ACCOMMODATION EFFECTS ON PERIPHERAL OCULAR BIOMETRY

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BSc (Optom), MSc (Optom)

Submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

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Institute Of Health and Biomedical Innovation

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Brisbane, Qld, Australia

2016

Keywords

Axial length
Accommodation
Biometry
Choroidal thickness
Emmetropia
IOLMaster
Lenstar
Myopia
Partial coherence interferometry
Peripheral eye length
Refractive error
Retina
Spectral domain optical coherence tomographer

Abstract

There is a well-known association between near work and myopia development. During myopia development, the axial length of eye increases and the choroid thins at the fovea. Traditionally the fovea was thought to drive myopia development, but the peripheral retina is now known to be important to refractive development. Accommodation may alter the peripheral ocular biometry. This project determined the impact of accommodation on the biometric properties of axial length and choroidal thickness along the horizontal visual field in emmetropic and myopic eyes.

In Experiment 1 (chapter 4), the effect of accommodation on peripheral axial length was measured in 83 young adults (29 emmetropes, 32 low myopes and 22 high myopes) using a modified Lenstar LS 900 partial coherence interferometer along the horizontal visual field out to ±30° for both 0 D and 6 D accommodation demands. There were significant increases in axial lengths with accommodation at all eccentricities. Axial length changes were significantly greater for higher myopes than for emmetropes on-axis (higher myopes 41 ± 29 μm, emmetropes 30 ± 22 μm, $p = 0.005$), for higher myopes than for low myopes at 30° nasal ($p = 0.03$), and for higher myopes than for the other groups at 20° nasal ($p < 0.05$). At all positions, there were significant negative correlations between changes in axial length along the horizontal meridian and spherical equivalent refraction of myopic eyes.

In Experiment 2 (chapter 5), peripheral axial length was monitored during eight min of accommodation to a 6 D stimulus and then during eight min of recovery. There were 23 emmetropic and 28 myopic adults, and measurements were taken at 0°, 20° nasal and 20° temporal visual field positions. There were sustained axial length elongations during the entire accommodation task. Elongations were greater for the myopes than for the emmetropes. The post-task recovery was slower and was still incomplete after 8 min. The recovery was similar for emmetropes and myopes in terms of percentage of the maximum elongations at all positions.

In Experiment 3 (chapter 6), choroidal thickness changes with accommodation were investigated in 69 young adults (24 emmetropes, 23 low myopes and 22 higher myopes). Choroidal thickness was measured with an optical coherence tomographer along the horizontal visual field out to ±35° for both 0 D and 6 D accommodation demands. For both demands, refractive group affected choroidal thickness significantly at most angles. For the 22 out of 28 accommodation/visual field combinations at which significance occurred, emmetropes and low myopes had significantly thicker choroids than higher myopes for 21 and 11 combinations, respectively. Choroids thinned with accommodation, with the thinning lessening away from the fovea. At the fovea, the thinning was affected significantly by refractive group where the higher myopes thinned more than the emmetropes (mean ± SE: 9.0 ± 2.4 μm), and at 30° temporal where the emmetropes thinned more than low myopes (4.6 ± 1.8 μm) and higher myopes (7.1 ± 1.9 μm). There were significant negative correlations between accommodation-induced changes in choroidal thickness and axial eye length for all refractive groups at all positions. The choroidal thickness changes were responsible for most of the axial length changes.

In conclusion, this project has found differences between refractive groups in their ocular biometry responses to accommodation across the horizontal visual field. These differences suggest a potential mechanism by which near work may alter axial length and choroidal thickness and thus lead to the development of myopia.

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List of Abbreviations

ACD	Anterior chamber depth
AL	Axial length
ASR	Accommodative stimulus response
ChT	Choroidal thickness
CCD	Charge coupled device
CCT	Central corneal thickness
CT	Computerised tomography
COAS	Complete ophthalmic analysis system
Cyl	Cylinder
D	Dioptre
DC	Dioptres of cylinder
Dh	Dioptre hour
DS	Dioptres of sphere
DDS	Decrease distance series
EMM	Emmetrope
EOM	Early onset myopia
HYP	Hyperope
IOP	Intraocular pressure
LED	Light-emitting diode
LOM	Late-onset myopia
LT	Lens thickness
MY	Myope

MRI	Magnetic resonance imaging
NITM	Near-work-induced transient myopia
N	Nasal
NLS	Negative lens series
OCT	Optical coherence tomography
PCI	Partial coherence interferometry
PLS	Positive lens series
RPE	Retinal pigment epithelium
SER	Spherical equivalent refraction
SLO	Scanning laser ophthalmoscope
SEM	Standard error of the mean
VCD	Vitreous chamber depth
T	Temporal
TA	Tonic accommodation

Statement of Original Authorship

The work contained in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

QUT Verified Signature

Signature:

Date: 27-04-2016

Acknowledgements

I express my thanks to Allah (God) for giving me the courage to complete the thesis.

I thank my principal supervisor Associate Professor Katina Schmid for her guidance, support and encouragement during my PhD study. I thank my associate supervisors Professor David Atchison and Dr Marwan Suheimat for their support. Professor Atchison helped in data analysis and gave me valuable comments to improve my thesis. Dr. Suheimat helped design and develop equipment required for the experiments.

I acknowledge the Kingdom of Saudi Arabia Government for awarding me a PhD Scholarship. The Queensland University of Technology provided the necessary facilities for my project. I thank the Research Methods Group in the Institute of Health and Biomedical Innovation (IHBI) for their advice on data analysis.

I am grateful to my fellow students at the Queensland University of Technology who participated in these experiments. I am especially grateful to my postgraduate friends at IHBI and my colleagues in the School of Optometry and Vision Science for their advice, encouragement and support.

Many thanks to my family, including my mother Guzial for her prayers for me, and my sisters and brothers.

Last but not least, I am immensely grateful to my wife Reem and children Mubarak, Faisal, Mohammed and Jana for their love, patience and great support throughout my PhD studies.

Chapter 1: Introduction

1.1 INTRODUCTION

The increase in the prevalence of myopia around the world, particularly in developed countries, appears to be linked to intensive education systems (Lin et al., 2001; Morgan et al., 2012; Morgan and Rose, 2013). This suggests that there is a strong relationship between environmental factors and the development of myopia (Mirshahi et al., 2014; Pan et al., 2011; Sherwin and Mackey, 2013; Williams et al., 2015; You et al., 2014). One of the environmental risk factors associated with myopia development is long periods of time performing near work (Chen et al., 2003; Fernandez-Montero et al., 2015; Goss, 2000). It has also been reported that reading at a close distance (< 30 cm) is likely to be a critical factor (Ip et al., 2008). Understanding why near work is linked to the development of myopia is very important.

Emmetropisation is the process by which infant refractive errors reduce in magnitude with age. This process takes place when the increase in the eye's axial length is co-ordinated with a corresponding decrease in optical power (reviewed in Wildsoet (1997)). The quality of the retinal image can be affected by ocular conditions such as congenital cataract and lid haemangioma. These conditions are thought to disrupt the normal process of emmetropisation and lead to eye elongation, causing myopia (Calossi, 1994; Hoyt et al., 1981). Therefore, a good quality visual signal is essential for normal visual development.

During near work the eye must increase its power through the act of accommodation if clear vision is to be maintained. Accommodation alters the biometry of the human eye with relatively large changes in lens thickness and anterior chamber depth (Bolz et al., 2007; Du et al., 2012; Zhong et al., 2014), and smaller changes in choroidal thickness (Woodman et al., 2012) and axial length (Drexler et al., 1998; Mallen et al., 2006; Woodman et al., 2012). There are suggestions that accommodation can alter the Stiles Crawford function, indicating foveal retinal stretching in the horizontal field meridian (Blank et al., 1975). However, Singh et al. (2009) observed only a small changes in orientation or directionality in the Stiles–Crawford effect with accommodation (6 D). Most measurements of the impact of accommodation on the eye have been made on-axis; there is no information (except for peripheral refractions and higher order aberrations) on the effect of accommodation on the eye's periphery.

Changes to the on-axis ocular biometry are associated with myopia (Flitcroft, 2013). Clinical studies have reported that myopia is associated with decrease in the corneal radius of curvature (Atchison, 2006; Shih et al., 2007) and increase in vitreous chamber elongation (McBrien and Adams, 1997). In the vast majority of cases, myopia progression is due to the latter. Less is known regarding the peripheral changes due to accommodation.

Hoogerheide et al. (1971) reported that relative to the central refraction, the peripheral retina tends to peripheral hyperopia and myopia in myopes and emmetropes, respectively. Subsequent research has also shown that the pattern of peripheral refractions of emmetropes and myopes is different and suggest that this difference could be due to the myopia (Charman and Radhakrishnan, 2010; Mutti et al., 2007). As the peripheral retina comprises the larger part of visual field it is conceivable that any defocus growth signal generated in the periphery would be stronger than that generated by the fovea (Wallman and Winawer, 2004). This speculation has been supported by animal studies which show that ablating the central 10° diameter of the retina while leaving the periphery intact does not prevent emmetropisation in young monkeys (Smith et al., 2005). This indicates that the peripheral retina may be able to modulate the growth of the eye (Smith et al., 2010; Smith et al., 2005).

Techniques such as magnetic resonance imaging (MRI), X-ray and computerised tomography, ocular coherence tomography, ultrasonography and partial coherence interferometry have been used to examine the retina. MRI is probably the best way of assessing retinal contour (Atchison and Smith, 2004). The image quality of MRI is better than that of X-ray tomography, but MRI has the disadvantages of high cost, long testing time and low resolution (~0.15 mm) (Duong, 2011).

Partial coherence interferometry instruments such as the IOLMaster V5 (Carl Zeiss Meditec AG Jena, Germany) and Lenstar LS 900 (Haag-Streit, Bern, Switzerland) have been used to measure axial length both on-axis and peripherally. These instruments contain a Michelson interferometer that creates partial coherence, but they differ in their mechanism of operation. The IOLMaster contains a diode laser producing a 780 nm infrared beam, whereas the Lenstar contains a superluminescent diode producing an 820 nm infrared beam (Jasvinder et al., 2011). The IOLMaster uses a partial coherence interferometry principle only for axial length measurements. It uses a lateral slit illumination to measure the anterior chamber depth and image analysis to obtain the corneal curvatures. The Lenstar uses partial coherence interferometry to obtain anterior chamber depth, lens thickness and axial length and retinal thickness distances. The Lenstar provides rapid results and has a better resolution (0.01–0.02 mm) than ultrasound (0.10 mm) or MRI (0.15 mm) (Kimura et al., 2007; Lam et al., 2001). Recent studies report good measurement repeatability for peripheral eye lengths with the Lenstar, better than that of the IOLMaster (Schulle and Berntsen, 2013; Verkicharla et al., 2013).

Previous studies define axial length as the distance from the anterior surface of cornea to the retinal pigment epithelium (Drexler et al., 1998; Mallen et al., 2006; Woodman et al., 2011). It is reasonable to suggest that changes in axial length may be due to changes in the thickness of the choroid during accommodation (Woodman et al., 2012) . In animal models, hyperopic defocus causes a thinning of the choroid and myopic defocus causes a thickening of the choroid, indicating that the choroid plays an important role in altering the vitreous chamber depth (Nickla and Wallman, 2010). Recently, optical imaging techniques such as spectral domain optical coherence tomography (SD-OCT) have been used to measure the retinal pigment epithelium and choroidal thickness and in the diagnoses of retinal pathologies (Cheng et al., 2010; Costa et al., 2006; Vujosevic et al., 2012; Wu and Alpizar-Alvarez, 2013). This device provides a high resolution cross section of choroidal structures and reliable measurements in both younger and older people (Ikuno et al., 2010a; Manjunath et al., 2010; Tuncer et al., 2014).

In summary, the development of myopia is associated with axial elongation of the eye. Accommodation during near work has been shown to increase the on-axis axial length of the eye and may alter foveal retinal photoreceptor orientation. It also causes changes in choroidal thickness. Although it has been held that the centre of the retina drives the refractive status, animal studies show that defocus on the peripheral retina can alter the growth of eye. There is the potential for accommodation to affect the peripheral axial length of the eye and choroidal thickness. This can be measured quickly with partial coherence interferometry.

This thesis explores the effect of accommodation on peripheral ocular biometry. It compares the length of the eye and the choroidal thickness peripherally at different accommodation demands in emmetropes and myopes using partial coherence interferometry and SD-OCT techniques, respectively. The study may provide a better understanding of accommodation-induced effects during near work associated with myopia development.

1.2 SCOPE OF THE THESIS

This thesis consists of seven chapters. The first chapter provides an introduction and the underlying basis of the research. The second chapter provides a summary of the current understanding of myopia development and the effect of accommodation on myopia progression. The third chapter details the design methods and equipment used in experiments. The fourth chapter describes Experiment 1, which investigates the effect of accommodation on peripheral axial length for emmetropes and myopes. The fifth chapter describes Experiment 2, which investigates the time course of axial length elongation during accommodation and its recovery for emmetropic and myopic participants. The sixth chapter describes Experiment 3, which investigates the effect of accommodation on peripheral choroidal thickness for emmetropic and myopic participants. Chapter seven provides a discussion of all three experiments and includes the overall final conclusion and future research questions.

Chapter 2: Literature Review

2.1 BACKGROUND ON MYOPIA

2.1.1 Definition and classification of myopia

Myopia, or short-sightedness, is the most common refractive anomaly in children and young adults (Pan et al., 2012; You et al., 2014). It is defined as refractive error in which the image of a distant object is focused in front of the retina when the eye is in a non-accommodated (relaxed) state (Figure 2.1). Myopia occurs when the eye has greater refractive power than normal or the eyeball is too long, or a combination of both (Van Alphen, 1961). Some studies (Edwards and Brown, 1996; Lam et al., 1994; Rosenfield and Gilmartin, 1987) define myopia as spherical equivalent refraction [SER] of ≤ –0.50 D, while others investigations (Kleinstein et al., 2003; Mutti et al., 2002; Zadnik et al., 1993) have used ≤ –0.75 D. In the majority of cases, myopia is due to axial elongation (Wallman et al., 1987).

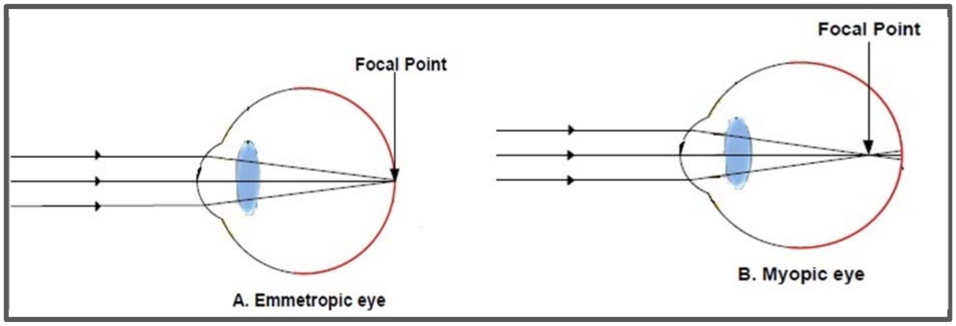


Figure 2.1: Definition of emmetropia and myopia. (A) Emmetropic eye: the optical power and axial length are correlated such that the image is formed on the retina. (B) Myopic eye: the optical power and axial length of myopic eyes are not matched, and typically the axial length is too long so that the image is formed in front of the retina.

Grosvenor (1987) classified myopia based on the age of onset into four groups:

1. Congenital myopia. This type occurs at birth and high myopia typically remains throughout life.
2. Youth-onset myopia. This type of myopia arises typically around six years of age or after.
3. Early-adult-onset myopia. This type arises between puberty and the age of 40 years, resulting in a low level of myopia.
4. Late-adult-onset myopia. This type occurs after 40 years of age and is usually associated with lens changes, causes lower levels of myopia than younger age groups, and is less common than other types.

