untreated eye	2548.800 (394.566)	N/A	N/A	N/A	N/A	2389.833 (389.900)
Average Cell Size	Treated eye	426.800 (99.027)	425.364 (95.374)	414.700 (54.408)	433.200 (93.615)	420.333 (80.167)	405.444 (62.698)
	Untreated eye	402.000 (70.233)	N/A	N/A	N/A	N/A	428.167 (72.824)
Percentage of Hexagonal Cells	Treated eye	45.200 (9.247)	45.000 (7.603)	48.200 (7.084)	51.100 (4.701)	46.750 (7.265)	45.250 (11.671)
	Untreated eye	53.100 (4.280)	N/A	N/A	N/A	N/A	50.333 (5.645)

Table 6.27. Descriptive statistics for the ALPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the SUPERIOR-TEMPORAL area of cornea. SD= Standard Deviation.

SUPERIOR POSITION ALPI Treated and Fellow Eyes Descriptive Statistics		Visit 6 Mean (SD)	Visit 7 Mean (SD)	Visit 8 Mean (SD)	Visit 9 Mean (SD)	Visit 10 Mean (SD)	Visit 11 Mean (SD)
Density	Treated eye	184.000 (49.891)	188.636 (66.634)	207.636 (69.773)	197.000 (73.062)	218.000 (80.416)	211.222 (35.570)
	Untreated eye	168.600 (62.399)	N/A	N/A	N/A	N/A	149.500 (31.628)
Average Cell Size	Treated eye	410.700 (100.222)	385.100 (53.295)	371.100 (62.788)	389.000 (56.105)	379.375 (55.939)	368.667 (35.433)
	Untreated eye	412.400 (57.163)	N/A	N/A	N/A	N/A	432.333 (65.479)
Percentage of Hexagonal Cells	Treated eye	155.778 (207.235)	48.200 (8.162)	51.100 (8.736)	49.778 (7.546)	49.000 (8.586)	52.333 (7.053)
	Untreated eye	316.222 (263.688)	N/A	N/A	N/A	N/A	49.167 (4.262)

Table 6.28 Descriptive statistics for the ALPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the SUPERIOR area of cornea. SD= Standard Deviation.

CENTRAL POSITION ALPI Treated Paired Sample T-test		Visit 7-Visit 6 Mean Diff (SD); P Value	Visit 8- Visit 6 Mean Diff (SD); P Value	Visit 9- Visit 6 Mean Diff (SD); P Value	Visit 10- Visit 6 Mean Diff (SD); P Value	Visit 11- Visit 6 Mean Diff (SD); P Value
Density	Treated eye	43.500 (126.321); P=0.304	-18.000 (175.620); P=0.753	32.889 (089.058); P=0.300	-17.250 (151.278); P=0.756	-9.778 (076.785); P=0.712
Average Cell Size	Treated eye	-10.300 (23.457); P=0.198	-2.300 (34.545); P=0.838	-11.222 (23.134); P=0.184	8.125 (28.276); P=0.443	0.333 (14.595); P=0.947
Percentage of Hexagonal Cells	Treated eye	1.200 (21.540); P=0.864	-3.900 (11.846); P=0.325	-3.000 (16.101); P=0.591	-3.875 (13.964); P=0.458	-5.222 (12.194); P=0.235
Corneal Thickness	Treated eye	-6.333 (23.532); P=0.443	-5.750 (8.860); P=0.109	-2.714 (11.470); P=0.554	1.167 (9.827); P=0.783	2.250 (8.876); P=0.497

Table 6.29. Paired Samples t test for the ALPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the CENTRAL area of cornea. Statistically significant results (P≤0.05) are flagged with an asterisk. Mean Diff= Mean Difference; SD= Standard Deviation.

SUPERIOR-NASAL POSITION ALPI Treated Paired Sample T-test		Visit 7-Visit 6 Mean Diff (SD); P Value	Visit 8- Visit 6 Mean Diff (SD); P Value	Visit 9- Visit 6 Mean Diff (SD); P Value	Visit 10- Visit 6 Mean Diff (SD); P Value	Visit 11- Visit 6 Mean Diff (SD); P Value
Density	Treated eye	0.818 (22.899); P=0.908	-23.000 (32.441); P=0.041*	-19.600 (31.837); P=0.083	-11.889 (33.554); P=0.319	0.667 (15.305); P=0.899
Average Cell Size	Treated eye	10.000 (26.554); P=0.264	3.600 (24.708); P=0.656	-3.556 (31.592); P=0.744	12.000 (12.166); P=0.027*	4.444 (18.056); P=0.481
Percentage of Hexagonal Cells	Treated eye	-5.800 (12.700); P=0.183	-6.900 (12.931); P=0.126	-5.889 (15.390); P=0.284	-7.750 (14.489); P=0.174	2.222 (14.007); P=0.647

Table 6.30. Paired Samples t test for the ALPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the SUPERIOR-NASAL area of cornea. Statistically significant results (P≤0.05) are flagged with an asterisk. Mean Diff= Mean Difference; SD= Standard Deviation.

INFERIOR-NASAL POSITION ALPI Treated Paired Sample T-test		Visit 7-Visit 6 Mean Diff (SD); P Value	Visit 8- Visit 6 Mean Diff (SD); P Value	Visit 9- Visit 6 Mean Diff (SD); P Value	Visit 10- Visit 6 Mean Diff (SD); P Value	Visit 11- Visit 6 Mean Diff (SD); P Value
Density	Treated eye	52.700 (149.045); P=0.292	-11.182 (133.737); P=0.787	15.100 (110.582); P=0.676	-46.222 (162.239); P=0.418	80.000 (167.470); P=0.219
Average Cell Size	Treated eye	-8.500 (24.681); P=0.304	2.818 (21.600); P=0.674	-3.700 (21.884); P=0.606	13.000 (41.331); P=0.373	-13.250 (27.139); P=0.210
Percentage of Hexagonal Cells	Treated eye	0.500 (9.490); P=0.871	-1.818 (7.373); P=0.432	-1.600 (14.049); P=0.727	1.667 (12.083); P=0.690	6.500 (12.059); P=0.171

Table 6.31. Paired Samples t test for the ALPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the INFERIOR-NASAL area of cornea. Statistically significant results (P≤0.05) are flagged with an asterisk. Mean Diff= Mean Difference; SD= Standard Deviation.

INFERIOR POSITION ALPI Treated Paired Sample T-test		Visit 7-Visit 6 Mean Diff (SD); P Value	Visit 8- Visit 6 Mean Diff (SD); P Value	Visit 9- Visit 6 Mean Diff (SD); P Value	Visit 10- Visit 6 Mean Diff (SD); P Value	Visit 11- Visit 6 Mean Diff (SD); P Value
Density	Treated eye	25.636 (175.702); P=0.639	-26.909 (99.281); P=0.390	0.500 (135.635); P=0.991	-64.556 (140.462); P=0.205	-52.889 (132.797); P=0.266
Average Cell Size	Treated eye	-12.364 (51.411); P=0.444	2.182 (22.036); P=0.749	-6.900 (37.743); P=0.577	11.667 (25.298); P=0.204	7.000 (20.549); P=0.337
Percentage of Hexagonal Cells	Treated eye	-3.273 (13.282); P=0.433	-3.545 (13.064); P=0.389	-8.900 (13.609); P=0.069	-1.444 (11.991); P=0.727	-4.667 (10.308); P=0.211

Table 6.32. Paired Samples t test for the ALPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the INFERIOR area of cornea. Statistically significant results (P≤0.05) are flagged with an asterisk. Mean Diff= Mean Difference; SD= Standard Deviation.

INFERIOR-TEMPORAL POSITION ALPI Treated Paired Sample T-test		Visit 7-Visit 6 Mean Diff (SD); P Value	Visit 8- Visit 6 Mean Diff (SD); P Value	Visit 9- Visit 6 Mean Diff (SD); P Value	Visit 10- Visit 6 Mean Diff (SD); P Value	Visit 11- Visit 6 Mean Diff (SD); P Value
Density	Treated eye	-6.818 (83.090); P=0.791	32.545 (209.827); P=0.618	21.500 (129.505); P=0.612	-92.444 (121.089); P=0.051	-11.875 (144.813); P=0.823
Average Cell Size	Treated eye	0.273 (17.263); P=0.959	-4.182 (38.217); P=0.724	-1.000 (21.034); P=0.884	22.000 (32.133); P=0.074	5.500 (30.350); P=0.624
Percentage of Hexagonal Cells	Treated eye	-1.364 (11.465); P=0.702	0.000 (9.940); P=1.000	0.000 (9.238); P=1.000	0.889 (9.020); P=0.775	9.375 (12.293); P=0.068

Table 6.33. Paired Samples t test for the ALPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the INFERIOR-TEMPORAL area of cornea. Statistically significant results (P≤0.05) are flagged with an asterisk. Mean Diff= Mean Difference; SD= Standard Deviation.

SUPERIOR TEMPORAL POSITION ALPI Treated Paired Sample T-test		Visit 7-Visit 6 Mean Diff (SD); P Value	Visit 8- Visit 6 Mean Diff (SD); P Value	Visit 9- Visit 6 Mean Diff (SD); P Value	Visit 10- Visit 6 Mean Diff (SD); P Value	Visit 11- Visit 6 Mean Diff (SD); P Value
Density	Treated eye	9.000 (123.586); P=0.823	89.000 (96.029); P=0.024*	1.111 (122.972); P=0.979	-8.625 (166.176); P=0.887	59.250 (59.249); P=0.025*
Average Cell Size	Treated eye	-1.800 (18.110); P=0.760	-14.778 (16.029); P=0.024*	-1.111 (21.619); P=0.881	8.125 (43.930); P=0.617	-10.625 (11.904); P=0.040*
Percentage of Hexagonal Cells	Treated eye	0.100 (6.757); P=0.964	-1.778 (8.700); P=0.557	-7.000 (8.602); P=0.040*	3.429 (7.368); P=0.264	1.500 (11.916); P=0.732

Table 6.34. Paired Samples t test for the ALPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the CENTRAL area of cornea. Statistically significant results (P≤0.05) are flagged with an asterisk. Mean Diff= Mean Difference; SD= Standard Deviation.

SUPERIOR POSITION ALPI Treated Paired Sample T-test		Visit 7-Visit 6 Mean Diff (SD); P Value	Visit 8- Visit 6 Mean Diff (SD); P Value	Visit 9- Visit 6 Mean Diff (SD); P Value	Visit 10- Visit 6 Mean Diff (SD); P Value	Visit 11- Visit 6 Mean Diff (SD); P Value
Density	Treated eye	-0.100 (50.316); P=0.995	-20.400 (45.906); P=0.194	-6.222 (51.205); P=0.725	-27.250 (68.329); P=0.296	-15.375 (40.746); P=0.321
Average Cell Size	Treated eye	-5.444 (20.659); P=0.452	10.778 (29.991); P=0.312	-2.000 (27.449); P=0.843	0.571 (26.532); P=0.956	12.250 (40.351); P=0.419
Percentage of Hexagonal Cells	Treated eye	64.250 (168.560); P=0.317	61.375 (168.088); P=0.336	69.857 (178.770); P=0.341	81.333 (193.904); P=0.351	67.000 (181.744); P=0.367

Table 6.35. Paired Samples t test for the ALPI treated eyes and fellow untreated eyes for the endothelial cell density, average cell size, percentage of hexagonal cells and corneal thickness for the SUPERIOR area of cornea. Statistically significant results ($P \leq 0.05$) are flagged with an asterisk. Mean Diff= Mean Difference; SD= Standard Deviation.