Other studies have classified myopia into two forms based on the age of onset, that is, early-onset and late-onset myopia (Gilmartin and Bullimore, 1991; McBrien and Millodot, 1987; Strang et al., 1994). The first type arises before the age of 15 years, whereas the second type occurs after 15 years. It has been suggested that congenital and early-onset myopia might be due to genetic factors, whereas late-onset myopia might be due to environmental factors (i.e. near work and accommodation).

2.1.2 Prevalence of myopia

It is difficult to directly compare the prevalence rates of myopia across studies due to differing classifications of myopia, the ages of participants, and research methodologies. With this proviso in mind, useful information about the effect of factors such as age, ethnicity and education demand can be inferred from myopia prevalence data. The prevalence of myopia reported in adults based on studies conducted in different countries of the world is summarised in Table 2.1. In the

United States, the Baltimore Eye Survey reported that the prevalence of myopia in adults (aged 40–89 years) was 23%, and similarly, the Beaver Dam Study reported that the prevalence of myopia (adults aged 43–84 years) was 26% (Katz et al., 1997; Wang et al., 1994). Thirteen years later Vitale et al. (2009) reported a much greater prevalence of myopia of 42% in white adults (aged 20–50 years). This increase is similar to what has been reported in some Asian countries. For example, in Singapore the myopia prevalence rate in adults (aged 40–79 years) was 39% (Wong et al., 2000), whereas the prevalence of myopia in younger age groups was much higher; the reported prevalence in young adult males (military conscripts) (aged 16–25 years) was 69%, 65% and 82% for those of Indian, Malaysian and Chinese backgrounds, respectively (Wu et al., 2001).

An association between the rapid rise in the prevalence of myopia in children in Asian countries and educational demands has been found (Rose et al., 2008a; Rose et al., 2008b; Saw et al., 2005; You et al., 2014). This prevalence has been stated to have reached epidemic levels (80–95%) by the time young adults go to university between 17 and 18 years of age (Jung et al., 2012; Lam et al., 2012; Lin et al., 2001; Matsumura and Hirai, 1999; Saw et al., 2005). Associated with an early age of onset, there is a corresponding increase in the prevalence of high myopia which has significant public health implications (Liu et al., 2010; Seet et al., 2001). Table 2.2 shows selected examples of the prevalence of myopia in children living in different parts of world.

Table 2.1: Myopia prevalence for adults in different countries.

Study	Location	Participant numbers (N)	Age (years)	Myopia definition (D)	Prevalence (%)
Lam et al. (1994)	Hong Kong	220	44–40 45–49 50–54 55–59 60–64	≤ –0.50	46 30 32 31 22
Katz et al. (1997)	United States	5028	40–89	≤ –0.50	28 white 19 black
Wong et al. (2000)	Singapore	2000	40-79	≤ –0.50	39
Wu et al. (2001)	Singapore	15095	16-25	≤ –0.50	79
Saw et al. (2002)	Sumatra, Indonesia	1043	20–50	≤ –0.50	48
Midelfart et al. (2002)	Norway	3137	20–25 40–45	≤ –0.50	35 33
Bourne et al. (2004)	Bangladesh	11189	≥ 30	≤ –0.50	24
Mallen et al. (2005)	Jordan	1093	17–40	≤ –0.50	54
Sawada et al. (2008)	Japan	3021	≥ 40	≤ –0.50	42
Jobke et al. (2008)	Germany	138	18–35	≤ –0.50	41
Shah et al. (2008)	Pakistan	14490	≥ 30	≤ –0.50	37
Vitale et al. (2008)	United States	12010	≥ 20	≤ –0.50	33
Vitale et al. (2009)	United States	9609	20-50	≤ –0.50	42
Krishnaiah et al. (2009)	India	2508	≥ 40	≤ –0.50	35
Anton et al. (2009)	Spain	417	40–49	≤ –0.50	25
He et al. (2009)	South China	1269	≥ 50	≤ –0.50	33
Landers et al. (2010)	Central Australia	1653	> 30	≤ –0.50	11
Rahi et al. (2011)	United Kingdom	2487	44	≤ –0.50	40
Ezelum et al. (2011)	Nigeria	13599	≥ 40	≤ –0.50	17
Pan et al. (2011)	Singapore	2805	≥ 40	≤ –0.50	28
Hashemi et al. (2012)	Iran	6311	40-64	≤ –0.50	30
Pan et al. (2013a)	United States	4430	45-84	≤ –1.00	31 white 22 black
Pan et al. (2013b)	Singapore	8772	40-70	< –0.50	31
Kim et al. (2013)	South Korea	2690	20-29	≤ –0.50	79
You et al. (2014)	Beijing, China	1278	18	≤ –0.50	73

Table 2.2: Myopia prevalence in children in different countries.

Study	Location	Participant numbers (N)	Age (years)	Myopia definition (D)	Prevalence (%)
Lithander (1999)	Oman	6292	12	≤ –1.00	5
He et al. (2004)	Guangzhou, China	4364	5–15	≤ –0.50	38
Saw et al. (2005)	Singapore	1453	7–9	≤ –0.50	37
Goh et al. (2005)	Malaysia	4634	7–15	≤ –0.50	21
Khader et al. (2006)	Jordan	1777	12–17	< –0.50	20
He et al. (2007)	Southern China	2454	13–17	≤ –0.50	42
Sapkota et al. (2008)	Kathmandu, Nepal	4282	10–15	≤ –0.50	19
Jobke et al. (2008)	Germany	186	12–17	≤ –0.50	21
Ip et al. (2008)	Australia	2353	12	≤ –0.50	12
Rudnicka et al. (2010)	United Kingdom	1053	10–11	≤ –0.50	4
O'Donoghue et al. (2010)	Northern Ireland	1053	6–7 12–13	≤ –0.50	3 18
Logan et al. (2011)	United Kingdom	327	12–13	≤ –0.50	30
Lan et al. (2013)	Shanghai, China	2478	3–6	≤ –0.50	2
Kumah et al. (2013)	Ghana	2435	12–15	≤ –0.50	3
Adhikari et al. (2013)	Nepal	484	3–5	≤ –0.50	24
French et al. (2013)	Australia	2760	12 17	≤ –0.50	14 30
(You et al., 2014)	Beijing, China	15066	7–17	≤ –0.50	65

2.1.3 Socioeconomic cost of myopia

Myopia leads to visual impairment and blinding complications (Saw et al., 2005). The economic costs of myopia are significant (Lim et al., 2009). In Singapore, the mean annual direct costs such as those of correcting refractive errors with spectacles and contact lenses for each Singaporean school child (aged 7–9 years) is estimated to be S$221.68 (US$148) (Lim et al., 2009). In the United States, the Health and Nutrition Examination Survey reported that the estimated direct cost of correcting myopia with spectacles or contact lenses is between US$3.9 and US$7.2 billion per year (Vitale et al., 2006). There are indirect medical costs associated with ocular diseases such as retinal detachment, glaucoma and cataracts (Lim et al., 2009; Saw et al., 2005). These conditions cost the Singapore government about $2.5 million annually and this is expected to rise with increases in the population over the next few decades (Seet et al., 2001). Uncorrected myopia affects quality of life and its negative effect upon vision can lead to difficulties with performing social and daily activities and it is associated with increased fall risk (Taylor, 2007; Vu et al., 2005).

2.2 AETIOLOGY OF MYOPIA

Many studies have attempted to identify the causative factors for myopia development (reviewed by Sherwin and Mackey (2013)). Several papers show the strong influence of genetic factors (Andrew et al., 2008; Duggal et al., 2011; Yang et al., 2009) whereas other papers show the importance of the environment (He et al., 2009; Pan et al., 2012; Schellini et al., 2009). Although there are significant differences in the research outcomes of various studies, collectively it is believed that both environmental and genetic factors contribute to the development of myopia (Chong et al., 2005; Duggal et al., 2011; Hammond et al., 2001; Saw et al., 2001; Shi et al., 2011).

2.2.1 Genetic factors

There is an association between family history of refractive error and the presence of myopia (Saw et al., 2006). The prevalence of myopia among children with myopic parents is greater than that observed among children with non-myopic parents (Ip et al., 2007; Mutti et al., 2002; Pacella et al., 1999; Saw et al., 2006). Pacella et al. (1999) reported that children with two myopic parents are six times more likely to be myopic than children with one myopic parent. In addition, even before the onset of myopia, children with myopic parents have longer eyes and are less hyperopic than children whose parents are not myopic (Lam et al., 2008). The correlations in the refractive errors of identical twins are higher than those observed in non-identical twins (Hammond et al., 2001). However, as most twins share their environment, the high correlation of refractive errors in twins may be due to both shared genetics and shared environment (Morgan and Rose, 2005).

2.2.2 Environmental factors

The influence of environmental factors on myopia development has been supported by epidemiology studies. The effect of education on the development of myopia has been demonstrated in many studies (reviewed in Morgan and Rose (2005)). For example, it has been reported that Orthodox school students in Israel have a higher prevalence of myopia than students who attend the secular schools due to intensive near work (Zylbermann et al., 1993). The high prevalence of myopia in urban East Asian countries may be associated with their high intensity education systems (Saw et al., 2005).

The volume of near work performed, such as reading and writing, may be considered a risk factor for myopia development. Cross-sectional studies involving school children report a strong association between myopia and the amount and intensity of reading-based near work, which is determined using dioptre-hours (exclusive of use of video display terminals and television viewing). The unit dioptre hours (Dh) is defined as: Dh = 3 x (hours spent studying + hours spent reading for pleasure) + 2 x (hours spent playing video games or working on the computer at home) + (hours spent watching television) (Mutti et al., 2002). Saw et al. (2002)

found that the prevalence of myopia among Singaporean children who read more than two books per week was greater than that of children who read less than this. The Sydney Myopia Study also found that greater time spent reading (> 30 min) or reading at nearer distances (< 30 cm) was associated with an increased risk of myopia development among school children (Ip et al., 2008). Longitudinal studies have found an increase in axial length due to increases in both the anterior and the vitreous chamber depths in emmetropic children conducting intensive near work compared with emmetropic children who were not performing intensive near work (Hepsen et al., 2001).

Myopia is correlated with the level of education (Shimizu et al., 2003; Wong et al., 2000). When compared to the general population, the prevalence of myopia was higher (47% *v*. 33%) among university students in Norway (Kinge et al., 1998).

Evidence from population-based studies report an association between high levels of myopia and occupations requiring long durations of near work activities (Shimizu et al., 2003; Wong et al., 2000; Wu et al., 1999). Wong et al. (2000) reported that professional and office workers had a higher prevalence of myopia (54%) than those in occupations such as cleaning and sales (26%). Textile workers (Simensen and Thorud, 1994) and microscopists (Adams and McBrien, 1992; Ting et al., 2004) have high prevalence of myopia, which could be due to excessive accommodation (Adams and McBrien, 1992) or to high lags of accommodation during near work (Ting et al., 2004). The above findings provide strong evidence that environmental factors are important in myopia development, but the mechanism is not understood.

2.3 OTHER RISK FACTORS

2.3.1 Intraocular pressure

An influence of the eye's intraocular pressure (IOP) on myopia progression and axial elongation has been proposed in several studies (Abdalla and Hamdi, 1970; Leydolt et al., 2007; Read et al., 2011). Leydolt et al. (2007) showed that elevations in IOP were associated with increases in axial length of 18 emmetropic healthy adult participants. Read et al. (2011) investigated the effect of short-term elevations of the IOP upon axial length in 20 emmetropic (+0.50 to −0.50 DS) and 20 myopic (≤ − 0.75 DS) participants. The IOP and axial length were measured using the Ocular Response Analyser and the IOLMaster, respectively. Both refractive groups showed small, but significant axial elongation (mean change, 18 ± 12 μm, $p < 0.0001$) associated with small elevations in IOP. Manny et al. (2008) and Song et al. (2008) suggested that the higher IOP of myopes occurs after axial elongation and myopia development, rather than before.

Jenssen and Krohn (2012) examined the change in IOP during a 3 D accommodative task in 33 healthy adults using Goldmann applanation tonometry, finding significant reduction in IOP during accommodation (mean change, –1.8 ± 1.2 mm Hg, $p < 0.0001$). Similarly, other studies using Goldmann applanation tonometry found a reduction in IOP with accommodation (Blake et al., 1995; Cassidy et al., 1998; Jenssen and Krohn, 2012; Mauger et al., 1984). This suggests that long periods spent performing near work and accommodation are unlikely to cause the development of myopia through increases in IOP.

2.3.2 Ocular aberrations

It has been proposed that higher than normal ocular aberrations may play an important role in the development of myopia (Cheng et al., 2003a). A possible mechanism involves retinal image blur caused by high ocular aberrations acting as a stimulus to eye growth. Paquin et al. (2002) and Marcos et al. (2002) found increased higher order aberration and levels of root mean square (RMS) errors in myopic compared with emmetropic participants. He et al. (2002) also found greater RMS in both myopic children and myopic young adults than in emmetropic participants. However, other studies have found no relationship between high ocular aberrations and refractive error (Atchison et al., 2006; Carkeet et al., 2002; Cheng et al., 2003a; Collins et al., 1995). Studies utilising model eyes have shown that if the myopia is due to an increase in axial length, the amount of spherical aberration should increase as myopia increases (Atchison and Charman, 2005; Cheng et al., 2003a).

The influence of accommodation on ocular aberrations across different refractive groups have been investigated in several studies (reviewed in Charman (2005)). Collins et al. (1995) examined monochromatic aberrations in 21 myopic and 16 emmetropic young adults using an aberroscope technique with accommodation demands ranging from 0 to 3 D. During accommodation, fourth-order aberrations (emmetropes, 0.03 ± 0.02 μm for 0 D with pupil size 3.1 ± 0.4 mm, 0.02 ± 0.02 μm for 3 D with pupil size 3.1 ± 0.4 mm; myopes, 0.02 ± 0.01μm for 0 D with pupil size 3.1 ± 0.3 mm, 0.02 ± 0.01 μm for 3 D with pupil size 3.0 ± 0.5 mm) were significantly lower in myopes than in emmetropes. Other studies have found higher negative spherical aberrations in myopic than emmetropic participants during accommodation (Buehren et al., 2005; He et al., 2002).

2.3.3 Force of extra-ocular muscles

Some studies have proposed that the axial elongation of the eye may be due to the extra-ocular muscles placing force on the sclera (mechanical stress) during accommodation (Drexler et al., 1998). Similarly, it has been suggested that mechanical force exerted by the extra-ocular muscles during near work could contribute to myopia development (Bayramlar et al., 1999).

Bayramlar et al. (1999) used ultrasound biometry to investigate the effect of convergence on axial length during near fixation under cycloplegia (i.e. with accommodation paralysed) in 124 young male participants. Axial length increased significantly with near fixation (from 23.64 ± 0.15 mm to 23.82 ± 0.15 mm, $p < 0.001$). Thus, the authors concluded that convergence may be involved in myopia development. However, Read et al. (2010a) did not find any significant change in axial length both during and after short period (15 min) of sustained convergence in young healthy adults.

Ghosh et al. (2012) examined the influence of 15° down gaze viewing on axial length using a Lenstar LS 900 in 20 myopic and 10 emmetropic participants. The axial length of the eye increased during infero-nasal gaze and this change was greater in myopic than emmetropic participants (18 ± 8 µm, $p < 0.001$). During downward gaze, the axial length increased the greatest amount for eye movement without head movement compared with primary gaze and thus the authors suggested that changes in axial length in down gaze are due to the influence of the extra-ocular muscles.

2.4 BIOMETRY OF THE MYOPIC EYE

2.4.1 Axial length measurement techniques

In the past, A-scan ultrasound was the most common technique used to determine the intraocular lens power required during cataract surgery and has been used for many years in vision research (Zadnik et al., 1993). However, the possible corneal indentation and requirement of corneal anaesthesia due to direct contact between the ultrasound probe and the eye present major disadvantages (Olsen, 1989). Recently, partial coherence interferometers such as the IOLMaster (IOLMaster V5, Carl Zeiss Meditec AG, Jena, Germany) and the Lenstar (Lenstar LS 900, Haag-Streit, Bern, Switzerland) have been developed for axial length measurements. These interferometers provide rapid results and have high resolution. Partial coherence interferometry has a better resolution (0.01–0.02 mm) than ultrasound (0.10 mm) and MRI (0.15 mm) (Kimura et al., 2007; Lam et al., 2001). The Lenstar uses an 820 nm super-luminescence diode and the IOLMaster uses a 720 nm diode laser. The IOLMaster uses partial coherence interferometry to measure only the axial length of the eye, whereas the Lenstar uses it to measure axial length, lens thickness, corneal thickness, anterior chamber depth and retinal thickness (Holzer et al., 2009; Jasvinder et al., 2011).

Several studies reported that partial coherence interferometry instruments for on-axis axial length measurements have good repeatability (Cruysberg et al., 2010; Salouti et al., 2011; Shammas and Hoffer, 2012; Zhao et al., 2013). Verkicharla et al. (2013) examined the repeatability of partial coherence interferometry instruments for peripheral axial length measurements in seven participants. The measurements were performed up to ±30° for horizontal and vertical visual fields. There was better repeatability of measurements for the Lenstar (0.02 ± 0.02 mm) than for the IOLMaster (0.04 ± 0.04 mm). The repeatability of off-axis axial length measurements using a partial coherence interferometer has also been examined by Schulle and Berntsen (2013). Twenty-nine healthy adults participated; measurements were repeated at two separate visits for central, ±10º and ±30º locations. There was better repeatability of the Lenstar instrument for both central and peripheral eye length measurements.

2.4.2 Anterior chamber depth

Anterior chamber depth (ACD) is the distance between the posterior surface of the corneal and anterior surface of the crystalline lens along the optical axis of the eye (Barrett et al., 1996). Cross-sectional studies have reported that variations in axial length are primarily mediated by the vitreous chamber depth and not the anterior chamber (Adams, 1987; Jiang and Woessner, 1996; McBrien and Adams, 1997). Hosny et al. (2000) investigated the relationship between axial length and ACD in 211 healthy participants. The ACD was deeper in participants with longer axial lengths. Park et al. (2010) examined the correlation between axial length and ocular parameters in 291 participants using optical biometry, pachymetry and optical coherence tomography. As the axial length increased, the central corneal thickness, corneal curvature and retinal nerve fibre layer decreased and the ACD increased.

2.4.3 Myopia and axial length

A number of studies have reported that the eyes of adult myopes have longer axial lengths than the eyes of emmetropic and hyperopic individuals (McBrien and Adams, 1997; Osuobeni, 1999; Wong et al., 2003). In 1093 Jordanian adult participants, Mallen et al. (2005) found a strong linear relationship between axial length and SER (r = −0.52, $p < 0.001$). Similarly, the earlier work of Carroll (1981) shows that refraction is strongly correlated to axial length (r = −0.76). Excessive axial length elongation may lead to ocular diseases (Saw et al., 2005).

It has been suggested that a long axial length in emmetropic children is a predictor that myopia will occur within the following 2–4 years (Mutti et al., 2007). The rate of change in axial length was fastest before the onset of myopia and slowed after the myopia had occurred (Mutti et al., 2007).

2.4.4 Retinal thickness

The retina is light sensitive tissue (~500µm thick) which consists of neural cells lining the inner posterior surface of the eye. The main function of the retina is the transduction of light into neural signals that can be transmitted to the brain (Dowling, 1987); this process is called phototransduction.

The axial elongation associated with myopia progression may cause a thinning of the retina. Previous studies using optical coherence tomography (OCT) have reported that elongation of the axial length is associated with reduced macular thickness (Lam et al., 2007; Luo et al., 2006; Song et al., 2014). A number of studies have investigated the thickness of the peripheral retina in myopic and non-myopic eye using OCT. The peripheral retinal thickness decreases as myopia and axial length increase. There is evidence that axial elongation leads to stretching and thinning of peripheral retina in myopic eyes that may cause changes in retinal thickness (Cheng et al., 2010; Luo et al., 2006; Wolsley et al., 2008). Using the Stiles–Crawford function, Hollins (1974) estimated that the central retina stretches by 4.5% during high accommodation demand (9 D) and Enoch et al. (1983) determined an average retinal stretch of 0.07 mm/D.

2.4.5 Choroidal thickness

The choroid is a vascular layer which provides the blood supply to the retinal pigment epithelium (RPE) and outer retina (Nickla and Wallman, 2010). The axial length is typically measured from the anterior surface of cornea to the retinal pigment epithelium (Drexler et al., 1998; Mallen et al., 2006; Woodman et al., 2011), and it is possible that changes in axial length are due to changes in the thickness of the choroid.

Studies in animal models show that the optical defocus can alter the thickness of the choroid by moving the retina (forward or backward movement) towards the image plane (Rada et al., 1992; Wallman et al., 1995; Wildsoet and Wallman, 1995). Wallman et al. (1995) found that wearing +15 D lenses (myopic defocus) increased the choroidal thickness within several hours after the imposed defocus and the myopia reduces by 7 D in chick eyes. With hyperopic defocus (−15 D lens), the choroid thinned. Further, there is a significant disruption to the natural diurnal rhythms that occur in the axial length and choroidal thickness during optical defocus in chick eyes (Nickla, 2006; Nickla et al., 1998), marmosets (Nickla et al., 2002) and primates (Troilo et al., 2000). Nickla et al. (1998) and Nickla (2006) investigated diurnal fluctuations in axial length and choroidal thickness in normal and form-deprived chick eyes using A-scan ultrasonography. In both normal and form-deprived eyes, significant diurnal variations in axial length and choroidal thickness were found. These rhythms were in anti-phase. For example, the axial length increased during the day and reduced overnight, while the choroid was at its maximum thickness during the night and thinnest during the day. The authors suggested that the phase correlation between axial length and choroidal thickness may play an important role in the regulation of eye growth.

Stone et al. (2004) found that there were diurnal variations in the axial length and choroidal thickness in 17 young, healthy participants. They observed significant diurnal fluctuation in the axial length and choroidal thickness at midday for all participants. Chakraborty et al. (2012) investigated the effect of 12 hours of monocular myopic defocus on axial length and choroidal thickness in 13 young emmetropic participants. Myopic defocus produced significant on-axis choroidal thickening in human eyes.

The choroidal thickness has been measured using B-scan ultrasound. However, this method provides poor axial resolution (Hewick et al., 2004). Although partial coherence interferometry can be used to measure both the retinal and choroidal thickness, the poor signal quality reflected from the choroidal/scleral interface and the manual or software based calculation of the location of the A-scan peaks required to measure the thickness of choroid present major disadvantages for this method. The SD-OCT provides high resolution in *vivo* imaging and provides measurement of the RPE and choroidal thickness.(Costa et al., 2006). It produces high resolution choroidal images in both younger and older people (Ikuno et al., 2010a; Manjunath et al., 2010; Tuncer et al., 2014).

Several studies have measured choroidal thickness using different instruments in normal individuals at the subfoveal region. These found an average thickness of ~250 μm to 350 μm (Table 2.3). A number of factors affect choroidal thickness, including axial length, refractive error and age. For instance, cross-sectional studies using OCT to measure and image the choroid in healthy adult participants aged between 19 and 93 years with different refractive errors (+7 to 20 D) have shown the choroidal thickness to be less in older people and in those with increasing levels of myopia (Ding et al., 2011; Esmaeelpour et al., 2010; Hirata et al., 2011; Ikuno et al., 2010a; Li et al., 2011; Wei et al., 2012). Vincent et al. (2013) used OCT to compare the choroidal thickness of the two eyes of non-amblyopic, myopic anisometropes (n = 22). They found subfoveal choroidal thickness was thinner in the more myopic eye (252 ± 46 µm) than in the less myopic eye (286 ± 58 µm). Further, the interocular differences in choroidal thickness and axial length were correlated significantly. These results are consistent with other studies which have identified a significant correlation between interocular differences in subfoveal choroidal thickness and axial length (Chen et al., 2012; Spaide et al., 2008).

Table 2.3: Choroidal thickness of healthy participants on-axis.

Study	No. of participants	Age (years)	Instrument	Choroidal thickness (µm)
Margolis and Spaide (2009)	30	19–85	Heidelberg Spectralis (SD-OCT)	287 ± 76
Manjunath et al.(2010)	34	22–78	Cirrus HD (SD-OCT)	272 ± 81
Ikuno et al. (2010b)	43	23–88	Swep-source (HP-OCT)	354 ± 111
Li et al. (2011)	93	20–33	Heidelberg Spectralis (SD-OCT)	342 ± 118
Yamahita et al.(2012)	43	19–40	Topcon 3 D (SD-OCT)	269 ± 61
Chen et al. (2012)	50	30–49	Heidelberg Spectralis (SD-OCT)	Right eye: 334 ± 94 Left eye: 333 ± 90
Wei et al. (2012)	3,468	50–93	Heidelberg Spectralis (SD-OCT)	254 ± 107
Tuncer et al. (2014)	154	16–87	Spectral domain (SD-OCT)	266 ± 60
Karaca et al. (2014)	110	18–70	Spectral domain (SD-OCT)	316 ± 79

Data are mean ± SD.

2.5 ACCOMMODATION

Accommodation is the ability of the eye to see clearly at different distances due to the variable focussing power of its intraocular lens (Rosenfield and Gilmartin, 1998). With accommodation, the anterior surface of the lens becomes more curved, there is a small increase in back surface lens curvature, the central thickness increases and the equatorial lens diameter decreases (Curtin and Jampol, 1986; Kasthurirangan et al., 2008; Koretz et al., 1997) (Figure 2.2). The refractive index of the lens is highest in the centre (≥ 1.40) and declines towards the periphery (~1.37), and with accommodation the rate of change of the refractive index at the periphery decreases relative to that of the unaccommodated state due to the change in the lens shape (Kasthurirangan et al., 2008).

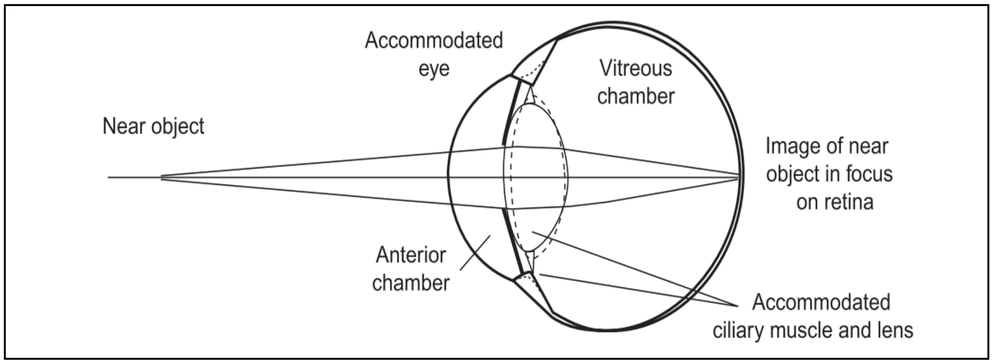


Figure 2.2: The anterior lens curvature and lens thickness increase during accommodation, such that divergent rays from the near object are imaged on the retina. The solid line represents the accommodated lens and the dashed line represents the unaccommodated lens.

There are several characteristics of the accommodation system that have been associated with myopia progression in both children and young adults. These include a high lag of accommodation at near distances (response is less than the demand), low tonic accommodation and high near-work-induced transient myopia (NITM) (Chen et al., 2003). The nature of these relationships is described in more detail below.

2.5.1 Tonic accommodation

Tonic accommodation is the resting state of accommodation in the absence of an adequate visual stimulus (e.g. in darkness) (Rosenfield et al., 1993). Tonic accommodation is approximately 0.50–1.0 D (Rosenfield et al., 1993) and this position represents the equilibrium between the parasympathetic and sympathetic inputs to the ciliary muscle (Gilmartin et al., 1984).

Several studies have investigated the relationship between tonic accommodation and myopia, and present conflicting findings. For example, Cawron (1981), Simonelli (1983) and Tokoro (1988) reported that myopes have a higher tonic accommodation than emmetropes, while Maddock et al. (1981) and Ramsdale (1985) reported the opposite. Other studies (Gilmartin et al., 1984; Whitefoot and Charman, 1992) have reported no association between tonic accommodation and myopia. When myopic participants are divided into subgroups based on the age of onset, studies have found that late-onset myopes have lower levels of tonic accommodation than early-onset myopes (Jiang, 1995; McBrien and Millodot, 1987). However, Strang and colleagues (2000) did not find significant differences between any of the refractive groups. Some studies found that tonic accommodation was higher in emmetropes who later became myopic compared with those who remained emmetropic (Jiang, 1995), while others (Owens et al., 1989) have reported that lower levels of tonic accommodation are associated with the development of myopia. Variations in findings may be at least partly attributed to factors such as techniques, viewing conditions, mental effort, surrounding propinquity, criteria of refractive error and inter-subject variability (Chen et al., 2003).

2.5.2 Accommodation response

Accommodative stimulus response (ASR) function is the term used to describe the relationship between the accommodative stimulus and the accommodation response. The ASR typically shows a lag of accommodation for both high and medium accommodation demands and a lead of accommodation for zero accommodation demands in young adults (Fisher et al., 1987; Gilmartin and Bullimore, 1987). A high lag of accommodation during extensive near work may produce a lack of accommodation accuracy and may lead to the development of myopia (Abbott et al., 1998). Myopes whose myopia is progressing tend to have higher lags of accommodation than those whose myopia is stable (Abbott et al., 1998).

Studies have used a range of protocols to compare the ASR of myopes and emmetropes. The results of these studies are inconsistent (Table 2.4). For example, Gwiazda et al. (1993) measured the ASR in myopic and emmetropic children under monocular viewing conditions using three different methods to stimulate accommodation (decreasing distance series, negative lens series and positive lens series). They found that myopic children accommodated less to near targets than did emmetropic children. Abbott et al. (1998) used the same protocol as Gwiazda et al. (1993) for myopic and emmetropic adults. Significant difference in ASR between groups occurred when myopes were classified based on their progression status and negative lenses were used to stimulate accommodation. Under binocular viewing conditions, McBrien and Millodot (1986) measured ASR in myopic, hyperopic and emmetropic adults using a decreasing distance series. Strong correlation between ASR and different refractive groups was found, suggesting that hyperopic participants accommodated more for near targets than emmetropic or myopic participants. Other studies have reported no significant differences between refractive groups (Subbaram and Bullimore, 2002; Yeo et al., 2006).

Table 2.4: Impact of the refractive error type on the accommodation response stimulus function (ASR).

Study	No. of participants	Age (years)	Apparatus	Accommodation stimulus	ASR
McBrien and Millodot (1986)	40	18–23	Canon R1 Autorefractor	NLS (Binocular)	H > E >M
Gwiazda et el. (1995b)	64	5–17	Canon R1 Autorefractor	NLS, PLS, DDS (Monocular)	PLS and DDS: No difference NLS: E > M
Abbott et al. (1998)	32	18–31	Canon R1 Autorefractor	NLS, PLS, DDS (Monocular)	PLS and DDS: No difference NLS: P > S
Subbaram and Bullimore (2002)	30	20–30	Canon R1 Autorefractor	DSS (Monocular)	No significant difference between M and E
Yeo et al. (2006)	50	16–23	Canon R1 Autorefractor	NLS, PLS, DDS (Binocular)	No significant difference between E and P

E, emmetropes; M, myopes; H, hyperopes; P, progressing myopes; S, Stable myopes; NLS, negative lens series, PLS, positive lens series; DDS, decreasing distance series.

A key question is whether a high lag of accommodation contributes to the development of myopia or if it occurs as a consequence of being myopic. Portello et al. (1997) examined the lag of accommodation in a group of emmetropic children. A greater lag of accommodation was found in participants who went on to develop myopia than in those children that remained emmetropic. Goss (1991) reported an increase in the lag of accommodation prior to the onset of myopia and also a high lag of accommodation in children developing myopia.