ALPI Analysis of Covariance	CENTRAL Visit 11 Mean Diff (SE); P Value	SUPERIOR-NASAL Visit 11 Mean Diff (SE); P Value	INFERIOR-NASAL Visit 11 Mean Diff (SE); P Value	INFERIOR Visit 11 Mean Diff (SE); P Value	INFERIOR-TEMPORAL Visit 11 Mean Diff (SE); P Value	SUPERIOR-TEMPORAL Visit 11 Mean Diff (SE); P Value	SUPERIOR Visit 11 Mean Diff (SE); P Value
Density	5.915 (49.823); P=0.908	44.417 (18.486); P=0.035*	13.095 (13.486); P=0.351	-73.939 (75.242); P=0.347	-105.960 (73.664); P=0.176	96.006 (61.123); P=0.145	44.417 (18.486); P=0.035*
Average Cell Size	-0.004 (8.316); P=1.000	-58.158 (29.937); P=0.078	-25.811 (10.697); P=0.033*	10.772 (12.538); P=0.409	17.964 (12.403); P=0.173	-16.923 (9.929); P=0.116	-58.158 (29.937); P=0.078
Percentage of Hexagonal Cells	6.028 (3.771); P=0.138	4.480 (3.848); P=0.274	-1.337 (7.054); P=0.853	8.260 (7.835); P=0.314	-0.153 (5.143); P=0.977	-6.691 (3.291); P=0.067	4.480 (3.848); P=0.274
Corneal Thickness	-0.152 (5.355); P=0.978	N/A	N/A	N/A	N/A	N/A	N/A

Table 6.36. Analysis of Covariance where the response variable has been adjusted using the Visit 6 data for the Central. Superior-Nasal. Inferior-Nasal. Inferior. Inferior-Temporal. Superior-Temporal and Superior areas of endothelium. (Diff=difference; SE= Standard Error)

Appendix 2. Justification for using the data of both eyes of every patient

This appendix was designed with the aim of testing the equality of the data collected for right and left eyes at baseline. If equality was found (no statistically significant differences between right and left) then both eyes could be included in the sample.

The only chapter of this thesis that used both eyes in the same sample was Chapter 3, where data of the Diurnal Intraocular Pressure (DIOP), the DIOP fluctuation, the Supine Intraocular Pressure (SIOP) and the Dark Room Provocation Test (DRPT) previous to any treatment was collected. Additionally, the irido-trabecular angle parameters of both eyes were used to explore associations with other factors such as Peripheral Anterior Synechiae (PAS) and DIOP fluctuation, SIOP and DRPT.

In the rest of this thesis Chapters, the sample of eyes was already randomly divided (50% block randomisation) into treated and untreated eyes. All the participants had two eyes and therefore there was always a fellow eye acting as a control eye through time in the statistical models. This gave the great advantage of adjusting the models for differences found between treated and fellows at baseline. Therefore, to look for equality after the first randomisation (Visit 1, baseline) was not necessary.

Consequently, the equality of the data for right and left eyes was studied only for that collected at Visit 1 (baseline). The parameters tested for equality were the IOP (DIOP, DIOP fluctuation, SIOP and DRPT) and the irido-trabecular angle parameters (as measured with the CASIA OCT).

1. <u>Equality of baseline IOP measurements between Right and Left eyes</u>

There is not a clear consensus whether the IOP measured in the two eyes of a given subject vary or not independently. Several examples defending an equal variation between eyes can be found in the studies performed by Ederer (1973) and Newcombe (1987). on the other hand, Wilensky, in a very extensive study of diurnal and nocturnal variations of IOP in different types of glaucoma, found a between-eye variation in the diurnal patterns. However, this variation was not specified and none of the cases were angle closure glaucoma (Wilensky, 1991). More recently, in 2001, Realini found what was considered a clinically significant asymmetry in IOP fluctuation between

eyes of the same patient. Asymmetry of at least 3mmHg in two consecutive visits was observed in 50% of the normal subjects (non-glaucomatous, no prior surgery and not using topical medication) and 63% of the glaucomatous (Realini, Barber and Burton, 2002).

As asymmetry between the IOP for right and left eyes of the same individual has been reported in the past, it was of interest to test the hypothesis of symmetry in the case of this sample of participants.

The aim of this part of this Appendix 2 is to justify the use of both eyes data from the same individual for the different IOP outcomes.

Equivalence of IOP measurements for left and right eyes was explored in order to ascertain whether all eyes could be included in the statistical analysis. This equality was studied in terms of the mean value of the IOP for the 3 following tests:

1.A. Equality assumption for the right and left eyes in the DIOP:
In order to perform this assessment, the means for the DIOP for right and left eyes were plotted (Figure A.2.1 below). There was no statistically significant difference between means for right and left eyes at all time points (Analysis Of Variance Between-Groups, P>0.05).

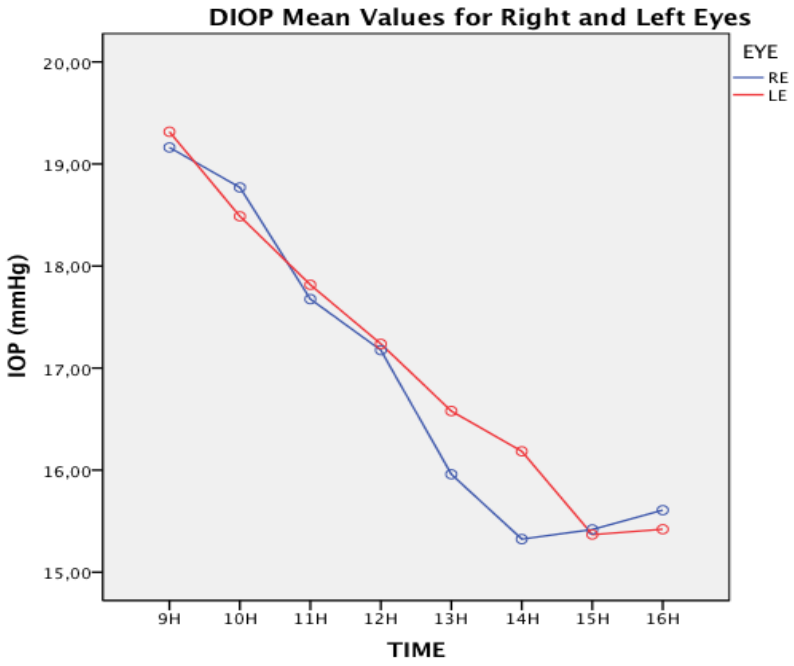


Figure A.2.1. Mean IOP value for right and left eyes of each patient during Visit 1.

Next, the diurnal fluctuation of IOP between two consecutive measurements was tested for right versus left eyes.

The P-values for the paired sample t-test analysis of the fluctuation between consecutive measurements for right versus left eyes during the day are shown in the following table:

IOP FLUCTUATION	9H-10H	10H-11H	11H-12H	12H-13H	13H-14H	14H-15H	15H-16H
RE/ LE*	1.6±4.5/ 1.6±5.0	1.7±8.5/ 1.4±3.5	1.8±8.0/ 1.7±6.0	1.7±6.5/ 2.1±8.0	1.6±5.5/ 1.8±5.0	1.8±6.0/ 1.8±5.5	1.52±6.0/ 1.5±6.5
Paired Sample P value	0.791	0.278	0.666	0.394	0.581	0.914	0.905

* RE /LE = $\{(\text{MEAN } |RE_{IOP(XH)} - RE_{IOP(XH-1H)}|) \pm \text{RANGE}(|RE_{IOP(XH)} - RE_{IOP(XH-1H)}|)\}$ versus $\{(\text{MEAN } |LE_{IOP(XH)} - LE_{IOP(XH-1H)}|) \pm \text{RANGE}(|LE_{IOP(XH)} - LE_{IOP(XH-1H)}|)\}$

Where the highest fluctuation between right and left eyes mean IOP was found to be 0.3 mmHg at the interval of time between 10:00 and 11:00h measurements. However, and as shown in the table this difference was not statistically significant.

1.B Equality assumption for right and left eyes in the Supine IOP (SIOP)

The graph below (Figure A.2.2) shows how the data for right and left eyes was distributed in this outcome. The mean and standard deviation for the SIOP result of right and left were 1.58 (1.84 SD) and 1.80 mmHg (2.39 SD) respectively. The difference between the means was found to be 0.21 mmHg (and statistically non-significant p=0.528 with the paired sample t-test). The SIOP result values represents the 'Supine Result' which is the difference in IOP between the IOP found 5 minutes laying in the supine position and the previous diurnal IOP measurement in the sitting position (SIOP minus DIOP previous measurement).

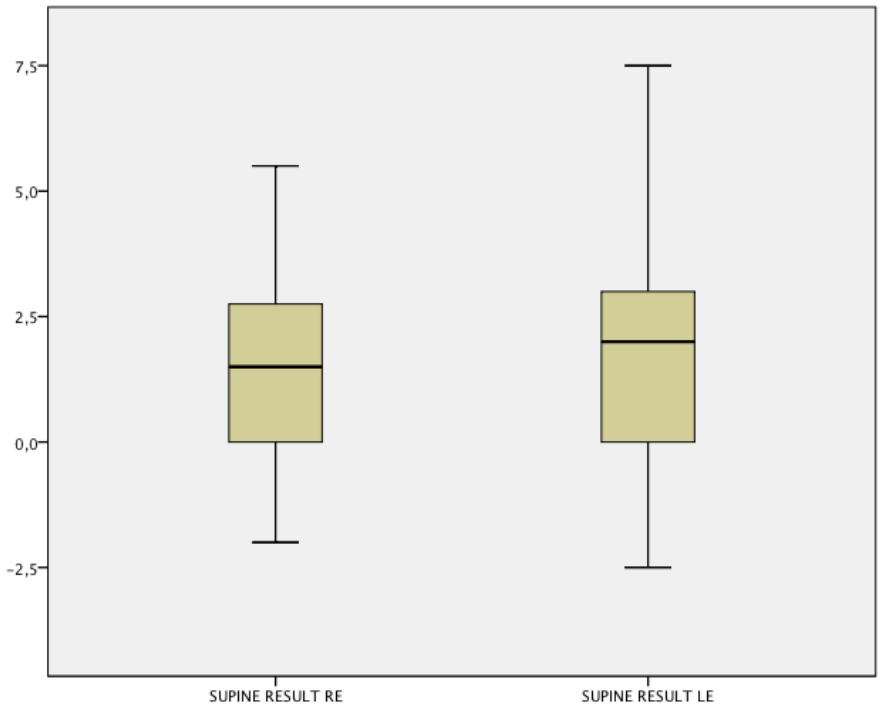


Figure A.2.2. Distribution of the SIOP result for right and left eyes.