Several stimulus factors such as the spatial frequency, size of the targets and instruction set may affect the accuracy of the accommodation response. Different studies have disputed whether accommodation accuracy is dependent on mid-or high spatial frequency targets (Ciuffreda, 1991). A further study noted that the effect of instructions (‘relax while viewing the target’ or ‘try to keep the target clear’) altered the pattern of the spatial frequency-dependent accommodation response (Ciuffreda and Hokoda, 1985). Owens (1980) and Ward (1987) concluded that spatial frequencies of about five cycles per degree (cyc/deg) provide good accommodation stimuli. Variations in the contrast of the targets does not change the accommodation response until the contrast is reduced to the point where the target is not visible (Tucker et al., 1986). Moreover, the stimulus response function slope falls to zero when the luminance of the target is reduced (Johnson, 1976). However, the accommodation accuracy does not vary much provided the luminance is higher than 5–10 cd/m^2 (Alpern and David, 1958; Johnson, 1976). This means that any reasonably large, detailed target of good contrast under reasonable illumination will provide a good stimulus for the accommodation system. Maintaining participants’ interest on the target may be a more crucial issue.

2.5.3 Near work-induced transient myopia (NITM)

NITM has been investigated using several test parameters such as visual acuity, far point and contrast sensitivity. NITM occurs when sustained near work induces a transient myopic shift in the far point refraction (Ong and Ciuffreda, 1995). This shift is usually measured under closed loop conditions. However, when the transient shift towards myopia is measured under open loop conditions (with reference to the amount of tonic accommodation), this phenomenon is called ‘accommodation adaptation’ or ‘hysteresis’ (Hung and Ciuffreda, 1992; Rosenfield et al., 1994). In comparison with other refractive groups, late-onset myopes show a higher accommodative adaptation in both open and closed loop conditions (Ciuffreda and Lee, 2002; Woung et al., 1993). Late-onset myopes under closed loop conditions are reported to have greater NITM (following both 10 min and four hour periods of near work) than emmetropes and hyperopes (Ciuffreda and Lee, 2002; Ciuffreda and Wallis, 1998). NITM under closed loop conditions and the myopic shift in accommodation under open loop conditions for some studies are presented in Tables 2.5 and 2.6, respectively.

Table 2.5: Near work-induced transient myopia (NITM) under closed loop conditions.

Study	No. of participants	Age (years)	Technique	Near task paradigm	Target details	Post-task monitoring period	Post-task decay time	NITM (D)
Ehrlich (1987)	15	18–30	Dioptron II infrared optometer	Binocular 20 cm for 2 hr	6/9 number table /number search	1 hr	Decay incomplete after 1 hr	0.29 ± 0.19
Rosenfield et al. (1992)	27 9 Hy 4 Emm 14 My	23–32	Infrared optometer	Binocular 20 cm for 20 min	Matrix of numbers (N6)/adding	50 s	Time constant of 10–20 s	Mean NITM of 0.14 ± 0.30
Ong et al.(1994)	16 LOM	21–31	Infrared optometer	Binocular 40 cm for 10 min	Matrix of numbers /adding	NA	Time constant of 51 s	0.21 ± not given
Ciuffreda and Wallis (1998)	44 11 Emm 9 HY 13 EOM 11 LOM	21–31	Infrared optometer	Binocular 20 cm for 10 min	6/9 Snellen letters\ maintaining clarity	120 s	Time constant of 35 s (EOM) 63 s (LOM	Myopes are susceptible to near work aftereffects LOM (0.36 ±1.00) > EOM (0.34 ± 1.0) > Emm (0.09 ± 1.00) > Hy (0.01 ± 1.00)
Ciuffreda and Lee (2002)	16 4 Hy 4 Emm 4 EOM 4 LOM	17–31	Infrared optometer	Binocular habitual working distance for 4 hr	Newspaper, lecture transcripts, novels	20 min	Time constant of < 8 minutes	Myopes are susceptible to near work aftereffects LOM (0.36 ± 1.00) > EOM (0.34 ± 1.00) > Emm (0.09 ± 1.00) > Hyp (0.01 ± 1.00)
Hazel et al. (2003)	30 10 Emm 20 My	20.8 ± 2 23.1 ± 3	Infrared optometer	Monocular 20 and 40 cm for 5 min	Letters at 0.00 logMAR maintaining clarity	120 s	Decay time 30 s My 20 s EM	My > 0.26 Emm < 0.20
Vasudevan and Ciuffreda (2008)	44 15 Emm 15 EOM 14 LOM	21–34	Infrared optometer	Monocular 35 cm and 40 cm for 2 hr	Optometry lecture notes, maintaining clarity	120 s	Decay time 60 s LOM 87 s EOM 50 s Emm	LOM: 0.20 ± 0.03 EOM: 0.29 ± 0.03 Emm: 0.15 ± 0.02

Table 2.6: Accommodation adaptation as a function of refractive error (open loop conditions).

Study	Participant numbers	Refractive error (criteria)	Age (years)	Technique	Near-task conditions	Accommodation adaptation (AA) (D)
Gilmartin and Bullimore (1991)	30 15 Emm 15 LOM	 0 to +0.50 D −0.50 to −2.25D	19–25	Infrared optometer	Counting task at 1, 3 and 5 D stimulus distance for 10 min contact lens correction	LOM have greater TA at 1 D distance than EM No significant at 3 D and 5 D task distances LOM 0.15 > Emm 0.00
Gwiazda et al. (1995b)	87 11 Hy 57 Emm 18 EOM	 +1.00 to +4.12 D −0.25 to +0.75 D −0.25 to −7.00 D	7–16	Infrared optometer	Video game at 0.25 m for 15 min Refractive correction	EOM have greater TA than Hy EOM (1.50) > Emm (0.68) > Hy (0.24)
Woung et al. (1998)	34 15 Emm 19 EOM	 −0.25 to −0.75 D −1.25 to −5.25 D	7–12	Infrared optometer	Internal asterisk at 8D for 2 min (no refractive correction)	No significant differences in TA EOM (0.50 ± 0.61 > Emm (0.39 ± 0.37)
Hazel et al. (2003)	30 10 Emm 20 My	 0 to +0.25D −0.75 to –5.75D	18–26	Infrared optometer	0.3 logMAR (contrast ~90%, luminance 55 cd/m^2) at 4 D for 10 min	My have greater TA than Emm My (0.70) > Emm (0.60)

Data are mean ± SD.

Ong and Ciuffreda (1995) reported that when repeated cycles of near work are performed over a long period of time, NITM may produce a substantial retinal defocus, which can lead to myopia development. It has been suggested that the myopic shift immediately after near work and subsequent transient periods of retinal defocus may lead to myopia development (Vera-Diaz et al., 2002). Chen et al. (2003) highlighted that longitudinal studies are essential to demonstrate whether NITM has a cause and effect correlation with myopia development or alters due to the presence of myopia.

2.6 IMPACT OF ACCOMMODATION ON BIOMETRY

2.6.1 Axial length

The effect of accommodation, particularly of high demand, on ocular biometry has been investigated in several studies. Drexler et al. (1998) gathered measurements using custom partial coherence interferometer to investigate the effect of accommodation on axial length in 11 emmetropic and 12 myopic participants. The axial elongation was higher in emmetropes (mean 13 µm) than in myopes (mean 5 µm). Mallen et al. (2006) measured axial length during accommodation (6 D stimulus) in 30 myopic and 30 emmetropes using the IOLMaster. The increase in the axial length of the eye during accommodation was greater in myopes (58 ± 37 µm) than in emmetropes (37 ± 27 µm). The difference between these studies may be related to the different methods used. Drexler et al. study measured axial lengths at the subjective near point for each participant which meant that the refractive groups had different accommodation demands (the myopic group accommodated by 1.0 D less than the emmetropic group), whereas Mallen et al. used the Badal system to correct the refractive errors of myopic participants and to provide equal accommodation demands for all different refractive groups.

Woodman et al. (2011) measured axial length changes after accommodation (30 min) in 20 myopes and 20 emmetropes using an IOLMaster with a 5 D stimulus. The axial elongation was greater in myopes (20 ± 20 µm) than in emmetropes (10 ± 15 µm). Similar trends were also observed by Woodman et al. (2012) who measured axial length before (0 D), during (4 D stimulus) and after a 30 minute accommodation task (0 D) in 37 myopic and 22 emmetropic participants using the Lenstar (LS 900). The axial length measurements with accommodation were obtained by using an external attachment containing the fixation target, Badal optometer (12 D), beam splitter and a light-emitting diode (LED) source. The axial length during accommodation increased for both emmetropic (6 ± 22 µm) and myopic (22 ± 34 µm) participants, but the difference between groups was not statistically significant ($p = 0.14$). The axial elongation after accommodation in myopic participants was significantly higher than that of the emmetropic participants (12 ± 28 µm *v.*−3 ± 16 µm, $p < 0.05$). It is feasible that the differences between the Woodman et al. studies is related to errors associated with lens thickness changes during accommodation highlighted by Atchison and Smith (2004) which results in overestimates of changes in axial length measurement. Woodman et al's first study was not able to correct the potential error in axial length measurement because the IOLMaster does not provide the lens thickness. Woodman et al's second study used Lenstar to measure axial length and because this instrument provides lens thickness, they were able to correct error in axial length measurement based on the method outlined by Atchison and Smith (2004). The above results suggest that the accommodation-induced change in the axial length is greater in myopes than in emmetropes. This could be one reason for the association between myopia and near work.

Zhong et al. (2014) used ultra-long scan depth optical coherence tomography (UL-OCT) to measure the changes in on-axis axial length with a 6 D of accommodative stimulus in 21 healthy adults participants (11 emmetropes and 10 myopes). The mean ± SD change of axial length was 26 ± 13 µm ($p < 0.001$). There was no significant difference in the axial changes of emmetropic and myopic participants ($p > 0.05$).

Both Drexler et al. (1998) and Mallen et al. (2006) have suggested that eye elongation during accommodation is due to force of the ciliary smooth muscle the contraction, which decreases the circumference of the sclera and choroid, causing axial elongation of the eye. Due to the reduced ocular rigidity associated with a myopic eye, axial elongation was observed (Mallen et al., 2006). Changes in the biomechanical and biochemical properties of the sclera structure have been found in myopia (McBrien et al., 2009). Another possible reason for increasing axial length is change in the refractive index distribution of the crystalline lens during accommodation, which may lead to axial length measurement artefacts (Dubbelman et al., 2003; Le Grand, 1980). However, some studies have found no change in the refractive index of the lens (Hermans et al., 2008; Kasthurirangan et al., 2008), whereas others report a small decrease in the central refractive index of the lens during accommodation (Jones et al., 2007).

2.6.2 Biometry of the anterior segment

Ostrin et al. (2006) measured the changes in crystalline lens biometry during accommodation in 18 myopic and three emmetropic healthy young participants and one hyperopic healthy young participant using A-scan ultrasonography. The lens thickness (0.067 ± 0.008 mm/D) increased significantly in all participants, while the increase in lens thickness led to a shallowing of the anterior chamber (0.051 ± 0.008 mm/D). Using A-scan ultrasonography, Shum et al. (1993) found that the lens thickness increased (0.16 ± 0.01 mm) and the anterior chamber decreased (0.12 ± 0.01 mm) during accommodation in all 106 participants. Leng et al. (2014) investigated the anterior segment of the eye with OCT during 3 D of accommodation in 20 healthy young adults. ACD was significantly smaller (0.10 ± 0.0 mm; p = 0.004), while the lens thickness was significantly increased (0.11 ± 0.01 mm; p < 0.05) during accommodation. Similarly Zhong et al. (2014) measured the anterior segment of eye with 6 D accommodative stimulus in 21 healthy adults participants (11 emmetropes and 10 myopes) with OCT. Compared to the rest state (0 D), anterior chamber depth was significantly decreased (0.17 ± 0.01 mm; p < 0.001) and the lens thickness significantly increased (0.24 ± 0.01 mm; p < 0.001).

2.7 EYE SHAPE MODELS

Four models, namely global expansion, equatorial stretching, posterior pole elongation and axial expansion (a combination of equatorial and posterior pole elongation) have been proposed to describe the changes in eye shape that occur with increase in the axial length of the eye (Figure 2.3) (Atchison et al., 2004; Strang et al., 1998).

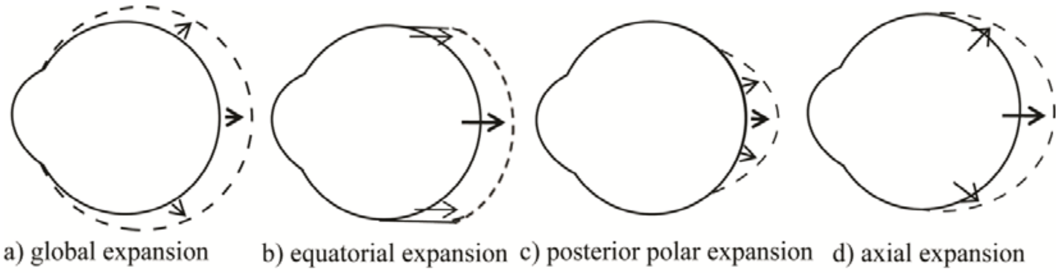


Figure 2.3: Models of retinal stretching in myopia. The solid circles represent the shape of the retina of an emmetropic eye. The dotted shapes represent the retina shapes of myopic eye models (Atchison et al., 2004; Strang et al., 1998).

The axial length has been measured from the anterior surface of the cornea to the inner surface of the retinal pigment epithelium However, Song et al. (2007) and Ishii (2011) measured the axial length from the posterior cornea to the posterior pole of the eye with X-ray tomography and MRI, respectively. In other studies, the axial length of the eye was measured from the anterior cornea to the outer sclera (Verkicharla et al., 2012). This distance can be measured through transverse axial or sagittal sections. The height, or the distance between the top and the bottom of the eye, can be obtained from both the sagittal and the coronal planes. The width, or the distance between the nasal and the temporal sides of the eye, can be obtained from the transverse axial plane or the coronal plane (Figure 2.4). In this thesis, the axial length will be measured from anterior surface of cornea to the inner surface of the retinal pigment epithelium.

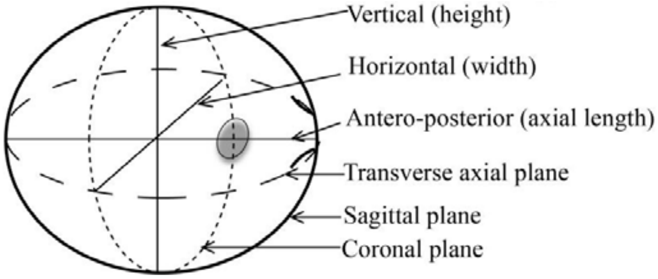


Figure 2.4: Scanning sections and axis of the eye, modified from Verkicharla et al. (2012).

2.7.1 Eye shape measurement

The eye shape can be measured directly using techniques such as MRI, A- and B-scan ultrasound and X-ray tomography, as well as indirectly via techniques such as peripheral refraction and partial coherence interferometry. Deller et al. (1947) measured ocular shape using the X-ray technique. Myopic eyes were prolate, while emmetropic and hyperopic eyes were spherical, prolate or oblate in shape. Several subsequent researches have supported these findings. Vohra and Good, (2000) used B-scan echography to measure equatorial horizontal widths in eyes of 50 myopic participants. They suggested that the expansion of highly myopic eyes was primarily axial, not global.

Chen et al. (1992) carried out MRI scans of three hyperopic, four emmetropic and four myopic eyes. Myopic eyes were more prolate than emmetropic or hyperopic eyes. In a large study of 131 Chinese adult participants using computerised tomography (CT) scans, Zhou et al. (1998) found that 96% of myopic eyes were prolate, 90% of hyperopic eyes were oblate and 43% of emmetropic eyes were oblate in shape. Cheng et al. (1992) found in a study of 21 adult participants (eight hyperopes, six emmetropes and seven myopes) using MRI that most eyes were spherical or oblate in shape, including most of the seven myopic eyes. Atchison et al. (2004) scanned 88 young healthy adult participants (22 myopes and 66 emmetropes) with refractive errors ranging from + 0.75 to −12 D. The length from the posterior pole to the anterior cornea, the width from nasal to temporal retina, and the height from the superior to inferior retina were measured. Myopic eyes were less oblate than emmetropic eyes. Singh et al. (2006) measured the retinal shape in seven participants with a wide range of refractive errors. There was substantial variation in ocular shape between participants and nasal-temporal asymmetry was found in some eyes. The differences between the studies mentioned above may be due to participant differences (such as age or ethnicity), sample size or to the limited resolution of MRI and computerised tomography scans used to identify eye shape (Stone and Flitcroft, 2004).

2.8 PERIPHERAL RETINA

The central part of the retina (fovea) is approximately 1.5 mm across, while the rest is considered peripheral retina (about 21 mm from the fovea to ora-serrata) (Rodieck, 1973). The peripheral area has more neurons and photoreceptors than the centre of the retina (Wallman and Winawer, 2004). Variations in structure across retina produce different distributions of visual performance such as hyper-acuities, contrast sensitivity and visual resolution (Ehsaei et al., 2013; Fahle and Schmid, 1988; Latham and Whitaker, 1996).

2.8.1 Accommodation and peripheral retina

Some studies have suggested that the accommodation response is controlled by foveal vision. Fincham (1951) observed in 55 participants that the accommodation response did not alter following the interposition of a negative lens (−0.75 D) when participants were attending to a point that was more than 10 min of arc from fixation. Campbell (1954) used Purkinje-Sanson images to determine the minimum amount of light required to stimulate the accommodation reflex in 13 participants. A −3 D lens was used to stimulate accommodation and the illumination of a target had to exceed a critical value (the foveal threshold) to elicit an accommodation response. This study concluded that foveal cones were responsible for the accommodation response. The notion that the fovea controls the accommodation response has been supported in other research (Crane, 1966; Toates, 1972). Bullimore and Gilmartin (1987) found that stimulation was effective up to field angles of approximately 10°. Gu and Legge (1987) used black discs on a uniform white background with different powers (from 0 D to −6 D) as stimuli. Different disc radii (1°, 7°, 15° and 30°) were used and an accommodation response was found for all radii, even when the stimulus was outside the fovea. Hartwig et al. (2011) reported that peripheral stimuli out to 15° are able to trigger accommodation response in absence of a central stimulus.

2.8.2 Peripheral defocus: animal studies

Animal studies have been used to examine the role of environmental factors such as near work in the development of myopia (Flitcroft, 2012). Experimental myopia can be induced through either applying diffusers, applying other vision deprivation devices over the eye or by applying negative powered lenses (optical defocus). It is believed that deprivation disrupts the emmetropisation system, blocking the critical retinal error signals which fine-tune eye growth. This leads to increased axial elongation (reviewed in Wallman and Winawer (2004)). Hyperopic defocus induced from the minus lenses increases the rate of axial growth, thus resulting in myopia (Wallman and Winawer, 2004).

Although it was long thought that the centre of the retina (fovea) drives myopia elongation, animal studies confirm the importance of peripheral retina to refractive development. Young rhesus monkeys raised with ring-shaped diffusing filters developed axial refractive errors, although the filters had central apertures allowing approximately 37° of unrestricted central vision (Smith et al., 2005). Similarly, lens-induced hyperopic defocus excluding the central 10° of the field, resulted in myopia (Smith et al., 2009). Ablating the central 10° diameter of the retina around the fovea, while leaving the periphery intact, resulted in emmetropia (Smith et al., 2007). Huang et al. (2011) found that form deprivation altered both the central and peripheral refractions out to ±45° along the horizontal meridian, but this was not affected by foveal ablation. Further, the imposition of hypermetropic defocus in selected parts of the visual field could produce changes in myopic refraction and shape changes in the corresponding areas of the retina (Smith et al., 2010). These findings indicate that the peripheral parts of the eye, not just the fovea, are sensitive to defocus and may lead to the development of axial refractive errors.

2.8.3 Eye shape and peripheral refraction

Peripheral measurements of refraction and the determination of eye shape have been made in response to the recent interest in the role of the peripheral retina in myopia (Verkicharla et al., 2012). There is general agreement across the literature that myopic eyes have prolate shapes and emmetropic eyes have oblate shapes along the horizontal meridian for both children and young adults. In a large longitudinal study, Mutti et al. (2000) measured the peripheral refractive error at 30° nasal visual field in children (n = 822 children, aged 5–14 years) using A-scan ultrasonography, videophakometry and videokeratography to assess the ocular shape based on relative peripheral refraction at this point. Myopic participants had relative peripheral hyperopia (+0.80 ± 1.29 D), which suggests that the axial length was longer than the equatorial diameter (prolate ocular shape). Emmetropic participants had relative myopia in the periphery (−0.41 ± 0.75 D), which suggests that the equatorial diameter was longer than the axial length of the eye (oblate ocular shape). Recently, Li et al. (2015) found similar results by measuring the peripheral refraction in a larger sample of children (n = 2134, aged seven years; n = 1780, aged 14 years) at 15° and 30° temporal and nasal along the horizontal visual field in different refractive groups using open field autorefractor. Myopic eyes had peripheral hyperopia, whereas hyperopic and emmetropic eyes had peripheral myopia relative to the fovea, with greater relative peripheral hyperopia in older children than in the younger children.

Schmid (2001, 2003a, 2003b, 2011) used optical low-coherence reflectometry to measure ocular contour and length both on-axis and peripherally. Schmid et al. (2001) determined the retinal shape by measuring the peripheral axial length up to ±10° in four participants along the horizontal visual field. High variation was reported, but with only one myopic eye (−2 D) exhibiting a prolate retinal shape. Schmid (2003b) measured the axial length of the eye again to ±15° along the horizontal and vertical meridian in 63 children aged 7–15 years old. The retina was steeper in myopes than in emmetropes and flattest in hyperopic participants (Schmid, 2003a; Schmid, 2003b). These findings were confirmed in a larger sample (140) of children (Schmid, 2011).

Logan et al. (2004) measured peripheral refraction to estimate retinal shape in 56 young healthy adults participants. The participants were divided into four groups: white and Taiwanese–Chinese anisomyopes and white and Taiwanese–Chinese isomyopes. Each group consisted of 14 participants. Peripheral refraction was measured using an open field objective infrared (IR) autorefractor under cyloplegia in the horizontal meridian out to ±30°. The ocular axial length was taken with A-scan ultrasonography. The eyes of both ethnic groups had global elongation, but those of white participants showed nasal and temporal quadrant axial asymmetry. Taiwanese–Chinese participants showed greater uniformity between nasal–temporal retinal shapes. The differences in nasal–temporal retina have also been found in other studies (Atchison et al., 2006; Mallen and Kashyap, 2007).

Kwok et al. (2012) investigated the horizontal retinal shape out to ±20° in 10 young adult (aged 20–26 years) participants with high myopia (> 6.00 D) using partial coherence interferometry. An open field autorefractor was used to measure the refraction on-axis and peripherally out to ±20°. Shapes of myopic eyes were inferred to be prolate. It has been suggested that if the eye has peripheral relative hyperopia, eye growth may be promoted even in the presence of on-axis myopia (Wallman and Winawer, 2004).

2.8.4 Impact of accommodation on peripheral refraction

The effect of accommodation upon horizontal peripheral retinal refraction remains in dispute. Most studies investigating the effect of accommodation on peripheral refraction found changes in the refractive profile of subjects as the accommodative demand increases. For example, Calver et al. (2007) measured the peripheral refraction out to 30° eccentricity for 0.4 D and 2.5 D accommodation demands in 10 myopic and 10 emmetropic participants. During accommodation, peripheral astigmatism increased with greater eccentricity in both groups. Lundström et al. (2009) also investigated the association between peripheral refractive errors and accommodation in five emmetropic and five myopic participants. Myopic participants had smaller relative peripheral myopia and larger asymmetry in defocus through a visual field with accommodation than emmetropic eyes. Relative peripheral myopia increased with accommodation in emmetropic participants.

Whatham et al. (2009) investigated the influence of accommodation on peripheral refractive errors in 20 myopic participants. Three accommodation demands induced by three target distances (2 m, 40 cm and 30 cm) were used and peripheral refractive errors were measured at 20°, 30° and 40°. A myopic shift in the relative peripheral refraction was observed as the accommodation demand increased.

Walker and Mutti (2002) used relative peripheral refractive error measurements to assess the ocular shape with 3 D of accommodation at 30° nasal visual field in 22 young healthy adults with the Canon R-1 autorefraction. A shift in relative peripheral hyperopia was found. It was hypothesised that prolonged accommodation may lead to sustained tension within the choroid and thereby sustained change in the eye shape.

Davies and Mallen (2009) found no significant effect of the accommodative level on the relative peripheral refraction at any position when they investigated the influence of accommodation on the peripheral refraction (21 emmetropic and 19 myopic participants) using different fixation targets across the field (0°, ±10°, ±20° and ±30°) with different accommodation demand (0.0 D, 1.0 D, 2.0 D and 3 D).

Accommodation only altered the peripheral refractive profile in the temporal J_0 astigmatic component ($p < 0.001$) for both myopic and emmetropic participants.

2.9 MEASUREMENT ISSUES

2.9.1 Effect of phenylephrine on accommodation

Accommodation is controlled by the autonomic nervous system. The classic dual innervation theory of accommodation is that accommodation increases with increased parasympathetic output. This stimulates the ciliary muscle and the activation of the sympathetic nervous system small decreases of accommodation (Gilmartin and Bullimore, 1991; Gilmartin et al., 1992). Differences in amplitudes of accommodation have been found due to variations in parasympathetic nervous system inputs to the ciliary muscle (Gilmartin et al., 1984). The low parasympathetic nervous system inputs may also induce lags in accommodation during near work, particularly in myopia progression (Abbott et al., 1998).

Phenylephrine is a sympathomimetic drug that is used to dilate the pupil without any accompanying cycloplegia (Gilmartin and Bullimore, 1991). Phenylephrine of 10% is usually used in the treatment of pupillary block glaucoma, while 2.5% phenylephrine is used for ocular fundus examination. It has been reported that high doses of phenylephrine (two drops of 10% solution) cause a reduction in the near point amplitude of accommodation and reduce accommodation response times (Biggs et al., 1959; Mordi et al., 1986). The former may be due to reduced depth of focus with large pupil.

Gilmartin (1986) reported that the effect of the sympathetic system on accommodation is small compared to that of the parasympathetic system. Gilmartin et al. (1984) and Bullimore and Gilmartin (1987) showed that after prolonged near work, the sympathetic system may affect accommodation. They also showed that the magnitude of sympathetic inhibitory activity is correlated to the magnitude of the underlying parasympathetic activity.

Phenylephrine is a selective α_1-adrenergic receptor agonist. Only 1% of the nerve terminals in monkey ciliary muscle are sympathetic (Ruskell, 1973). The ciliary muscle sympathetic receptor in humans has been shown to be primarily of the β_2 subtype, rather than of β_1 and α_1. A small population of α_1-adrenergic receptors has been found in humans (Zetterström, 1988). As the ciliary muscle has few α_1-adrenergic receptors, phenylephrine does not greatly affect accommodation. Garner et al. (1983) have reported that phenylephrine did not change the resting state of accommodation and Zetterström (1988) found that phenylephrine did not cause a myopic shift in the resting level of accommodation. These findings are supported by a recent study showing that 2.5% phenylephrine does not have an effect on ciliary muscle contractility or the accommodation response (Richdale et al., 2012). Thus, phenylephrine is the agent of choice when a dilated pupil and a functioning accommodation system are required.

2.10 RATIONALE OF THE STUDY

As mentioned in the literature review, myopia development is multifactorial in nature. Changes in the biometry of eye such as increased axial length and thinned choroid occur during development of myopia, but the aetiology of myopia is still not clear. Several studies have investigated the accommodation impact on myopia development in order to develop preventative strategies.

There is considerable evidence of an association between near work and the development of myopia. The on-axis choroid thins more in myopic than in emmetropic eyes during accommodation, causing greater changes in axial lengths for the former.

Although traditionally the fovea has been thought to drive myopia elongation, the peripheral retina is now known to also be important to refractive development. There is no information regarding the effect of accommodation on peripheral ocular biometry. This project contains a number of experiments using partial coherence interferometry and advanced spectral domain optical coherence tomographer aimed at understanding the influence of accommodation on the biometric properties of axial length and choroidal thickness along the horizontal visual field in emmetropic and myopic eyes. Since the association between near work and development of myopia is well documented, I hypothesized that the changes in peripheral axial length and choroidal thickness during accommodation are different between refractive groups (as have been found centrally), with myopic eyes exhibiting greater axial length increases and more choroidal thinning than emmetropic eyes. The identification of differences between refractive groups during accommodation may provide a better understanding of the association between near work and development of myopia.

The objectives of this thesis are to:

1. Investigate the effect of accommodation on peripheral axial length among myopic and enmmetropic participants. The hypothesis to be tested is that peripheral axial length will increase with accommodation and the increases will be greater in myopes than in emmetropes (as has been found centrally).

2. Investigate the peripheral axial length during periods of accommodation and recovery. The hypothesis to be used is that the axial length will increase with periods of accommodation and this increase will be greater in myopes than in emmetropes.

3. Investigate the effect of accommodation on peripheral choroidal thickness. The hypothesis to be tested is that peripheral choroidal thickness will thin during accommodation and more so in myopes than in emmetropes (as has been found centrally).

Chapter 3: Methodology

This chapter describes the experimental methodology in detail. There were three major experiments conducted in this project. Experiment 1 explored the effect of accommodation on peripheral axial length using the Haag-Streit Lenstar LS 900 (Haag-Streit, Bern, Switzerland) with an external attachment. Experiment 2 used the same equipment with a different fixation target (white OLED microdisplay) to investigate the time course of change in peripheral axial length during and in recovery for eight minutes of accommodation demand. Experiment 3 investigated changes in peripheral choroidal thickness with accommodation using the Nidek OCT (Retinascan advanced RS-3000, Gamagori, Japan).

3.1 ETHICAL CONSIDERATIONS

The project followed the Tenets of the Declaration of Helsinki and was approved by the Queensland University of Technology Human Research Ethics Committee (1300000162). After explaining the details of the experiment to all participants, written informed consent was obtained. All the data obtained during the study were kept confidential. Appendix 1 shows the information sheet and consent form provided to participants.

3.2 RECRUITMENT OF PARTICIPANTS AND SCREENING

Healthy young adults aged 18–25 years were invited to participate in this project. Participants from different ethnic backgrounds were recruited from the student population of the Queensland University of Technology.

All participants underwent a comprehensive ophthalmic examination including subjective refraction and ocular health status. None had previous or present ocular disease. Refractive errors were measured using a Shin-Nippon-SRW-5000 autorefractor (Grand-Seiko, Osaka, Japan). This instrument has been found to be accurate and have a higher repeatability than subjective refraction (Mallen et al., 2001). Based on the mean spherical equivalent refraction (SER), participants were classified as emmetropes (SER +1.00 to −0.25 D), low myopes (SER −0.50 to −3.00 D) and higher myopes (SER < −3.00). All participants had corrected logMAR visual acuity of 0.00 or better and no more than 1.00 D of cylinder, or anisometropia greater than 1.00 D. Myopic participants who wore soft contact lenses were asked to refrain from contact lens wear for the preceding 24 hours as contact lens wear can influence corneal thickness (Freiberg et al., 2012). Stable myopes (the refractive error changes less than 0.50 D over the previous two years) rather than progressing myopes were recruited, as progressing adult myopes may have poorer accommodation responses (Abbott et al., 1998; Vera-Diaz et al., 2002). Progression data were obtained from a questionnaire provided to the participant or from an eye care practitioner if the participant did not know his or her past refraction information.