1.C. Equality assumption for right and left eyes in the Dark Room Provocation Test (DRPT)

The DRPT had a similar effect over right and left eyes. The mean difference between right and left eyes IOP values for the DRPT was found to be non-statistically significant with the Paired Samples T-test, mean difference 0.15 mmHg, (p=0.664). The mean and standard deviation for right and left eyes were 2.94 (2.44 SD) and 3.1 (3.22 SD) respectively. The table below shows how the data was distributed for both eyes (figure A.2.3).

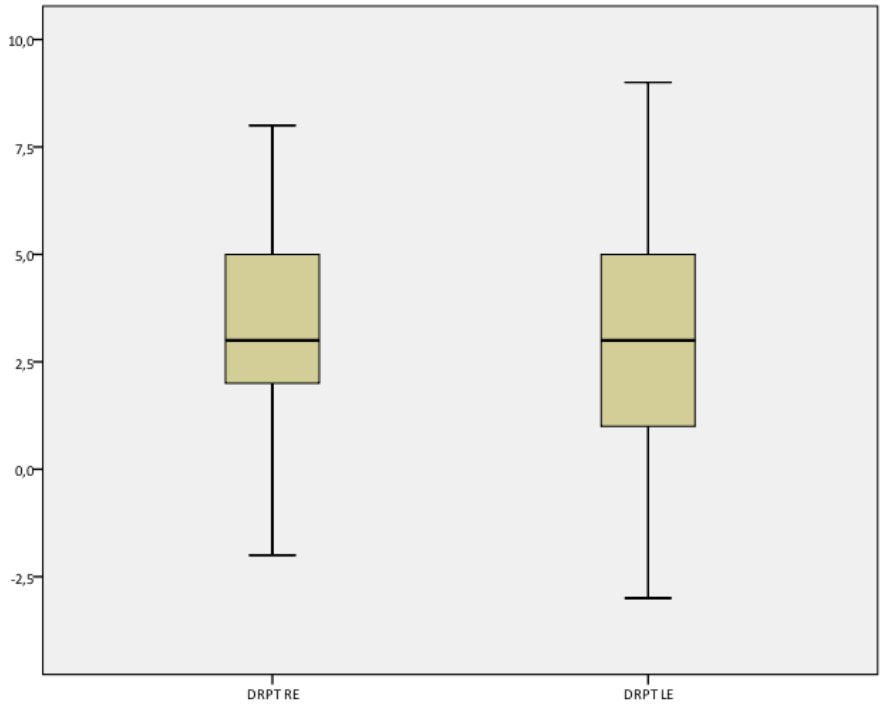


Figure A.2.3. Distribution of the SIOP for right and left eyes

Conclusion:

It was concluded that, due to the small variation between the mean values for the IOP levels found for right and left eyes and the fact that differences between eyes were statistically non-significant, all eyes were to be included in the subsequent analyses regarding IOP.

2. Equality of baseline angle parameters measurements between Right and Left eyes in dark and light conditions

The angle parameters to be used at baseline (Visit 1) where compared between the right and the left eyes. The comparison was carried out for Angle Opening Distance (AOD (mm)), Angle Recess Area (ARA (mm^2)), Trabecular Iris Space Area (TISA (mm^2)) and Trabecular-Iris Angle (TIA (°)) in dark and light conditions. The paired samples t test showed no statistically significant differences between the parameters measured for right and those measured for left in light or dark lighting conditions. This is shown in the following table (Table A.2.4):

Right versus Left eyes at Visit 1	LIGHT	DARK
Paired Samples t test	Mean Diff (SD); P Value	Mean Diff (SD); P Value
SUPERIOR AOD500	-0.004(0.074); P=0.760	0.008(0.064); P=0.497
SUPERIOR ARA500	0.006(0.030); P=0.282	0.000(0.033); P=0.935
SUPERIOR TISA500	0.005(0.029); P=0.329	0.000(0.030); P=0.936
SUPERIOR TIA500	-0.223(5.684); P=0.829	0.632(4.885); P=0.456
SUPERIOR AOD750	-0.009(0.106); P=0.641	-0.006(0.099); P=0.715
SUPERIOR ARA750	-0.001(0.052); P=0.895	-0.005(0.043); P=0.484
SUPERIOR TISA750	-0.002(0.051); P=0.851	-0.005(0.042); P=0.521
SUPERIOR TIA750	-0.327(5.851); P=0.750	-0.212(5.206); P=0.816
INFERIOR AOD500	0.016(0.126); P=0.456	0.000(0.097); P=0.992
INFERIOR ARA500	0.018(0.057); P=0.074	0.011(0.041); P=0.129
INFERIOR TISA500	0.015(0.050); P=0.084	0.010(0.038); P=0.134
INFERIOR TIA500	1.254(8.894); P=0.410	1.111(6.941); P=0.350
INFERIOR AOD750	0.010(0.150); P=0.709	0.009(0.135); P=0.694
INFERIOR ARA750	0.021(0.088); P=0.162	0.013(0.061); P=0.221
INFERIOR TISA750	0.018(0.080); P=0.194	0.012(0.059); P=0.238
INFERIOR TIA750	0.606(7.686); P=0.644	0.760(6.960); P=0.523
SUPERIOR-NASAL AOD500	-0.005(0.095); P=0.753	-0.004(0.083); P=0.773
SUPERIOR-NASAL ARA500	0.001(0.043); P=0.941	-0.005(0.041); P=0.486
SUPERIOR-NASAL TISA500	0.000(0.040); P=0.960	-0.004(0.038); P=0.498
SUPERIOR-NASAL TIA500	-0.937(9.092); P=0.546	-0.023(8.343); P=0.987
SUPERIOR-NASAL AOD750	-0.001(0.131); P=0.947	0.010(0.116); P=0.619
SUPERIOR-NASAL ARA750	-0.002(0.070); P=0.841	-0.006(0.065); P=0.604
SUPERIOR-NASAL TISA750	0.018(0.153); P=0.500	-0.005(0.061); P=0.607
SUPERIOR-NASAL TIA750	-0.631(8.578); P=0.666	0.789(7.811); P=0.554
INFERIOR-TEMPORAL AOD500	-0.006(0.104); P=0.722	-0.005(0.089); P=0.758
INFERIOR-TEMPORAL ARA500	0.001(0.050); P=0.927	-0.003(0.040); P=0.618
INFERIOR-TEMPORAL TISA500	0.002(0.046); P=0.812	-0.004(0.039); P=0.564
INFERIOR-TEMPORAL TIA500	0.186(9.623); P=0.910	-0.457(9.645); P=0.781
INFERIOR-TEMPORAL AOD750	0.012(0.141); P=0.619	-0.019(0.126); P=0.375
INFERIOR-TEMPORAL ARA750	0.001(0.074); P=0.915	-0.008(0.055); P=0.393
INFERIOR-TEMPORAL TISA750	0.006(0.073); P=0.659	-0.006(0.056); P=0.507
INFERIOR-TEMPORAL TIA750	1.263(9.084); P=0.417	-0.834(7.567); P=0.519
NASAL AOD500	-0.019(0.114); P=0.343	-0.010(0.124); P=0.621
NASAL ARA500	-0.008(0.056); P=0.391	-0.005(0.058); P=0.634
NASAL TISA500	-0.009(0.050); P=0.304	-0.002(0.052); P=0.827
NASAL TIA500	-0.889(10.581); P=0.623	-0.397(10.719); P=0.828
NASAL AOD750	0.002(0.135); P=0.944	-0.011(0.142); P=0.644
NASAL ARA750	-0.011(0.084); P=0.451	-0.006(0.084); P=0.656
NASAL TISA750	-0.013(0.079); P=0.343	-0.004(0.079); P=0.756
NASAL TIA750	0.551(8.805); P=0.713	-0.217(7.975); P=0.873
TEMPORAL AOD500	0.003(0.076); P=0.813	0.001(0.073); P=0.936
TEMPORAL ARA500	0.006(0.041); P=0.393	0.005(0.036); P=0.448
TEMPORAL TISA500	0.017(0.085); P=0.256	0.003(0.032); P=0.555
TEMPORAL TIA500	-0.240(7.534); P=0.852	-0.391(7.255); P=0.752
TEMPORAL AOD750	0.000(0.095); P=0.990	0.010(0.092); P=0.535
TEMPORAL ARA750	0.006(0.057); P=0.564	0.007(0.050); P=0.436

TEMPORAL TISA750	0.003(0.053); P=0.743	0.005(0.047); P=0.505
TEMPORAL TIA750	-0.489(6.639); P=0.666	0.203(6.405); P=0.852
INFERIOR-NASAL AOD500	-0.011(0.116); P=0.570	-0.016(0.118); P=0.419
INFERIOR-NASAL ARA500	-0.003(0.054); P=0.757	-0.009(0.053); P=0.326
INFERIOR-NASAL TISA500	-0.003(0.049); P=0.686	-0.006(0.049); P=0.472
INFERIOR-NASAL TIA500	-1.071(10.481); P=0.549	-0.759(10.856); P=0.682
INFERIOR-NASAL AOD750	-0.016(0.154); P=0.536	-0.028(0.139); P=0.240
INFERIOR-NASAL ARA750	-0.004(0.080); P=0.753	-0.014(0.081); P=0.314
INFERIOR-NASAL TISA750	-0.005(0.077); P=0.714	-0.012(0.078); P=0.367
INFERIOR-NASAL TIA750	-1.066(9.769); P=0.523	-0.977(8.809); P=0.516
SUPERIOR-TEMPORAL AOD500	0.000(0.086); P=0.974	0.001(0.075); P=0.968
SUPERIOR-TEMPORAL ARA500	-0.001(0.037); P=0.859	-0.002(0.031); P=0.697
SUPERIOR-TEMPORAL TISA500	0.017(0.116); P=0.386	-0.001(0.030); P=0.799
SUPERIOR-TEMPORAL TIA500	0.194(8.264); P=0.890	0.246(7.503); P=0.848
SUPERIOR-TEMPORAL AOD750	0.003(0.117); P=0.891	-0.009(0.093); P=0.565
SUPERIOR-TEMPORAL ARA750	-0.002(0.058); P=0.872	-0.003(0.049); P=0.707
SUPERIOR-TEMPORAL TISA750	-0.001(0.057); P=0.923	-0.003(0.048); P=0.758
SUPERIOR-TEMPORAL TIA750	0.249 7.751); P=0.851	-0.197 6.172); P=0.851

Table A.2.4. Paired Samples t test comparing the parameters found for right eyes versus left eyes

Conclusion:

There were no statistically significant differences between right and left eyes angle parameters at baseline and therefore it was justified to use them in the same sample.

After the baseline visit (Visit 1) the eyes were randomly allocated at Visit 2 to receive laser peripheral iridotomy or to act as fellow untreated eyes. Differences between right and left eyes would not affect the results after the randomisation took place.

Appendix 3. Benefits and Limitations of the Instrumentation

Cornea/Anterior Segment Optical Coherent Tomography: CASIA SS-1000, Tomey GmbH

The benefits of the CASIA SS-1000 and the Swept Source technology have already been discussed in depth in the present thesis.

Limitations of this device:
This device do not present many limitations, but as any other current anterior segment OCT that provides quantification of the iridotrabecular angle, the scleral spur needs to be identified by the examiner. Other limitations such as fixation control may be improved in the future.

1. Fixation Control:
One other limitation that may not be attributable to the device is that there was a variation of the location of the iridotomy between visits. For example, participant 1002 receives laser peripheral iridotomy and when the scans taken with the OCT are analysed, the iridotomy appears to be placed at 95°. The same patient's eye is scanned at Visits 3, 4, 5,…, and the iridotomy has now varied positions in the scans, being 100, 92, 89,…, respectively.

A solution for this limitation could be the implementation for customised iris tracking devices similar to the technology used in refractive surgery to follow the uncontrolled ocular movements.

2. Intraobserver repeatability
Only one examiner (LSP) analysed all the scans used in the present study. To perform an intraobserever study, 35 scans taken at Visit 1 in light and dark were analysed twice.
These scans belonged to those eyes randomised to be left untreated in Visit 2. The scans were quantified in the Superior, Inferior, Temporal and Nasal sections. AOD (Angle Opening Distance), ARA (angle Recess Are), TISA (Trabecular-Iris Space Area) and TIA (Trabecular-Iris Angle) at 500 and 750μm were quantified for these four sections.

The quantifications were performed in two different settings separated by two days to avoid memorisation bias. The first day all the 35 eyes were quantified in dark and light and the same was repeated in the second setting.

Tables A.3.1 shows the intraobserver repeatability for the parameters in light conditions and Tables A.3.2 shows the same for the dark conditions.
Repeatability is assessed in terms of differences between pairs of values of two measurements. The mean of the differences indicates the bias between the two assessments and should be close to zero.
In general, the Bland-Altman (B-A) mean difference between visits found for the eight parameters in the Superior, Nasal, Inferior and Temporal sections were quite close to zero.
There is another study showing intraobserver repeatability in similar examinations with the CASIA OCT. Liu et al. (2011), quantified the scans in 30 healthy individuals in the same four quadrants and in the darkness. Their intraobserver repeatability coefficients were higher than in the present study with only one exception (Inferior TIA 500). This finding can be observed in the following tables:

PARAMETER in Dark	**PRESENT STUDY** Repeatability (95% confidence limits)	→	**Liu et al. (2011)** Repeatability (95% confidence limits)
SUPERIOR AOD 500	0.043 (0.032-0.053)	→	0.140 (0.115-0.156)
SUPERIOR TISA 500	0.016 (0.012-0.020)	→	0.074 (0.061-0.087)
SUPERIOR TIA 500	4.265 (3.214-5.317)	→	7.7 (6.4-9.1)
INFERIOR AOD 500	0.128 (0.097-0.160)	→	0.252 (0.207-0.297)
INFERIOR TISA 500	0.046 (0.035-0.058)	→	0.090 (0.074-0.106)
INFERIOR TIA 500	13.351 (10.007-16.694)	→	9.5 (7.8-11.2)
NASAL AOD 500	0.046 (0.035-0.057)	→	0.141 (0.116-0.166)
NASAL TISA 500	0.021 (0.016-0.026)	→	0.050 (0.041-0.059)
NASAL TIA 500	4.983 (3.755-6.211)	→	8.9 (7.3-10.5)
TEMPORAL AOD 500	0.047 (0.035-0.058)	→	0.224 (0.184-0.265)
TEMPORAL TISA 500	0.018 (0.013-0.023)	→	0.086 (0.071-0.101)
TEMPORAL TIA 500	4.294 (3.236-5.353)	→	8.2 (6.8-9.8)

This intraobserver repeatability study showed a good agreement within the examiner judgment (LSP) in the quantification of the majority of the parameters for light and dark conditions.

First variable	Second variable	Number of pairs	Mean difference	Limits of agreement		Repeatability	Standard error	95% confidence limits	
				Lower	Upper			Lower	Upper
REPIT_LIGHT_SUPERIOR_AOD500	LIGHT_SUPERIOR_AOD500	35	-0.005200	-0.058777	0.048377	0.053577	0.006497	0.040373	0.066781
REPIT_LIGHT_SUPERIOR_ARA500	LIGHT_SUPERIOR_ARA500	35	-0.001457	-0.024231	0.021317	0.022774	0.002762	0.017162	0.028387
REPIT_LIGHT_SUPERIOR_TISA500	LIGHT_SUPERIOR_TISA500	35	-0.002543	-0.024795	0.019709	0.022252	0.002698	0.016768	0.027736
REPIT_LIGHT_SUPERIOR_TIA500	LIGHT_SUPERIOR_TIA500	35	-0.780000	-5.725063	4.165063	4.945063	0.599677	3.726373	6.163753
REPIT_LIGHT_SUPERIOR_AOD750	LIGHT_SUPERIOR_AOD750	35	-0.000829	-0.060286	0.058629	0.059457	0.007210	0.044804	0.074110
REPIT_LIGHT_SUPERIOR_ARA750	LIGHT_SUPERIOR_ARA750	35	-0.000400	-0.040547	0.039747	0.040147	0.004869	0.030253	0.050042
REPIT_LIGHT_SUPERIOR_TISA750	LIGHT_SUPERIOR_TISA750	35	-0.001486	-0.039546	0.036574	0.038060	0.004615	0.028680	0.047440
REPIT_LIGHT_SUPERIOR_TIA750	LIGHT_SUPERIOR_TIA750	35	-0.362857	-4.333954	3.608240	3.971097	0.481566	2.992437	4.949758
REPIT_LIGHT_INFERIOR_AOD500	LIGHT_INFERIOR_AOD500	35	0.006314	-0.069294	0.081923	0.075609	0.009169	0.056975	0.094242
REPIT_LIGHT_INFERIOR_ARA500	LIGHT_INFERIOR_ARA500	35	0.005943	-0.030512	0.042397	0.036454	0.004421	0.027470	0.045439
REPIT_LIGHT_INFERIOR_TISA500	LIGHT_INFERIOR_TISA500	35	0.004086	-0.024870	0.033042	0.028956	0.003511	0.021820	0.036092
REPIT_LIGHT_INFERIOR_TIA500	LIGHT_INFERIOR_TIA500	35	-0.100000	-5.050104	4.850104	4.950104	0.600288	3.730171	6.170037
REPIT_LIGHT_INFERIOR_AOD750	LIGHT_INFERIOR_AOD750	35	0.000771	-0.083039	0.084582	0.083811	0.010164	0.063156	0.104466
REPIT_LIGHT_INFERIOR_ARA750	LIGHT_INFERIOR_ARA750	35	0.006000	-0.046029	0.058029	0.052029	0.006309	0.039207	0.064852
REPIT_LIGHT_INFERIOR_TISA750	LIGHT_INFERIOR_TISA750	35	0.004457	-0.041423	0.050338	0.045881	0.005564	0.034573	0.057188
REPIT_LIGHT_INFERIOR_TIA750	LIGHT_INFERIOR_TIA750	35	-0.297143	-4.616316	4.022031	4.319174	0.523777	3.254731	5.383616
REPIT_LIGHT_NASAL_AOD500	LIGHT_NASAL_AOD500	35	0.000171	-0.045432	0.045775	0.045603	0.005530	0.034364	0.056842
REPIT_LIGHT_NASAL_ARA500	LIGHT_NASAL_ARA500	35	-0.000457	-0.024751	0.023837	0.024294	0.002946	0.018307	0.030281
REPIT_LIGHT_NASAL_TISA500	LIGHT_NASAL_TISA500	35	-0.000829	-0.024376	0.022719	0.023547	0.002856	0.017744	0.029350
REPIT_LIGHT_NASAL_TIA500	LIGHT_NASAL_TIA500	35	-0.288571	-4.902813	4.325670	4.614242	0.559559	3.477081	5.751402
REPIT_LIGHT_NASAL_AOD750	LIGHT_NASAL_AOD750	35	-0.005057	-0.058823	0.048709	0.053766	0.006520	0.040516	0.067017
REPIT_LIGHT_NASAL_ARA750	LIGHT_NASAL_ARA750	35	-0.001486	-0.032353	0.029382	0.030867	0.003743	0.023260	0.038474
REPIT_LIGHT_NASAL_TISA750	LIGHT_NASAL_TISA750	35	-0.002057	-0.032018	0.027903	0.029961	0.003633	0.022577	0.037344
REPIT_LIGHT_NASAL_TIA750	LIGHT_NASAL_TIA750	35	-0.625714	-4.984436	3.733007	4.358722	0.528573	3.284533	5.432910
REPIT_LIGHT_TEMPORAL_AOD500	LIGHT_TEMPORAL_AOD500	35	-0.004171	-0.039064	0.030722	0.034893	0.004231	0.026294	0.043492
REPIT_LIGHT_TEMPORAL_ARA500	LIGHT_TEMPORAL_ARA500	35	-0.003771	-0.027728	0.020185	0.023956	0.002905	0.018052	0.029860
REPIT_LIGHT_TEMPORAL_TISA500	LIGHT_TEMPORAL_TISA500	35	-0.003400	-0.021224	0.014424	0.017824	0.002161	0.013431	0.022217
REPIT_LIGHT_TEMPORAL_TIA500	LIGHT_TEMPORAL_TIA500	35	-0.534286	-4.985840	3.917269	4.451554	0.539830	3.354487	5.548621
REPIT_LIGHT_TEMPORAL_AOD750	LIGHT_TEMPORAL_AOD750	35	-0.005143	-0.070043	0.059757	0.064900	0.007870	0.048906	0.080895
REPIT_LIGHT_TEMPORAL_ARA750	LIGHT_TEMPORAL_ARA750	35	-0.004486	-0.035242	0.026271	0.030757	0.003730	0.023177	0.038336
REPIT_LIGHT_TEMPORAL_TISA750	LIGHT_TEMPORAL_TISA750	35	-0.004314	-0.029676	0.021048	0.025362	0.003076	0.019112	0.031613
REPIT_LIGHT_TEMPORAL_TIA750	LIGHT_TEMPORAL_TIA750	35	-0.522857	-5.316501	4.270787	4.793644	0.581315	3.612271	5.975018

Table A.3.1. The Limits of Agreement indicate the interval within which 95% of the differences are expected to fall. The Repeatability Coefficient indicates the distance that the Limits of Agreement are from the mean. A judgement needs to be made as to whether this distance is acceptable in practice.