3.3 ACCOMMODATION MEASUREMENT WITH THE COAS ABERROMETER

The Hartmann-Shack type of aberrometer has been used for many years to study the refractive error and monochromatic aberration in human eyes (Salmon et al., 2003). This device has provided new information on the eye’s aberrations in myopia (Cheng et al., 2003b; Paquin et al., 2002), during accommodation (Pallikaris et al., 2001), in dry eye (Montés-Micó et al., 2004; Thibos and Hong, 1999), in cataract (Kuroda et al., 2002), with contact lenses (Dietze and Cox, 2004; Lu et al., 2003) and following refractive surgery (Joslin et al., 2003; Oshika et al., 2002). It is more popular than other types of aberrometers because it is faster to use and unaffected by the scattering of light (Cerviño et al., 2008).

The COAS-HD Hartmann–Shack Aberrometer (Wavefront Sciences, Albuquerque, USA) was used to measure accommodation response. It uses a monochromatic light source, a lenslet array and a charge coupled device (CCD) camera to measure the monochromatic wave aberrations of a human eye. A narrow beam of light from the source (λ = 840 nm) is focused on the retina; some of this is reflected back from the retina and passes through a lenslet array onto the CCD camera, which is placed at the focal plane of the lenslet array. When the light arriving at the sensor comes from a perfect optical system, the plane wavefront will cause a uniform grid of spots on the CCD camera. However, when light comes from an aberrated optical system, the wavefront will be distorted, causing a non-uniform grid due to different slopes at each lenslet (Figure 3.1).

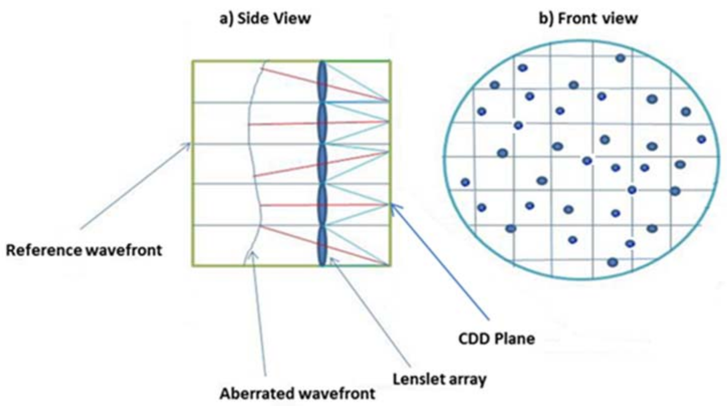


Figure 3.1: The Hartmann-Shack Aberrometer. (A) Side view illustrating an aberrated wavefront focused on the CDD camera via lenslet array. (B) distorted lattice of spots produced by an aberrated wavefront on the CCD camera. Adapted from Atchison (2005).

The COAS was modified using an external attachment consisting of a LED source, Maltese cross-fixation target, a beamsplitter (Pellicle, Edmund Optics, USA; 72% transmission), a +13 D Badal lens to measure the refraction for 0 D and 6 D accommodation demands (Figure 3.2). Participants did not need to wear any optical correction during the experimental procedure. The Badal lens apparatus was attached to the top of the COAS frame using a pair of right-angle retort clamps, allowing participants to use the instrument’s usual chin and head position. To ensure measurements were taken only on-axis, the external fixation target was adjusted until its centre was aligned with the red target of the COAS wavefront sensor.

Additionally, using the joystick, the corneal reflection of a set of circularly arranged LEDs was centred on the pupil (Figure 3.3). The target was moved longitudinally to produce the required accommodation demand, taking into account each participant's refraction. The room lighting was turned off and the target was illuminated with the white LED. The target luminance was 10 cd/m^2 as measured with a BM-7 luminance-colorimeter (Topcon, Tokyo); this lighting level is able to produce a robust accommodative response (Johnson, 1976).

The internal alignment target of the wavefront sensor was turned off during accommodation measurements; participants were asked to focus on the centre of the fixation target and to make it 'as clear as possible' (Stark and Atchison, 1994). Participants were given a short practice (10 min) to familiarise themselves with the procedure. The right eye was used for all measurements and the non-tested eye was covered by a patch. Three measurements were taken using 4th order Zernike polynomial coefficients for a 4 mm pupil at each test condition and the results were saved manually in separate files. The measurements were taken without dilation of the pupil and then repeated 60 min later following instillation of 1 drop 2.5% phenylephrine hydrochloride (Chauvin Pharmaceuticals Ltd., UK). The measurements took about five minutes across both 0 D and 6 D stimulus conditions. The accommodation response was calculated as the difference between the spherical equivalents within both conditions (0 D and 6 D).

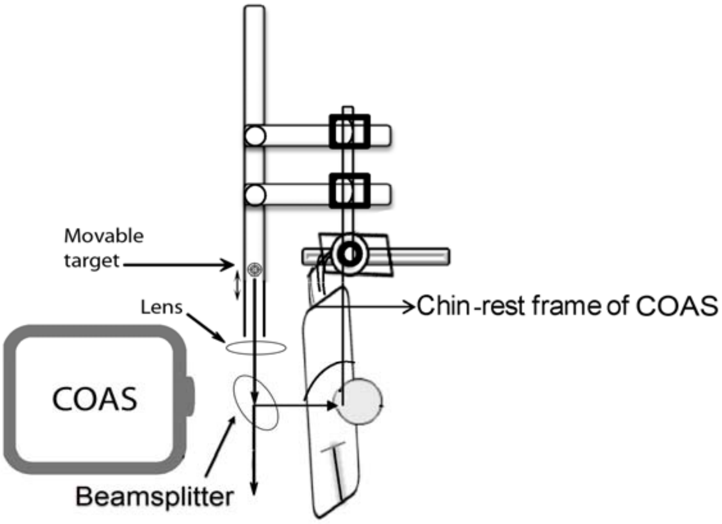


Figure 3.2: Experimental setup using external attachment with the COAS-HD to measure accommodative response.

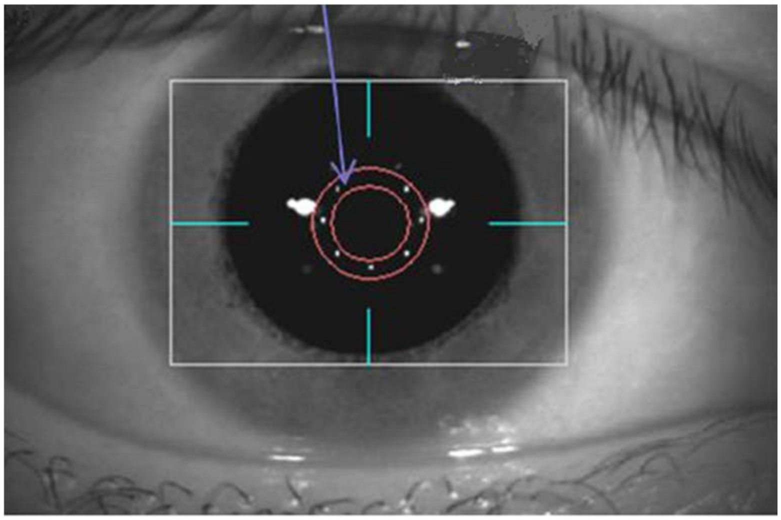


Figure 3.3: Alignment of the eye using the COAS-HD. The arrow points to the reflection of LEDs from the corneal surface to assist with on-axis alignment.

3.4 PERIPHERAL AXIAL LENGTH MEASUREMENT WITH LENSTAR LS 900

A commercial Lenstar LS 900 was modified using an external attachment to allow the measurement of the axial length at different angles in the horizontal meridian under 0 D and 6 D accommodation demands.

The Lenstar is an ocular biometer produced by Haag-Streit. Like the IOLMaster, it contains a Michelson interferometer which creates partial coherence. Both provide a higher axial resolution (0.01–0.02 mm) than ultrasound (0.10 mm) and MRI (0.15 mm) (Kimura et al., 2007; Lam et al., 2001). The basic principle of partial coherence interferometry is shown in Figure 3.4. The laser diode produces a beam with a low-coherence length and it passes through the beam splitter (BS1), dividing into two separate coaxial beams (A_1 and A_2). M_1 is a fixed mirror and the M_2 is movable mirror, causing shift of light frequency. These beams enter the eye and are reflected from the cornea (C) and retina (R), respectively. After, they pass through the beam splitter (BS2) to the photodetector system, thus, determining the optical path length (OPL) in the eye. When the optical path length is less than coherence length of 160 µm, the interference between different components will be calculated (Haigis et al., 2000).

The Lenstar uses an 820 nm super-luminescence diode with a 25 nm bandwidth. It uses four interferometers to measure the different layers of the ocular eye including central corneal thickness (CCT), anterior chamber depth (ACD), crystalline lens thickness (LT), axial length (AL) (Holzer et al., 2009; Jasvinder et al., 2011; Suheimat et al., 2015). The Lenstar reports the axial length from the anterior corneal surface to the internal limiting membrane (ILM). It does so by measuring the length to the retinal pigment epithelium (RPE) and subtracting the retinal thickness (assumed to be 200 µm by default). This was done to match the IOLMaster and ultrasound measurements (Suheimat et al., 2015). The axial length in this study will be measured from anterior surface of cornea to the inner surface of the retinal pigment epithelium.

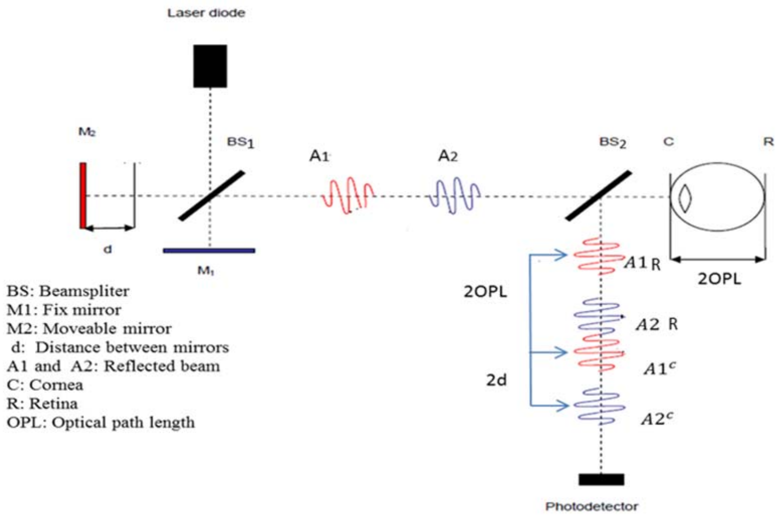


Figure 3.4: Principle of partial coherence interferometry (modified from Haigis et al. (2000)).

In Experiment 1, prior to measurement, the pupil was dilated with one drop of phenylephrine (2.5%). Twenty minutes after instillation of one drop of 2.5% phenylephrine, eye lengths were measured in 5° steps out to ±30° across the horizontal visual field. Measurements at more peripheral locations were not possible because the edge of pupil (iris boundary) blocked the passage of the beam, particularly with the accommodation level.

The attachment consisted of a goniometer, a beam splitter (Pellicle, Edmund Optics, USA; 72% transmission), a Maltese cross-fixation target, a 13 D Badal lens and a white LED source (Mallen and Kashyap, 2007) (Figure 3.5). A goniometer was attached to the top of the Lenstar frame using a pair of right-angle retort clamps and allowed measurements of the eye length at different eccentricities and accommodative demands (0 D and 6 D). To ensure that the target rotation corresponded to the eye's centre of rotation, the goniometer was moved along the base rail until the target could be seen at all positions of goniometer rotation.

When the goniometer attachment was in its central position, the beam splitter was adjusted so that the Lenstar beam was aligned with the fixation target. The participant was asked to make the target clear during all measurements. For measurement along the horizontal visual field, participants were required to turn their eye to the fixation target at each eccentric location without any head movement. They were asked to blink before each measurement to ensure there was a smooth tear film that would allow the alignment mires of the instrument to be clearly imaged on the corneal surface. All measurements were taken by the same examiner and were collected from the right eye while the left eye was occluded. The 0 D accommodation demand measurement was recorded as baseline and the longitudinal position of the fixation target was adjusted to produce a 6 D accommodation stimulus. Axial length was measured across the field for the 0 D stimulus, with four measurements at each position. The process was repeated with the 6 D stimulus. All the measurements took about sixty minutes.

Experiment 2 used the same attachment as in Experiment 1, except that the fixation target was replaced by a white OLED microdisplay (eMagin Corporation, New York, USA; screen resolution 800 × 600 pixel with luminance ~21 cd/m^2) connected to computer. Since this experiment takes 16 min to measure the axial length with 6 D and 0 D of accommodation stimulus, I used videos as the fixation target to maintain the accommodation response, and thus assist the participant to focus on the target all the times. The axial length was measured at 0°, 20° nasal (N) and 20° temporal (T) along the horizontal visual field 20 min following instillation with one drop of 2.5% phenylephrine. Before commencing measurement, the beam splitter was adjusted so that the Lenstar beam aligned with the centre of the fixation target. The participant was asked to look at the video and keep it clear at all times (both during measurements and between measurements). The order in which the measurements were conducted was pseudo-randomised. One-third each of the participants were measured in the following orders: (1) 0°, 20°N and 20°T; (2) 20°N, 20°T and 0°; (3) 20°T, 0° and 20°N (Figure 3.6).

Baseline measurements were made at a selected location at 0 D accommodation demand. The accommodation demand was increased to 6 D and measurements were made at the following time intervals: 45 s, 120 s, 240 s, 360 s and 480 s. As it takes approximately 45 s to complete three measurements, measurements commenced 45 s before the indicated time (the time will indicate the end point of the measurement period). The accommodation demand was reduced immediately to 0 D and measurements made at the following time intervals: 45 s, 120 s, 240 s, 360 s and 480 s. After the completion of a location run the participant received a five min break, then the next location run commenced. The untested left eye was occluded.

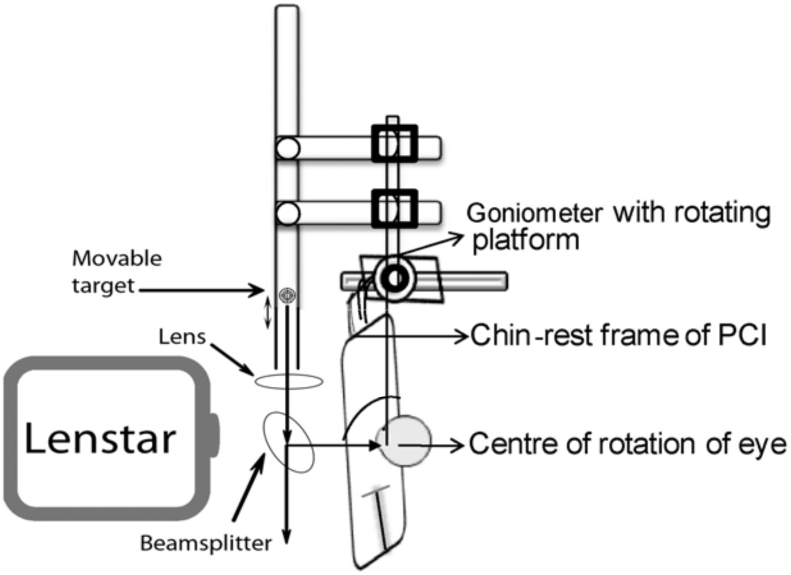


Figure 3.5: Experiment 1 setup with external attachment to measure on-axis and peripheral axial length.