First variable	Second variable	Number of pairs	Mean difference	Limits of agreement		Repeatability	Standard error	95% confidence limits	
				Lower	Upper			Lower	Upper
REPIT_DARK_SUPERIOR_AOD500	DARK_SUPERIOR_AOD500	35	-0.007257	-0.050230	0.035716	0.042973	0.005211	0.032382	0.053563
REPIT_DARK_SUPERIOR_ARA500	DARK_SUPERIOR_ARA500	35	-0.001114	-0.019178	0.016949	0.018064	0.002191	0.013612	0.022515
REPIT_DARK_SUPERIOR_TISA500	DARK_SUPERIOR_TISA500	35	-0.001400	-0.017686	0.014886	0.016286	0.001975	0.012272	0.020299
REPIT_DARK_SUPERIOR_TIA500	DARK_SUPERIOR_TIA500	35	-0.951429	-5.216849	3.313992	4.265421	0.517258	3.214226	5.316616
REPIT_DARK_SUPERIOR_AOD750	DARK_SUPERIOR_AOD750	35	0.005800	-0.063250	0.074850	0.069050	0.008374	0.052033	0.086068
REPIT_DARK_SUPERIOR_ARA750	DARK_SUPERIOR_ARA750	35	-0.000000	-0.030498	0.030498	0.030498	0.003698	0.022982	0.038014
REPIT_DARK_SUPERIOR_TISA750	DARK_SUPERIOR_TISA750	35	-0.000571	-0.030186	0.029043	0.029614	0.003591	0.022316	0.036913
REPIT_DARK_SUPERIOR_TIA750	DARK_SUPERIOR_TIA750	35	-0.057143	-4.433627	4.319341	4.376484	0.530727	3.297918	5.455050
REPIT_DARK_INFERIOR_AOD500	DARK_INFERIOR_AOD500	35	0.023429	-0.104785	0.151642	0.128213	0.015548	0.096616	0.159811
REPIT_DARK_INFERIOR_ARA500	DARK_INFERIOR_ARA500	34	0.007412	-0.041178	0.056002	0.048590	0.005981	0.036422	0.060759
REPIT_DARK_INFERIOR_TISA500	DARK_INFERIOR_TISA500	34	0.005147	-0.041428	0.051722	0.046575	0.005733	0.034911	0.058239
REPIT_DARK_INFERIOR_TIA500	DARK_INFERIOR_TIA500	34	1.544118	-11.806737	14.894972	13.350854	1.643377	10.00738	16.69432
REPIT_DARK_INFERIOR_AOD750	DARK_INFERIOR_AOD750	35	0.027629	-0.164907	0.220165	0.192536	0.023348	0.145086	0.239986
REPIT_DARK_INFERIOR_ARA750	DARK_INFERIOR_ARA750	35	0.013629	-0.068068	0.095325	0.081697	0.009907	0.061563	0.101831
REPIT_DARK_INFERIOR_TISA750	DARK_INFERIOR_TISA750	35	0.006743	-0.091545	0.105031	0.098288	0.011919	0.074065	0.122511
REPIT_DARK_INFERIOR_TIA750	DARK_INFERIOR_TIA750	35	1.154286	-11.415739	13.724310	12.570024	1.524339	9.472194	15.66785
REPIT_DARK_NASAL_AOD500	DARK_NASAL_AOD500	35	0.000629	-0.045499	0.046756	0.046128	0.005594	0.034760	0.057496
REPIT_DARK_NASAL_ARA500	DARK_NASAL_ARA500	35	0.000486	-0.024496	0.025467	0.024982	0.003029	0.018825	0.031138
REPIT_DARK_NASAL_TISA500	DARK_NASAL_TISA500	35	0.001343	-0.019956	0.022642	0.021299	0.002583	0.016050	0.026548
REPIT_DARK_NASAL_TIA500	DARK_NASAL_TIA500	35	-0.442857	-5.426191	4.540476	4.983334	0.604318	3.755212	6.211455
REPIT_DARK_NASAL_AOD750	DARK_NASAL_AOD750	35	-0.002686	-0.068528	0.063157	0.065843	0.007985	0.049616	0.082069
REPIT_DARK_NASAL_ARA750	DARK_NASAL_ARA750	35	-0.000743	-0.033374	0.031888	0.032631	0.003957	0.024589	0.040673
REPIT_DARK_NASAL_TISA750	DARK_NASAL_TISA750	35	0.000143	-0.027996	0.028282	0.028139	0.003412	0.021204	0.035074
REPIT_DARK_NASAL_TIA750	DARK_NASAL_TIA750	35	-0.588571	-4.293503	3.116361	3.704932	0.449289	2.791867	4.617997
REPIT_DARK_TEMPORAL_AOD500	DARK_TEMPORAL_AOD500	35	0.000543	-0.046437	0.047523	0.046980	0.005697	0.035402	0.058558
REPIT_DARK_TEMPORAL_ARA500	DARK_TEMPORAL_ARA500	35	-0.000171	-0.022744	0.022401	0.022573	0.002737	0.017010	0.028136
REPIT_DARK_TEMPORAL_TISA500	DARK_TEMPORAL_TISA500	35	0.000943	-0.016700	0.018586	0.017643	0.002140	0.013295	0.021991
REPIT_DARK_TEMPORAL_TIA500	DARK_TEMPORAL_TIA500	35	-0.405714	-4.700429	3.889000	4.294714	0.520811	3.236300	5.353129
REPIT_DARK_TEMPORAL_AOD750	DARK_TEMPORAL_AOD750	35	0.001171	-0.049593	0.051936	0.050765	0.006156	0.038254	0.063275
REPIT_DARK_TEMPORAL_ARA750	DARK_TEMPORAL_ARA750	35	0.002486	-0.043841	0.048813	0.046327	0.005618	0.034910	0.057744
REPIT_DARK_TEMPORAL_TISA750	DARK_TEMPORAL_TISA750	35	0.003114	-0.039621	0.045850	0.042735	0.005182	0.032203	0.053267
REPIT_DARK_TEMPORAL_TIA750	DARK_TEMPORAL_TIA750	35	-0.540000	-3.576716	2.496716	3.036716	0.368256	2.288330	3.785103

Table A.3.2. The Limits of Agreement indicate the interval within which 95% of the differences are expected to fall. The Repeatability Coefficient indicates the distance that the Limits of Agreement are from the mean. A judgement needs to be made as to whether this distance is acceptable in practice.

Benefits and Limitations of the Tomey 3000 Specular Microscope

The main benefits of this specular microscope are the non-contact nature of the measurements and that it permits to sample the endothelium in 7 different areas of cornea.
It additionally has analysis and storage software that permits to have a quantification of the data.

Limitations of this device:

1. Fixation Control:
The device does not possess recognition software that allows identifying the exact same area as scanned as baseline (similar to the technology used in the Heidelberg Retinal Tomography for recognition of the optic nerve head contour at baseline). Although the participants were carefully instructed on how to perform the test and to keep fixating at the set target while the measurement was taken, micro-movements of the eye could not be controlled. This may have led to a slightly different testing location within the same area of corneal endothelium.

2. Peripheral Sampling:
The Tomey 3000 specular microscope can test in 6 peripheral areas of cornea (Superior, Superior-Nasal, Inferior-Nasal, Inferior, Inferior-Temporal and Superior-Temporal). Its technology is based on corneal specular reflection. When there is a sufficient distance between the anterior surface of the iris and the endothelium, the device can take the sample with a good quality of image. However, when a more peripheral area of the endothelium is intended to be sampled (the distance between iris and endothelium becomes narrower), the image experience a high degree of scatter of light and the device cannot sample the area. The Tomey 3000 can reach a maximum of approximately 3mm radius from the corneal apex, dependent on the keratometrical measurements of the subject's eye (Tomey Corporation, 2006).

3. Automatic analysis reliability
This specular microscope allows performing a manual or an automatic analysis of the endothelial scans. In the manual analysis the examiner has to select the area of the scan that wishes to analyse and has to manually trace or modify the contour of the cells if the examiner does not agree with the device judgement. In the automated analysis, the software runs its own analysis. The automated option was selected in the present thesis due to logistical reasons (approximately 4500 scans were quantified). Although it would have been interesting to know the differences

between manual and automatic quantification, this would have not had any effect on the outcome of the present study. The main reason being the presence of a control eye.
If the automatic analysis would have been less or more accurate than the manual analysis for the endothelial cells, it would have been equally accurate for treated and untreated eyes.

4. Repeatability

The Bland-Altman (B-A) coefficients were found for the three parameters under measurement for the central area. The data was obtained from the untreated eye and using Visit 1 as baseline. The comparisons were carried out with the same parameters measured at the subsequent visits (Visits 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11). The closer the B-A mean value was to zero the closer the value for Visit 1 was to another visit. It is down to the examiner to judge if this differences from cero can have a clinical relevance. More information can be found in the Table A.3.3 (next page).

Repeatability indicates the level of clinical trust that an examiner can have regarding a tested device. Basically, it answers the question, if I test a patient today and I test the same patient tomorrow, what are the chances of getting the same value? 95% of the times the mean difference for the parameter tested today and the same parameter tested tomorrow will fall within the plus/minus B-A repeatability coefficients.

In the present study, repeatability of the Tomey 3000 Specular Microscope was of a limited relevance as what was used to calculate differences in the parameters within visits was the mean value of many measurements (n participants). Differences found for the mean value given by many participants' endothelial cells between visits could only be explainable with repeatability if all the participants measurements would have deviated from the mean in the same direction (positive or negative).

Bland-Altman For Central Corneal measurements	Corneal Thickness			Cell density			Polymegethism			Pleomorphism		
	Mean	Coefficient	Limit of agreement (Lower-Upper)	Mean	Coefficient	Limit of agreement (Lower-Upper)	Mean	Coefficient	Limit of agreement (Lower-Upper)	Mean	Coefficient	Limit of agreement (Lower-Upper)
Visit 1-Visit 2	0.65	37.09	(-36.44-37.74)	3.67	287.51	(-291.18-283.84)	0.20	49.29	(-49.49-49.09)	1.21	19.30	(-18.09-20.51)
Visit 1-Visit 3	7.41	38.30	(-30.89-45.70)	31.60	297.07	(-265.47-328.67)	-5.36	49.31	(-54.68-43.95)	3.17	22.57	(-19.40-25.74)
Visit 1-Visit 4	-0.21	38.27	(-38.48-38.06)	-8.62	250.82	(-259.44-242.19)	2.52	45.06	(-42.55-47.58)	0.93	21.16	(-20.23-22.09)
Visit 1-Visit 5	1.33	35.62	(-34.29-36.95)	14.03	270.01	(-255.98-284.04)	-1.67	44.39	(-46.06-42.72)	4.20	21.82	(-17.62-26.02)
Visit 1-Visit 6	3.61	32.80	(-29.18-36.42)	-1.94	287.24	(-289.18-285.31)	0.03	50.87	(-50.85-50.91)	-5.17	30.46	(-35.63-25.30)
Visit 1-Visit 7	1.00	31.75	(-30.75-32.75)	60.40	318.41	(-258.01-378.81)	-9.00	48.02	(-57.03-39.03)	1.21	19.30	(-18.09-20.51)
Visit 1-Visit 8	-8.55	18.00	(-26.56-9.45)	63.00	260.41	(-197.41-323.41)	-9.00	44.61	(-53.61-35.61)	3.17	22.57	(-19.40-25.74)
Visit 1-Visit 9	-6.33	29.84	(-36.18-23.51)	30.55	257.15	(-226.60-287.71)	-3.44	46.85	(-50.30-43.41)	0.93	21.16	(-20.23-22.09)
Visit 1-Visit 10	13.42	70.05	(-56.63-83.48)	-100.89	735.39	(-836.28-634.50)	18.33	117.52	(-99.18-135.85)	4.20	21.82	(-17.62-26.02)
Visit 1-Visit 11	-0.17	40.21	(-40.38-40.04)	-16.00	284.12	(-300.12-268.11)	2.37	49.93	(-47.56-52.30)	-5.17	30.46	(-35.63-25.30)

Table A.3.3. Bland-Altman mean, coefficients and limits of agreement for the three parameters under study (Polymegethism, Pleomorphism, Cell Density and Corneal Thickness). They were studied comparing every visit to baseline (Visit 1).

Appendix 4. Forms

Letter for General Practitioner

REC Reference: 10/H0301/14

Hinchingbrooke Health Care NHS
NHS Trust

Information for General Practitioner

Dear Dr …

Re: *insert patient sticker with patient demographics*

This is to inform you that your patient (details above) has agreed to participate in a research study named:

Investigating Management of Primary Angle Closure and Treatment Study (IMPACT)

The explanation of the study provided to this patient is attached in addition to a record of the patient's consent to participate in the study.

This study has been approved by Essex 1 Research Ethics Committee.

Yours sincerely

Professor Rupert Bourne
BSc MD, FRCOphth
Consultant Ophthalmic Surgeon
Chief Investigator

A copy of the explanation of the study given to the patient.

1. Title of Study: Investigating Management of Primary Angle Closure and Treatment Study (IMPACT)

2. An invitation

You are being invited to take part in a research study. Before you decide if you wish to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.
Thank you for reading this.

3.Background to the condition

Inside the eye there is fluid which keeps the shape of the eye and helps it function. There are two types of fluid, aqueous and vitreous humour which create a pressure inside the eye. This eye pressure is of interest to this study.
Aqueous humour is found in the front part of the eye between the front window of the eye (the cornea) and the lens, in an area known as the 'anterior chamber'. Aqueous humour is continuously produced by the 'ciliary body', and drained by the 'trabecular meshwork', which is located at the base of the corner of the anterior chamber. When access to the trabecular meshwork is narrow or closed, the eye is said to have an 'occludable angle' and patients are designated "primary angle closure suspects (PACS)". A further stage, termed "primary angle closure (PAC)" involves permanent closure of this area and/or a rise in eye pressure. A persistently raised eye pressure may lead on to damage to the optic nerve, "primary angle closure glaucoma (PACG)".

4. What is the current ("standard") treatment for PAC/PACS patients?

Many patients are found to have the features of PAC or PACS and unaware of it. There are different ways of looking after these patients but among the medical profession there is no agreement on how care should be delivered. Current care is therefore quite varied and, among others, it includes the decision of simply to watch these patients in hospital clinics, discharge them from the hospital or treat them with laser procedures aimed to open the access to the drainage area. These laser procedures are called Peripheral Iridotomy (PI) and Argon Laser Peripheral Iridoplasty (ALPI), and involve the following:
PI = Laser Peripheral Iridotomy = a laser procedure used to make a microscopic hole in the upper part of the iris.
ALPI = Argon Laser Peripheral Iridotomy = a laser procedure that stretches the iris away from the drainage area of the eye to open it to drain fluid from the eye

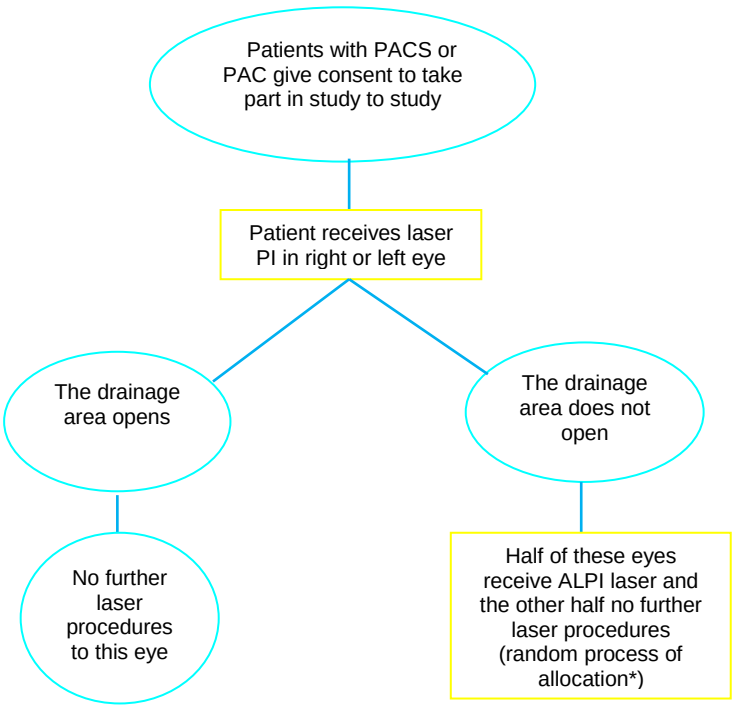
5. What is the purpose of the study?

The current study is designed to find out how best to care for these patients through a better understanding of how an eye with PACS can change to a state of PAC and then to PACG and how laser procedures mentioned above can affect this risk of change by altering the dimensions of the front chamber of the eye and drainage of fluid from the eye.

6. How is this going to be done?

The study will involve patients with PAC or PACS in both eyes, with no symptoms, who will receive a PI in one eye while the other eye is left untreated. This treated eye will be randomly chosen using computer software; this means neither the participant nor the doctors will be able to decide which eye will receive the laser. Examination of your eyes before and after laser treatment will allow us to gather information about how the conditions of PAC and PACS can be affected by laser.
If the drainage area does not open up after laser treatment ('an occludable angle'), the eye will be either left with no further laser treatment or will receive a further different type of laser treatment, an ALPI. The decision whether to offer no further treatment or ALPI will be made by the computer programme in a randomised process.

This process of laser procedures is illustrated below:



Laser PI = Laser Peripheral Iridotomy = a laser procedure used to make a microscopic hole in the upper part of the iris.

ALPI = Argon Laser Peripheral Iridotomy = a laser procedure that stretches the iris away from the drainage area of the eye to open it to drain fluid from the eye

* ‘’random process of allocation’ involves a computer programme randomly selecting an eye for treatment with the laser procedure. Neither the participant nor the doctors will be able to decide which eye will receive the laser

7. Why have I been invited to participate in this study?

You have been invited to take part in this study because we believe that you are a suitable participant. You have been recently diagnosed with PACS/ PAC in both eyes and you have no signs of glaucoma in either.

8. Do I have to take part?

Taking part in this research is entirely voluntary. You can decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

9. What will happen to me if I take part?

After being informed about the study you will be given an appointment to return to the eye clinic. This will happen within the next 3 weeks. At that appointment you will be able to ask any other questions you have about the study. If you agree to take part, we will ask you to sign a consent form so that you can be enrolled into the study.
You will be asked to attend on various dates. If you undergo laser PI only this will be done in 7 visits and if you receive ALPI as well it will be done in 11 visits.

<u>What type of tests/laser procedures are going to be done when I attend the research clinic (visits) and what do they involve?</u>

1. Visual acuity- this is an evaluation of the sharpness of your vision
2. Visual field- measures the quality of your eyesight in central and surrounding areas
3. Slit- lamp examination- we will use a microscope to evaluate the health of the front and the back of your eye, to assess what is the interior of the front chamber of the eye and to measure the eye pressure of each eye.
4. Laser PI (laser peripheral iridotomy)- an explanation is given above.
5. Supine and darkroom provocation tests- these measurements of eye pressure are made to understand how your eye pressure behaves when lying down on your back and also after 10 minutes in a dark environment (to simulate the conditions at night).
6. Cameras and other devices that take images of the front part of the eye

7. Cameras and other devices that take images of the surface of the eye and the fluid in the front chamber of the eye
8. Measurement of thickness of the surface of the eye- this is important because the thickness of the surface has an effect on the accuracy of eye pressure measurements.
9. Subjective refraction- this is the same procedure as when you go to see an optometrist for an assessment for glasses. We need to know if the laser procedures have an effect on the power of the eye
10. Retinal examination, eye pressure measurement and laser and photographic imaging after pupil dilation- we need to widen the pupil using eyedrops to have a better view of the back of the eye and to allow more detailed pictures of the back of the eye to be taken. At the same time we will be able to see if eye pressure changes when your pupil is bigger.
11. Argon Laser Peripheral Iridoplasty- described in sections above.

<u>Are all of these tests going to be done at every visit?</u>

No. We have designed the following table where you can see what we are going to do at each of the visits. Please note that we have numbered the tests/laser procedures using the same sequence given above.

	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11
Test 1	X	X	X	X	X	X	X	X	X	X	X
Test 2	X										X
Test 3	X		X	X	X	X		X	X	X	X
Test 4		X									
Test 5	X					X					X
Test 6	X		X	X	X	X		X	X	X	X
Test 7	X	X	X	X	X	X	X	X	X	X	X
Test 8	X		X	X	X	X		X	X	X	X
Test 9	X					X					X
Test 10	X			X				X			X
Test 11							X				

How many of these tests would be done on me as part of my routine care at the Eye Clinic?

	Number of tests/procedures to be received as part of the study	Number of tests/procedures to be received as part of routine care if I was not part of the research study
Test 1	11	4
Test 2	2	1
Test 3	9	4
Test 4	1	0 or 1
Test 5	3	0
Test 6	9	2
Test 7	11	0
Test 8	9	1
Test 9	3	0
Test 10	4	0 or 1
Test 11	1	0 or 1

When exactly are those visits going to be done?

VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7*	VISIT 8*	VISIT 9*	VISIT 10*	VISIT 11
This is your start date.	4 weeks since visit 1	4 weeks + 1 day since visit1	5 weeks since visit 1	10 weeks since visit 1	16 weeks since visit 1	18 weeks since visit 1	18 weeks + 1 day since visit 1	19 weeks since visit 1	24 weeks since visit 1	28 weeks since visit 1

* these visits are only attended by patients who undergo an ALPI laser treatment.

How long is each visit going to take approximately?

VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11
2 hours	2 hours	1 hour	1 hour	1 hour	3.5 hours	2 hours	1 hour	1 hour	1 hour	2 hours

Please note that we advise patients who have appointments at the routine (non-research) eye clinic expect to spend up to 3 hours at the clinic.

10. What are the possible disadvantages and risks of taking part?

1. Risks to the eye that receives laser treatment.

a. In the case of laser Peripheral Iridotomy (PI):

Complications are uncommon. The most common complications are a rise in eye pressure shortly after the treatment. The pressure will be checked before you go home and if very high you will need extra treatment (usually eye drops or tablets). You will also need to remain in the Eye Clinic until the pressure has dropped to a safe level.