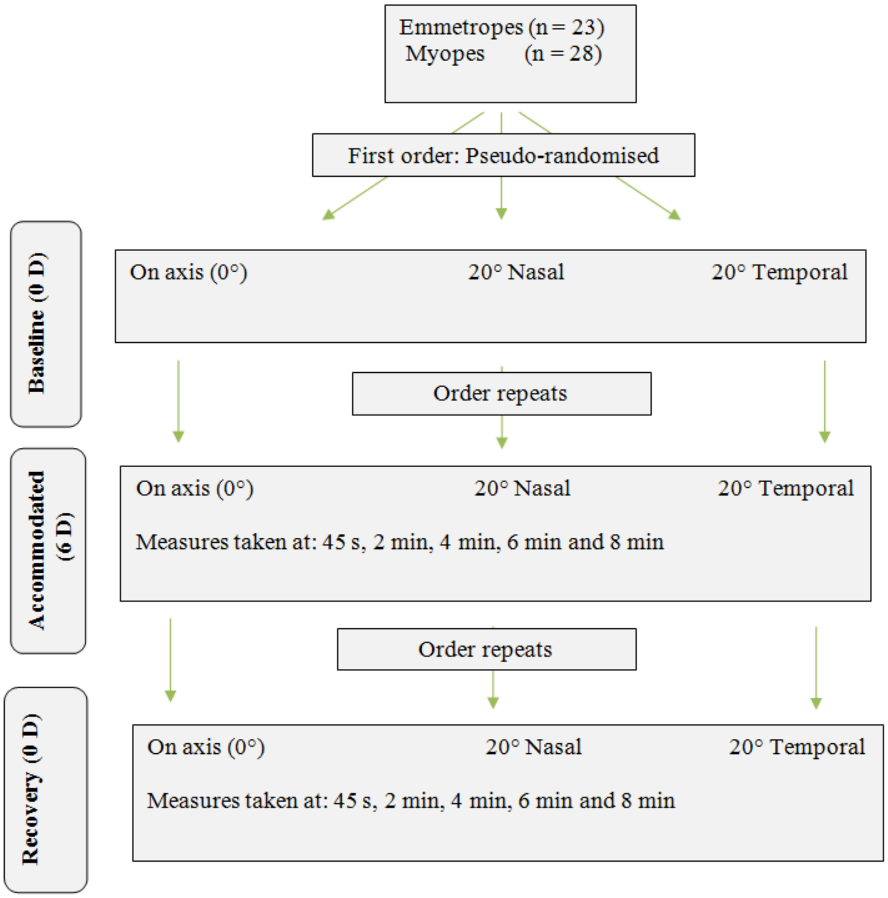


Figure 3.6: Flow chart of the procedure used to measure the time course of peripheral axial elongation during and following an extended period of accommodation.

3.4.1 Effect of the beamsplitter on Lenstar measurements

Before taking measurements, a pilot study was performed to examine the effect of the beam splitter in biometric measures on five participants. A paired *t*-test was conducted to compare the measurements with and without the beam splitter. The beamsplitter did not affect measurements significantly ($p > 0.05$)

(Table 3.1). No checking of beamsplitter effect was necessary for peripheral field measurements as the beam splitter was not in the instrument beam path.

Table 3.1: Mean (± SD) for Lenstar measurement with and without a beam splitter.

Ocular measurements	**The mean differences between with and without beamsplitter (n = 5)**
Axial length	0.00 ± 0.01 mm
Central corneal thickness	0.00 ± 0.02 mm
Anterior chamber depth	0.02 ± 0.07 mm
Lens thickness	0.02 ± 0.08 mm

3.4.2 Repeatability of on-axis and peripheral eye length measurements

A pilot study was performed to evaluate the repeatability of the axial length measurement during accommodation. Five healthy participants (18–23 years), consisting of two emmetropes (ranging from −0.25 D and +0.75 D) and three myopes (−0.75 D, −2.00 D and −5.00 D) were recruited. The eye length was measured with 0 D and 6 D of accommodation demand centrally and 10° temporally, 25º temporally, 10º nasally and 25º nasally by the same observer at two visits, three to five days apart at approximately the same time. The mean central intra-sessional repeatability (SD) between visit 1 and visit 2 varied between 0.01 and 0.03 mm across the visual field positions and accommodation demands.

Figures 3.7 and 3.8 show Bland-Altman plots of difference in axial length between visits as a function of the mean of the two visits, for five field locations with 0 D and 6 D accommodation demands. Different symbols represent data of individual participants. The 95% limits for agreements were −0.06 to +0.07 mm and −0.08 to +0.07 mm for 0 D and 6 D accommodation demands, respectively. The mean inter-sessional repeatability (SD) with 0 D and 6 D accommodation demands for the Lenstar (five locations) were ± 0.03 mm and ± 0.05 mm, respectively. Repeatability increased from the centre for 0 D (0.02 mm) and 6 D (0.01 mm) of accommodation to the periphery at 25° temporal and 25° nasal field positions (both 0.06 mm). The repeatability of the Lenstar for peripheral eye length measurement along the horizontal visual field was similar to previous studies (Schulle and Berntsen, 2013; Verkicharla et al., 2013). Since this pilot study showed the Lenstar has good repeatability with accommodation, it was used for experiments 1 and 2.

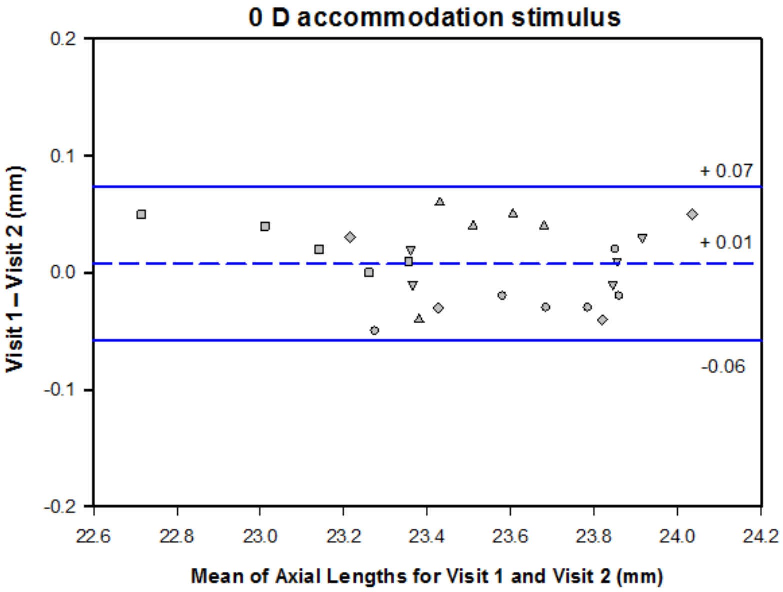


Figure 3.7: Bland-Altman axial length difference versus mean plots with 0 D of accommodation stimulus. Different symbols are given for different participants, with five points for each participant along the horizontal field. The dotted line represents the mean difference between Visit 1 and Visit 2. The solid lines represent the 95% limits of agreement.

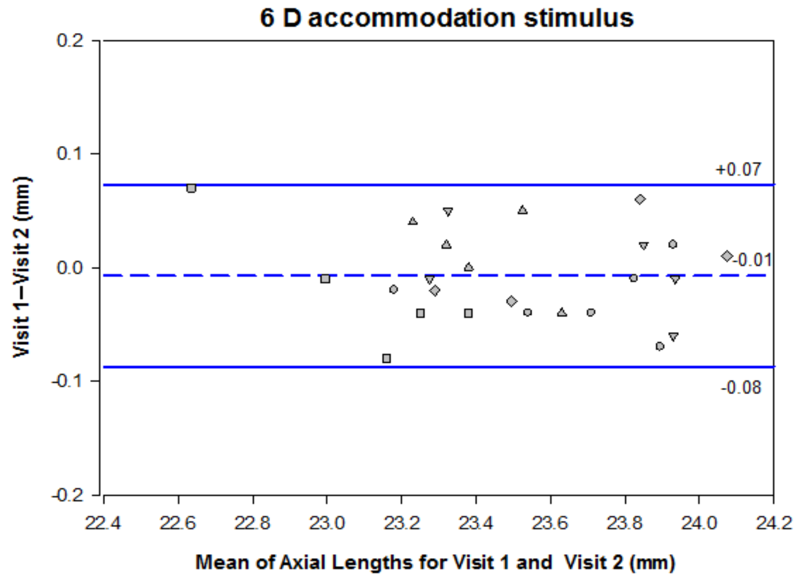


Figure 3.8: Bland-Altman axial length difference versus mean plots with 6 D of accommodation stimulus. Other details are as for Figure 3.6.

3.4.3 Correction factors

Partial coherence interferometry has been used to measure axial length during accommodation. During accommodation, a thicker high index lens displaces parts of the lower anterior chamber and vitreous, therefore optical instruments overestimate the change in axial length of the eye. Atchison and Smith (2004) suggested that an equation be used to estimate the on-axis axial length error during accommodation. This equation is

$$\mathrm{E} = \frac{OPL_a}{n_{ave}} - L_u \quad (1)$$

where E is the error in the estimated axial length of the accommodated eye, OPL_a is the optical path length of the accommodated eye, n_{ave} is the average refractive index of the unaccommodated eye, and L_u is the geometrical length of the unaccommodated eye. In the approach here, optical path lengths were converted to axial lengths using the Lenstar equation (Suheimat et al., 2015):

$$L = (OPL - 1.9587)/1.2866 \quad (2)$$

Using accommodated and unaccommodated schematic eye models, the axial length E during accommodation is

$$E = (AL_a - AL_u) + (GPL_a - GPL_u) \quad (3)$$

where AL_a and AL_u are the axial lengths the Lenstar would give for the schematic model eyes according to equation (1), and GPL_a and GPL_u are the geometrical path lengths of the traced rays in those schematic eyes.

To date, there is no study that introduces a correction factor for peripheral axial length during accommodation. This was done utilising model eye simulations. Six theoretical model eyes were simulated using Zemax software (Radiant Zemax, Redmond, USA) to estimate the error in axial length during accommodation. These models included the Le Grand model eye without and with 7.053 D accommodation, the variable accommodating model (Navarro et al., 1985) and the Gullstrand No.1 model eye without accommodation and with 10.88 D accommodation (Atchison and Smith, 2000). Ray tracing was performed at normal incidence to the cornea at seven eccentricities (0°–30° in 5° steps), using a retina with a radius of curvature of 12 mm. Geometrical and optical axial lengths were determined for all models.

This study uses the equation 2 to convert the optical path length to axial length for all models. The over-estimation in axial length due to accommodation was calculated as the difference between the accommodated and unaccommodated eye axial length after accounting for any real geometrical path length between the schematic models eyes (equation 2). To make sure this model does not produce strange results peripherally, the ray-traces were performed on the other model eyes (Table 3.2 and Table 3.3). Atchison and Smith (2004) used the Gullstrand No.1 model eye to estimate the error in on- axis axial length due to accommodation during IOLMaster measurement. They reported that the error was 18 µm for an accommodation of 10.9 D, which is similar to my value of 19.2 µm. Since the Gullstrand No.1 and the Le Grand model eyes have models for one accommodation stimulus only (7.05 D and 10.88 D), to determine the error for 6 D of accommodation I assumed that the error due to accommodation is proportional to accommodation. To provide corrected axial length measurements across all locations, these errors were subtracted from the measured axial length (6 D) at each angle for each participant. Table 3.4 shows the errors in the Lenstar due to accommodation in all models eyes.

Table 3.2: Gullstrand model No. 1 (exact) without accommodation.

Medium	n	R	d	Surface	Equivalent powers component	Whole eye power
Air	1.0000					
Cornea	1.376	7.700	0.500	48.831		
Aqueous	1.336	6.800	3.100	−5.882	43.053	58.636
Lens cortex	1.386	10.000	0.546	5.000		
Lens core	1.406	7.911	2.419	2.528		
Lens cortex	1. 386	−5.760	0.635	3.472	19.111	
Vitreous	1.336	−6.000	17.18540	8.333		
Retina		−12.0				

Table 3.3: Gullstrand model No. 1 (exact) with accommodation (10.88 D).

Medium	n	R	d	Surface	Equivalent powers component	Whole eye power
Air	1.0000					
Cornea	1.376	7.700	0.500	48.831		
Aqueous	1.336	6.800	2.700	−5.882	43.053	70.576
Lens cortex	1.366	5.333	0.6725	9.376		
Lens core	1.406	2.655	2.6550	7.533		
Lens cortex	1. 386	−2.655	0.6725	7.533	33.057	
Vitreous	1.336	5.333	17.18540	9.376		
Retina		−12.0				

Table 3.4: Errors in Lenstar measurement due to accommodation (µm)

Eccentricity	0°	5°	10°	15°	20°	25°	30°
Le Grand (7.05 D)	56.7	56.4	55.4	53.8	51.5	48.6	44.9
Gullstrand (10.88 D)	19.2	18.7	17.1	14.4	10.5	5.5	1.0
Le Grand (6 D)	48.2	48.0	47.1	45.8	43.8	41.3	38.2
Gullstrand (6 D)	10.6	10.3	9.4	7.9	5.8	3.0	0.6
Navarro (6 D)	40.7	40.1	39.6	38.8	37.8	36.7	35.4

For all models, errors were highest on-axis and reduced into the periphery. Errors were highest for eyes with a constant refractive index lens. Changes in corrections from the centre to periphery are small (0.005 – 0.02 mm) and near the instrument's resolution of 0.01 mm. To correct the errors in axial length during accommodation, I chose the Gullstrand No.1 model eye because with its shell lens it is the closest in optical structure to real human lens.

3.5 PERIPHERAL CHOROIDAL THICKNESS MEASUREMENT WITH NIDEK RS-3000 ADVANCED

SD-OCT is a non-contact ophthalmic imaging system which uses the low-coherence interferometry principle to measure the difference between the reflected beam from ocular structures and the reference beam of light (Costa et al., 2006) (Figure 3.9). The axial resolution of OCT images is produced through the bandwidth of the source and the coherence length. The coherence length is dependent on the central wavelength. The low coherence light produces a high axial resolution. Transverse resolution is also dependent on the size of the light spot that is focused on the tissue. The best image resolution is achieved when the light is focused on the examined layer (Keane et al., 2011).

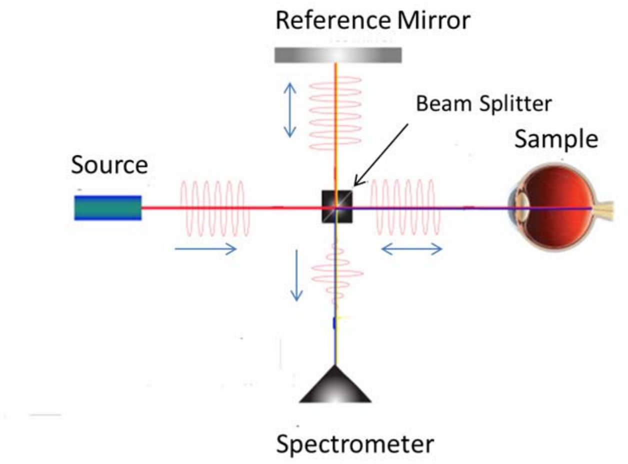


Figure 3.9: Schematic of SD-OCT system. Light from the source is divided by the beam splitter to reference and sample arms. Light reflected from both sample and reference arms is analysed by the spectrometer.

The repeatability of OCT instruments for measuring the choroidal thickness has been investigated in several studies. Shao et al. (2013) measured the inter-observer and intra-observer reproducibility of subfoveal choroidal thickness using the enhanced depth imaging of EDI-OCT in 3233 Chinese adults. A good inter-observer and intra-observer reproducibility was reported (ICC = 1.00; mean coefficient of variation was 0.85% ± 1.48%). Vujosevic et al. (2012) measured the inter-observer repeatability of subfoveal choroidal thickness using Nidek SD-OCT in 150 participants. Highly significant correlation between measurement obtained by two examiner were found ($r = 0.99$, $p < 0.001$). Rahman et al. (2011) examined the repeatability of the manual measurement of choroidal thickness using OCT in 50 healthy participants. Using the manual callipers provided by the device software, two observers measured the choroidal thickness of the horizontal and vertical line scans for all eyes. No significant differences in choroidal thickness between all pairs of measurements were found. This is in agreement with research by Spaide et al. (2008) who found good inter-observer repeatability when measuring choroidal thickness in healthy participants. In their study, highly significant correlations between measurements performed by the two examiners were found (right eye, $r = 0.93$; left eye, $r = 0.97$; $p < 0.001$ for both).