Other rarer risks include:

- Slight haze lasting up to a few hours due to blood in the front of the eye
- Some research has suggested cataract can be caused by laser PI while other studies have contradicted this.
- Detachment of the retina (very rare).
- Possible mild discomfort during the laser treatment

b. In the case of Argon Laser Peripheral Iridoplasty (ALPI)

Complications are the same as those described for PI with the exception that there is no risk of bleeding in this procedure. Pigmented burn marks may develop at the sites of laser applications in some eyes treated with ALPI, although this is unusual.

2. Risks to the eye that does not receive laser treatment.

The risk of not treating an eye with your condition over a 24 week period from first diagnosis is unknown. Many patients do not receive laser procedures during routine care. The close follow-up of eyes that have not received laser treatment over 24 weeks is more intensive than that of routine care and will detect eyes that develop a rise in eye pressure or increasing closure of the drainage area of the eye.

Patients will be withdrawn from the study if the eye pressure rises above a certain level (35mmHg) or if they develop signs of glaucoma in either eye.

3. Risks associated with measuring devices:

The measuring devices used in this study carry no additional risk to that involved in routine standard care. In the case of devices in contact with the surface of the eye (cornea) the possible risks are irritation of the cornea or a scratch to the cornea. These symptoms/signs are very rare after a single measurement per visit as this study proposes. If any of these symptoms/signs are noticed by the researchers during the measurements they will be confirmed and the measurements will be stopped. Patients will be asked to stay in the clinic for a few hours and the abrasions allowed to heal with or without the use of an antibiotic eye drop. Patients will be followed up by an

ophthalmologist/eye nurse in the eye clinic.

4. Confidentiality:

In order to minimize the potential loss of confidentiality, each participant in this study will have the information collected from them anonymised. Thus it will not be possible to track to an individual without access to the hospital records.

11. What are the possible benefits of taking part?

Benefits to the eye treated by laser:
Prevention of a possible acute angle-closure episode, which involves a sudden painful rise in eye pressure. This would be a rare event in such a short period of follow-up. The laser peripheral iridotomy may lower the eye pressure which may reduce the risk of glaucoma in the future. The laser iridotomy may also prevent new/further areas of closure of the drainage area of the eye, which may also reduce the risk of glaucoma in the future.

Benefits to the eye untreated by laser:
No laser treatment will be undertaken therefore the eye concerned will not be exposed to the risks detailed above.

Other benefits:
The potential benefits of this study for society are a better understanding of the behaviour of eyes with the conditions of PAC and PACS and the short-term effects of the laser iridotomy or argon laser peripheral iridoplasty, the practice of which is variable within the UK due to lack of substantial evidence.

12. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He will explain the reasons and arrange for your care to continue.

13. What happens when the research study stops?

You will be followed regularly in the glaucoma clinic and you may be contacted to have a Peripheral Iridotomy in your observed eye.

14. What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you. They can be contacted as follows:

Patient Advice and Liaison Service (PALS)
Hinchingbrooke Healthcare NHS Trust
Hinchingbrooke Park
Huntingdon
Cambs PE29 6NT
Telephone: 01480 428964
E-mail: pals@hinchingbrooke.nhs.uk

15. Will my taking part in this study be kept confidential?

For this study, we will need to ask your permission to have access to your medical notes. All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/ surgery will have your name and address removed so that you cannot be recognised from it. An exception to this is correspondence to your GP, who, with your permission, will be informed about your participation in the study.

16. What will happen to the results of the research study?

The results of the study will be published in a scientific journal. The results are likely to be published several months after the study has ended. Basic information will be accessible from any university or hospital library. The complete paper will be obtainable from the British Library, although a fee may be charged. You will not be personally identified in the published study.

17. Who is organising and funding the research?

The study is being funded by a pharmaceutical company. The research doctor will receive no personal payment for conducting the study and looking after patients during its course.

18. Who has reviewed the study?

This study has received ethics approval by the Essex 1 Research Ethics Committee.

Thank you

Thank you for reading this information leaflet, we hope it has helped you in making your decision. The research team is really appreciative of you taking the time to read this document.

Contact for Further Information

If you have any questions about the study or your participation in the study, please do not hesitate to contact us:

Miss Laura Sánchez Parra (Research optometrist , 079 838 379032)

Professor Rupert Bourne (Chief Investigator, 01480 418757)

Appendix 4 Forms

Patient Information Sheet

REC Reference: 10/H0301/14

Hinchingbrooke Health Care NHS
NHS Trust

Hinchingbrooke Park
Huntingdon
Cambs PE29 6NT

Patient Information Sheet

For patients with a diagnosis of Primary Angle Closure and/or Primary Angle Closure Suspect in both eyes

Dear ……..

insert patient sticker with patient demographics

This letter gives you information about the following research study in which your eye doctor has suggested that you may like to be involved.

Investigating Management of Primary Angle Closure and Treatment study (IMPACT)

A full explanation is given in subsequent pages. The last page gives contact details for the individuals running the study if you require more information. If you decide to participate in the study your local doctor (general practitioner) will also be given the same information.

This study has been approved by the Essex 1 Research Ethics Committee.

Yours sincerely

Professor Rupert Bourne
BSc MD, FRCOphth
Consultant Ophthalmic Surgeon
Chief Investigator

Summary of this document

You are being invited to take part in a research study that involves patients whose eyes are at risk of glaucoma, which involves damage to the optic nerve. These risk factors involve a shallow front chamber to the eye which may lead on to high pressure in the eye and subsequent damage to the nerve. Some doctors treat eyes at risk of this form of glaucoma (angle-closure glaucoma) with a laser (laser iridotomy), however there is limited evidence to support the use of laser in this situation. The purpose of the study is to compare the effect of laser in one eye with no treatment in the fellow eye if both of your eyes are at risk. Various painless tests will be performed to establish the effect of laser. Patients will be followed up for a period of 6 months after the treatment and will then return to normal NHS follow-up as appropriate.

An Invitation

You are being invited to take part in a research study. Before you decide if you wish to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

Background to the condition

Inside the eye there is fluid which keeps the shape of the eye and helps it function. There are two types of fluid, aqueous and vitreous humour which create a pressure inside the eye. This eye pressure is of interest to this study.

Aqueous humour is found in the front part of the eye between the front window of the eye (the cornea) and the lens, in an area known as the ‘anterior chamber’. Aqueous humour is continuously produced by the ‘ciliary body’, and drained by the ‘trabecular meshwork’, which is located at the base of the corner of the anterior chamber. When access to the trabecular meshwork is narrow or closed, the eye is said to have an ‘occludable angle’ and patients are designated “primary angle closure suspects (PACS)”. A further stage, termed “primary angle closure (PAC)” involves permanent closure of this area and/or a rise in eye pressure. A persistently raised eye pressure may lead on to damage to the optic nerve, “primary angle closure glaucoma (PACG)”.

What is the current ("standard") treatment for PAC/PACS patients?

Many patients are found to have the features of PAC or PACS and unaware of it. There are different ways of looking after these patients but among the medical profession there is no agreement on how care should be delivered. Current care is therefore quite varied and, among others, it includes the decision of simply to watch these patients in hospital clinics, discharge them from the hospital or treat them with laser procedures aimed to open the access to the drainage area. These laser procedures are called Peripheral Iridotomy (PI) and Argon Laser Peripheral Iridoplasty (ALPI), and involve the following:

PI = Laser Peripheral Iridotomy = a laser procedure used to make a microscopic hole in the upper part of the iris.

ALPI = Argon Laser Peripheral Iridotomy = a laser procedure that stretches the iris away from the drainage area of the eye to open it to drain fluid from the eye

What is the purpose of the study?

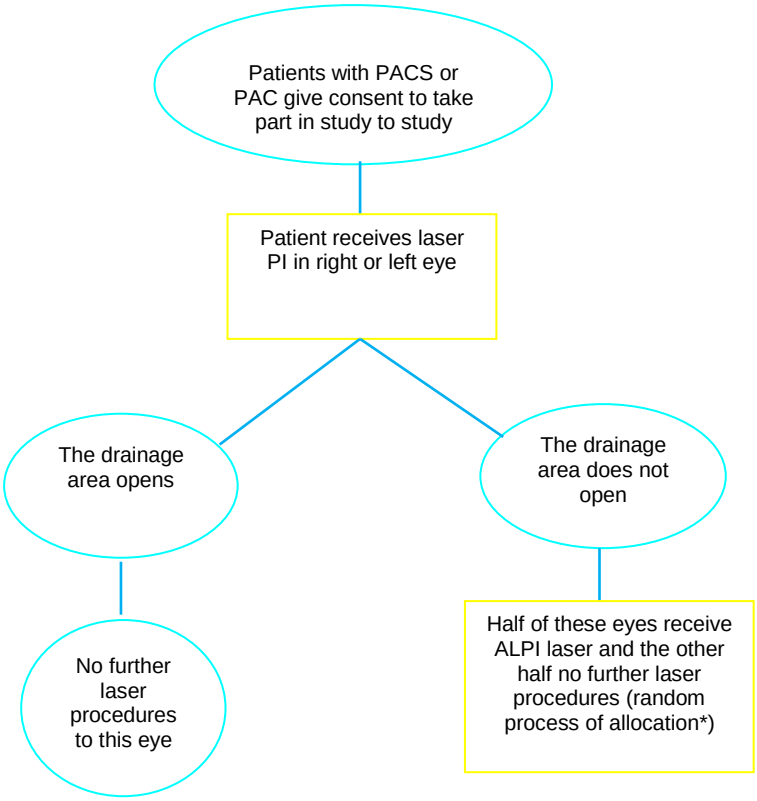
The current study is designed to find out how best to care for these patients through a better understanding of how an eye with PACS can change to a state of PAC and then to PACG and how laser procedures mentioned above can affect this risk of change by altering the dimensions of the front chamber of the eye and drainage of fluid from the eye.

How is this going to be done?

The study will involve patients with PAC or PACS in both eyes, with no symptoms, who will receive a PI in one eye while the other eye is left untreated. This treated eye will be randomly chosen using computer software; this means neither the participant nor the doctors will be able to decide which eye will receive the laser. Examination of your eyes before and after laser treatment will allow us to gather information about how the conditions of PAC and PACS can be affected by laser.

If the drainage area does not open up after laser treatment ('an occludable angle'), the eye will be either left with no further laser treatment or will receive a further different type of laser treatment, an ALPI. The decision whether to offer no further treatment or ALPI will be made by the computer programme in a randomised process.

This process of laser procedures is illustrated below:



Laser PI = Laser Peripheral Iridotomy = a laser procedure used to make a microscopic hole in the upper part of the iris.

ALPI = Argon Laser Peripheral Iridotomy = a laser procedure that stretches the iris away from the drainage area of the eye to open it to drain fluid from the eye

* ''random process of allocation' involves a computer programme randomly selecting an eye for treatment with the laser procedure. Neither the participant nor the doctors will be able to decide which eye will receive the laser

Why have I been invited to participate in this study?

You have been invited to take part in this study because we believe that you are a suitable participant. You have been recently diagnosed with PACS/ PAC in both eyes and you have no signs of glaucoma in either.

Do I have to take part?

Taking part in this research is entirely voluntary. You can decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a

consent form. If you decide to take part you are still free to withdraw at any time without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

After being informed about the study you will be given an appointment to return to the eye clinic. This will happen within the next 3 weeks. At that appointment you will be able to ask any other questions you have about the study. If you agree to take part, we will ask you to sign a consent form so that you can be enrolled into the study.

You will be asked to attend on various dates. If you undergo laser PI only this will be done in 7 visits and if you receive ALPI as well it will be done in 11 visits.

<u>What type of tests/laser procedures are going to be done when I attend the research clinic (visits) and what do they involve?</u>

The co-researchers will perform the following measurements/procedures:

12. Visual acuity- this is an evaluation of the sharpness of your vision
13. Visual field- measures the quality of your eyesight in central and surrounding areas
14. Slit- lamp examination- we will use a microscope to evaluate the health of the front and the back of your eye, to assess the interior of the front chamber of the eye and to measure the eye pressure of each eye.
15. Laser PI (laser peripheral iridotomy)- an explanation is given above.
16. Supine and darkroom provocation tests- these measurements of eye pressure are made to understand how your eye pressure behaves when lying down on your back and also after 10 minutes in a dark environment (to simulate the conditions at night).
17. Cameras and other devices that take images of the front part of the eye
18. Cameras and other devices that take images of the surface of the eye and the fluid in the front chamber of the eye
19. Measurement of thickness of the surface of the eye- this is important because the thickness of the surface has an effect on the accuracy of eye pressure measurements.
20. Subjective refraction- this is the same procedure as when you go to see an optometrist for an assessment for glasses. We need to know if the laser procedures have an effect on the power of the eye
21. Retinal examination, eye pressure measurement and laser and photographic imaging after pupil dilation- we need to widen the pupil using eyedrops to have a better view of the back of the eye and to allow more detailed pictures of the back of the eye to be taken. At the same time we will be able to see if eye pressure changes when your pupil is bigger.
22. Argon Laser Peripheral Iridoplasty- described in sections above.

Are all of these tests going to be done at every visit?

No. We have designed the following table where you can see what we are going to do at each of the visits. Please note that we have numbered the tests/laser procedures using the same sequence given above.

	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11
Test 1	X	X	X	X	X	X	X	X	X	X	X
Test 2	X										X
Test 3	X		X	X	X	X		X	X	X	X
Test 4		X									
Test 5	X					X					X
Test 6	X		X	X		X		X	X	X	X
Test 7	X	X	X	X	X	X	X	X	X	X	X
Test 8	X		X	X	X	X		X	X	X	X
Test 9	X					X					X
Test 10	X			**X**					**X**		**X**
Test 11							X				

Crosses marked in bold type above indicate that the test is only performed on the eye that has received laser treatment.

How many of these tests would be done on me as part of my routine care at the Hinchingbrooke Hospital Eye Clinic?

	Number of tests/procedures to be received as part of the study	Number of tests/procedures to be received as part of routine care if I was not part of the research study
Test 1	11	4
Test 2	2	1
Test 3	9	4
Test 4	1	0 or 1
Test 5	3	0
Test 6	9	2
Test 7	11	0

Test 8	9	1
Test 9	3	0
Test 10	4	0 or 1
Test 11	1	0 or 1

When exactly are those visits going to be done?

VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7*	VISIT 8*	VISIT 9*	VISIT 10*	VISIT 11
This is your start date.	4 weeks since visit 1	4 weeks + 1 day since visit1	5 weeks since visit 1	10 weeks since visit 1	16 weeks since visit 1	18 weeks since visit 1	18 weeks + 1 day since visit 1	19 weeks since visit 1	24 weeks since visit 1	28 weeks since visit 1

* These visits are only attended by patients who undergo an ALPI laser treatment.

How long is each visit going to take approximately?

VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 9	VISIT 10	VISIT 11
8 hours	2 hours	1 hour	1 hour	1 hour	3.5 hours	2 hours	1 hour	1 hour	1 hour	**8 hours**

Please note that we advise patients who have appointments at the routine (non-research) eye clinic expect to spend up to 3 hours at the clinic.

Travel and parking expenses

Travel **and parking** expenses will be reimbursed either at the end of each visit or alternatively at the end of the study, whichever is more convenient to you. **Refreshments will be provided on the two full-day visits.**

What are the possible disadvantages and risks of taking part?

2. Risks to the eye that receives laser treatment.

a. In the case of laser Peripheral Iridotomy (PI):

Complications are uncommon. The most common complications are a rise in eye pressure shortly after the treatment. The pressure will be checked before you go home and if very

high you will need extra treatment (usually eye drops or tablets). You will also need to remain in the Eye Clinic until the pressure has dropped to a safe level.
Other rarer risks include:

- Slight haze lasting up to a few hours due to blood in the front of the eye
- Some research has suggested cataract can be caused by laser PI while other studies have contradicted this.
- Detachment of the retina (very rare).
- Possible mild discomfort during the laser treatment
- Change in the inner layer of the front surface of the eye (the corneal endothelium). Previous studies involving small numbers of eyes have noted a change in the inner lining of the front surface of the eye (corneal endothelial cells) that occurs after laser iridotomy treatment. It is unknown whether this has an effect on eyesight in the long-term. The risk is likely to very low as this procedure has been performed for several decades with adverse effects to vision being very rare.

<u>b. In the case of Argon Laser Peripheral Iridoplasty (ALPI)</u>

Complications are the same as those described for PI with the exception that there is no risk of bleeding in this procedure. Pigmented burn marks may develop at the sites of laser applications in some eyes treated with ALPI, although this is unusual.

2. Risks to the eye that does not receive laser treatment.

The risk of not treating an eye with your condition over a 28 week period from first diagnosis is unknown. Many patients do not receive laser procedures during routine care. The close follow-up of eyes that have not received laser treatment over 28 weeks is more intensive than that of routine care and will detect eyes that develop a rise in eye pressure or increasing closure of the drainage area of the eye.
Patients will be withdrawn from the study if the eye pressure rises above a certain level (35mmHg) or if they develop signs of glaucoma in either eye.

3. Risks associated with measuring devices:

The co-researchers will be taking the measurements. The measuring devices used in this study carry no additional risk to that involved in routine standard care. In the case of devices in contact with the surface of the eye (cornea) the possible risks are irritation of the cornea or a scratch to the cornea. These symptoms/signs are very rare after a single measurement per visit as this study proposes. If any of these symptoms/signs are noticed by the researchers during the measurements they will be confirmed and the measurements will be stopped. Patients will be asked to stay in the

clinic for a few hours and the abrasions allowed to heal with or without the use of an antibiotic eye drop. Patients will be followed up by an ophthalmologist/eye nurse in the eye clinic.

4. Confidentiality:

In order to minimize the potential loss of confidentiality, each participant in this study will have the information collected from them anonymised. All information that is collected about you during the course of the research will be kept strictly confidential. Each participant in this study will have the information collected from them anonymised using a unique study code which will be used on all the data collection forms. It will not possible to identify you from the code. Only the Research Team will have access to the code. If you take part in the research we will inform your GP of your participation, unless you prefer your GP is not informed.

What are the possible benefits of taking part?

Benefits to the eye treated by laser:
Prevention of a possible acute angle-closure episode, which involves a sudden painful rise in eye pressure. This would be a rare event in such a short period of follow-up. The laser peripheral iridotomy may lower the eye pressure which may reduce the risk of glaucoma in the future. The laser iridotomy may also prevent new/further areas of closure of the drainage area of the eye, which may also reduce the risk of glaucoma in the future.

Benefits to the eye untreated by laser:
No laser treatment will be undertaken therefore the eye concerned will not be exposed to the risks detailed above.

Other benefits:
The potential benefits of this study for society are a better understanding of the behaviour of eyes with the conditions of PAC and PACS and the short-term effects of the laser iridotomy or argon laser peripheral iridoplasty, the practice of which is variable within the UK due to lack of substantial evidence.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He will explain the reasons and arrange for your care to continue.

What happens when the research study stops?

You will be followed regularly in the glaucoma clinic and you may be contacted to have a Peripheral Iridotomy in the eye that did not receive laser treatment in the study.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you. They can be contacted as follows:

Patient Advice and Liaison Service (PALS)
Hinchingbrooke Healthcare NHS Trust
Hinchingbrooke Park
Huntingdon
Cambs PE29 6NT
Telephone: 01480 428964
E-mail: pals@hinchingbrooke.nhs.uk

Will my taking part in this study be kept confidential?

For this study, we will need to ask your permission to have access to your medical notes. All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/ surgery will have your name and address removed so that you cannot be recognised from it. An exception to this is correspondence to your GP, who, with your permission, will be informed about your participation in the study.

What will happen to the results of the research study?

The results of the study will be published in a scientific journal. The results are likely to be published several months after the study has ended. Basic information will be accessible from any university or hospital library. Results of the study will be provided free of charge if requested. You will not be personally identified in the published study.

Who is organising and funding the research?

The study is being funded by a pharmaceutical company by providing an educational grant. The research doctor will receive no personal payment for conducting the study and looking after patients during its course.

Who has reviewed the study?

This study has received ethics approval by the Essex 1 Research Ethics Committee.

Thank you

Thank you for reading this information leaflet, we hope it has helped you in making your decision. The research team is really appreciative of you taking the time to read this document.

Contact for Further Information

If you have any questions about the study or your participation in the study, please do not hesitate to contact us:
Miss Laura Sánchez Parra (Research optometrist, 01480 416416 ext 8437)
Professor Rupert Bourne (Chief Investigator, 01480 418757)

Glossary of Terms

Primary angle closure suspects (PACS) and **primary angle closure (PAC)**
these are 'diagnostic labels' given to patients who have a shallow front chamber to the eye which is a risk factor for a form of glaucoma, named **primary angle closure glaucoma (PACG).**

PI = Laser Peripheral Iridotomy = a laser procedure used to make a microscopic hole in the upper part of the iris.

ALPI = Argon Laser Peripheral Iridotomy = a laser procedure that stretches the iris away from the drainage area of the eye to open it to drain fluid from the eye

Appendix 4 Forms

Randomization Forms

Randomized Allocation
1st Randomization
IMPACT Pilot Study

Patient Study No	
Patient Initials	
Date of Birth	
Hinchingbrooke Hospital Medical Records No.	
Date of Consent/Randomisation	
Eye which will undertake PI	

This envelope and slip should be returned to:

Laura Sanchez Parra
Research Coordinator
Eye Clinic
Hinchingbrooke Hospital

Form 1

Randomized Allocation
2nd Randomisation
IMPACT Pilot Study

Randomisation Patient Number	

Patient Study No	
Patient Initials	
Date of Birth	
Hinchingbrooke Hospital Medical Records No.	
Date of Consent/Randomisation	
Outcome	

This envelope and slip should be returned to:

Laura Sanchez Parra
Research Coordinator
Eye Clinic
Hinchingbrooke Hospital

Form 2