The Nidek RS-3000 Advanced spectral domain optical coherence tomographer (Ganmgori, Japan) is used for in vivo imaging and measurement of the RPE and choroidal thickness and in the diagnosis of retinal pathologies. This device includes a SD-OCT and confocal scanning laser ophthalmoscope (SLO). The internal structure of the retina images are obtained by calculating the signal from a CCD line scan sensor, which detects a spectrum of different wavelengths obtained from the observation and image capture of super luminescent light scanned across, and reflected from, the fundus of the eye. The confocal SLO captures and tracks fundus surface images using a near-infrared light source. Every A-scan has a depth of 2 mm with 512 pixels which produce 4 µm resolution. It uses an 880 nm wavelength source with a scanning speed of 53,000 A-scans/second to provide cross-sectional posterior images of the eye. It provides an axial resolution of 7 µm (Dag et al., 2013; Morooka et al., 2012; Vujosevic et al., 2012).

Choroidal thickness was measured using the Nidek OCT Advance. The right eye was measured, while the left eye was occluded by a patch. Before taking measurements, the participant was aligned to the machine by using a chin-rest and the up/down button. The participant was instructed to focus on an internal fixation target in the form of a cross symbol (see Figure 3.10B). In this experiment the external target similar to Experiment 1 and 2 could not be used due to limited space between the eye of participant and the OCT.

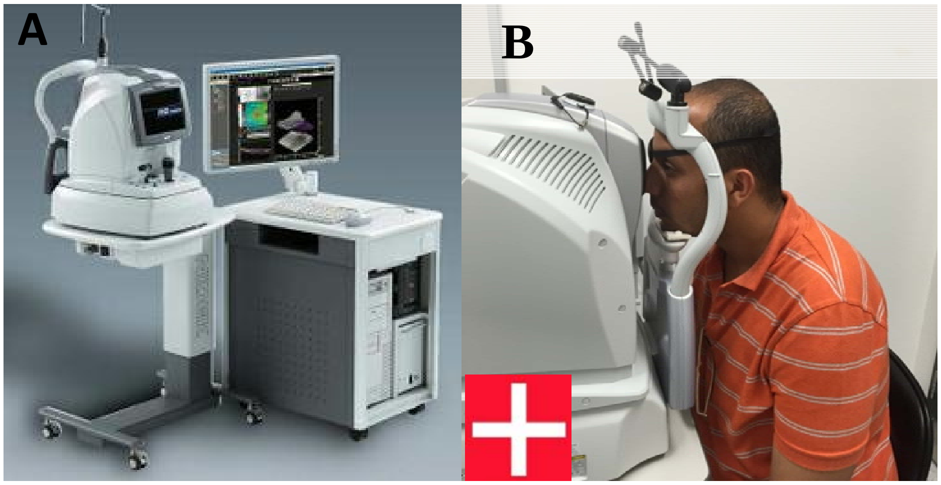


Figure 3.10: (A) OCT to measure on-axis and peripheral choroidal thickness. (B) The participant was instructed to focus on a red cross symbol for all positions along the horizontal meridian.

To obtain cross-sectional images of the choroidal thickness horizontally at the centre of the fovea (on axis), the system was programmed along the macula line to image the choroidal thickness for all of the participants. The scan pattern was a 12 mm line (±20°) on the retina consisting of 1024 A-scans to image the choroidal thickness, with high definition (50 HD) frame enhancement software.

Peripheral choroidal thickness measurements were obtained by moving the normal internal target size on the SLO capture screen 17.25° (visual field angle) from the centre to the nasal/temporal of the eye (furthest point horizontality, information obtained through personal communication with Nidek Company). After removing the overlap, the choroidal thickness was measured up to ±35° in 5° steps (1500 µm using OCT NAVIS-EX software) across the horizontal visual field. Using a one-surface paraxial model eye of 60 D power, a 1° angle corresponds to 291 µm on an emmetropic retina. Figure 3.11 shows the internal target moving on the SLO screen. The spherical refractive error of each participant was corrected by the OCT system internally before the participant was imaged. Accommodative stimuli (6 D) were presented to the participant using the internal system of the OCT.

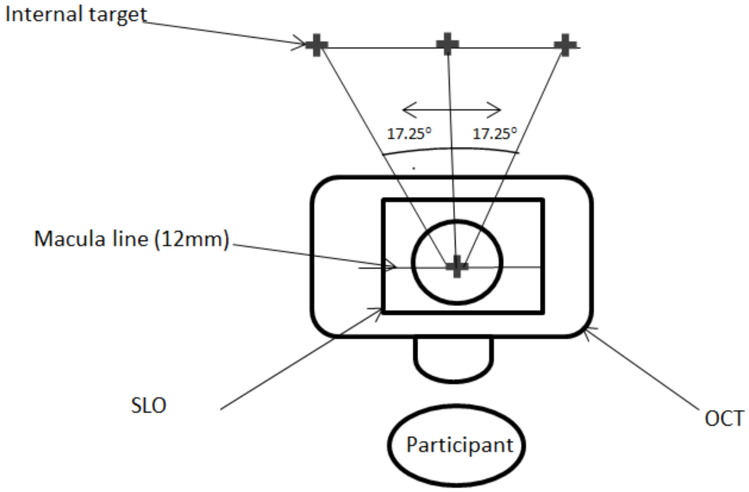
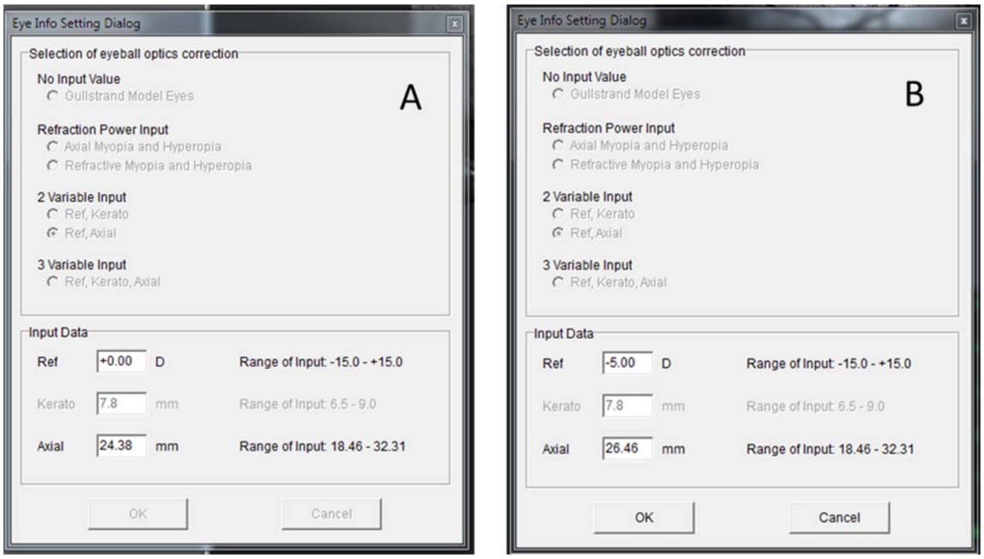


Figure 3.11: Schematic diagram of experimental setup to measure the choroidal thickness out to ±35°.

To determine the thickness of the choroid, the vertical distance between the posterior edge of the hyper-reflective RPE which is detected automatically by the system, and the sclerochoroidal interface which is manually labelled by the examiner using OCT NAVIS-EX software. The instrument took approximately 1.5 s to scan the thickness of the choroid and three separate scans were performed for the same location for 0 D and 6 D of accommodation stimulus. As suggested by the manufacturer, the signal strengths of the images should not be less than 6 of 10 intensity score. If the scans did not get a value of 6/10 or higher, the scan was repeated until the 6/10 or higher values were obtained.

Given the variability in the axial length of the eyes among the participants, the actual transverse length for each participant varied. For eyes with a short axial length, the OCT scans a smaller area of the retina, while it scans a larger area for eyes with longer axial lengths. The final actual scan length was corrected using individual axial length obtained with Lenstar LS 900. To achieve actual transversal resolution, the OCT NAVIS-EX software provides functions for measuring the actual scan length after taking the images by entering the real axial length and the refractive error in the input data dialog box for each participant (Figure 3.12).



A

Selection of eyeball optics correction

No Input Value
○ Gullstrand Model Eyes

Refraction Power Input
○ Axial Myopia and Hyperopia
○ Refractive Myopia and Hyperopia

2 Variable Input
○ Ref, Kerato
● Ref, Axial

3 Variable Input
○ Ref, Kerato, Axial

Input Data

Ref	+0.00	D	Range of Input: -15.0 - +15.0
Kerato	7.8	mm	Range of Input: 6.5 - 9.0
Axial	24.38	mm	Range of Input: 18.46 - 32.31

B

Selection of eyeball optics correction

No Input Value
○ Gullstrand Model Eyes

Refraction Power Input
○ Axial Myopia and Hyperopia
○ Refractive Myopia and Hyperopia

2 Variable Input
○ Ref, Kerato
● Ref, Axial

3 Variable Input
○ Ref, Kerato, Axial

Input Data

Ref	-5.00	D	Range of Input: -15.0 - +15.0
Kerato	7.8	mm	Range of Input: 6.5 - 9.0
Axial	26.46	mm	Range of Input: 18.46 - 32.31

Figure 3.12: The dialog box of eyeball optics correction. (A) Actual axial length assumed by the system, (B) Actual axial length after input of the data by the examiner.

To achieve good quality images, the ‘toggle switch’ was used to allow the examiner to get closer to the participant’s eye (better in depth penetration by adjusting the z position) without moving the scan out of the monitor. By manipulating the brightness and contrast settings of the monitor, the details of the choroidal layers were clearer. Three images were taken at the central (Figure 3.13A), nasal (Figure 3.13B) and temporal (Figure 3.13C) visual field at horizontal gazes for both 0 D and 6 D accommodation stimulus.

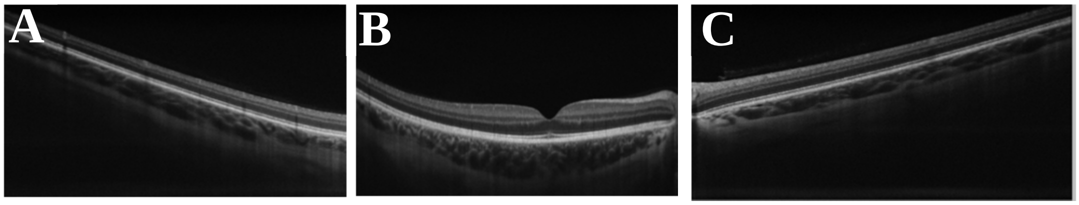


Figure 3.13: Raw OCT view of (A) nasal, (B) central and (C) temporal choroid obtained using the Nidek OCT (Participant JA).

3.6 DATA ANALYSIS - EXPERIMENTS 1, 2 AND 3

One of the assumptions of ANOVA and regression is normality. Although this assumption is generally the one given the highest importance compared to the other assumptions (independence and constant variance) it is in fact the least important one, especially when there are no missing data (Fitzmaurice et al., 2004). In that last case any symmetrical distribution would suffice. Furthermore, it should be kept in mind that the assumption is made for the population where the data come from using the current sample as a proxy. In my case I have no missing data and thus this assumption is not important. The assumption was explored via skewness and kurtosis as well as by applying formal normality tests such as the Kolmogorov-Smirnov. In the majority of the angles the data were normally distributed with very few angles yielding non-normality. Given the number of tests, I decided to use a simple linear regression to analyse the data rather than a non-parametric test.

For Experiment 1, to investigate changes in axial length with accommodation and differences of these changes between refractive groups, SPSS statistical software (Version 21, SPSS Incorporated, IBM Company, Chicago, USA) was used to perform one way analysis of variance (ANOVA) for each visual field position, with refractive group (emmetropes, low myopes and higher myopes) as the between-subject factor. These ANOVAs were done for 0 D accommodation, for 6 D accommodation, and for the differences between the two accommodation levels. Where refractive group was a significant factor, post hoc pair-wise comparisons were made with *t*-tests incorporating a Bonferroni correction.

Independent sample t-tests were performed to investigate the effects of race and gender on axial length. Linear regression was used to investigate the correlation of changes in axial length with spherical equivalent refraction.

For Experiment 2, one way ANOVAs were conducted to compare axial lengths between groups (emmetropes and myopes) at baseline, separately for each position. One way ANOVAs were conducted to compare changes in axial length (relative to baseline) at each point of time and visual field position combination. To investigate the changes (relative to baseline) over time in the axial length of the eye with accommodation between refractive groups, two-way ANOVAs were performed, with time as a within-subject factor and refractive group (emmetropes and myopes) as the between-subject factor for each visual position. These ANOVAs were done for 6 D accommodation and for 0 D accommodation. Linear regression was used to estimate the correlation between axial length change and spherical equivalent refraction for three positions.

For Experiment 3, one-way ANOVAs for choroidal thickness were conducted at each visual field position with refractive group (emmetropes, low myopes and higher myopes) as the between-subject factor. These ANOVAs were done for 0 D accommodation, for 6 D accommodation, and for the differences between the two accommodation levels. Where refractive group was a significant factor in choroidal thickness, post hoc pair-wise comparisons were made with *t*-tests incorporating a Bonferroni correction. Linear regressions of accommodation-induced changes in axial length with changes in choroidal thickness were conducted. These were restricted to within ±30° because the edge of the pupil blocked the beam of the Lenstar LS 900 at the 35° angles.

The significance level of $p \leq 0.05$ was used during all analyses.

Chapter 4: The Effect of Accommodation on Peripheral Eye Lengths of Emmetropes and Myopes

ABSTRACT

Purpose: To investigate the effect of accommodation on both on-axis and peripheral axial lengths in young adult emmetropes and myopes.

Methods: On-axis and peripheral axial lengths were measured with the Haag-Streit Lenstar in 83 young adult participants for 0 D and 6 D accommodation demands. A Badal system was used to both correct refractive errors and induce accommodation. Participants were classified as emmetropes (n = 29, spherical equivalent refraction mean ± standard deviation +0.35 ± 0.35 D), low myopes (n = 32, −1.38 ± 0.73 D) and higher myopes (n = 22, −4.30 ± 0.73 D). Pupils were dilated with 2.5 % phenylephrine to allow a large field to be measured when maintaining active accommodation. Axial length was measured in 5° steps to ±30° across the horizontal visual field and gives as the means of four measurements at each location for each accommodation demand. Errors in axial length due to changes in the crystalline lens thickness during accommodation were corrected.

Results: There were statistically significant axial length differences between refractive groups for the unaccommodated state, with higher myopes having longer eyes on-axis (mean ± SD: emmetropes 23.33 ± 0.60 mm, low myopes 24.15 ± 0.89 mm, and higher myopes 25.38 ± 0.89 mm) and in the periphery. With accommodation, axial length increased for all refractive groups at all positions. Axial length changes were greater for higher myopes than for emmetropes on-axis (higher myopes 41 ± 29 µm, emmetropes 30 ± 22 µm, $p = 0.005$), and for higher myopes than for low myopes at 30° nasal field ($p = 0.03$), and for the higher myopes than for the other groups at 20° nasal field ($p < 0.05$). There were significant negative correlations between the changes in axial length along the horizontal meridian and spherical equivalent refraction of myopic eyes at all positions, with the highest correlation on-axis ($R^2 = 0.30$).

Conclusions: During accommodation, eye length increased to at least ±30° across the horizontal visual meridian field in young adult myopes and emmetropes. Increases were significantly greater for higher myopes than for the other groups on-axis and at some nasal visual field positions. At all positions, there were significant negative correlation between the changes in axial length along the horizontal meridian and spherical equivalent refraction of myopic eyes. It is possible that over longer periods of time, the short-term changes in axial length might become a permanent elongation.

4.1. INTRODUCTION

Myopia is a highly prevalent condition worldwide, especially in Asia where it is thought to have reached epidemic levels (Pan et al., 2012). The notion that excessive near work predisposes towards the development of myopia is supported by several studies (Chen et al., 2003; Fulk et al., 2002; Goss, 2000; Ip et al., 2008; Jacobsen et al., 2008; Onal et al., 2007), although a few studies have found only a weak relationship between near work and the development of myopia (Goldschmidt et al., 2001; Saw et al., 2000). The biological factors that lead to the development of myopia remain poorly understood.

The finding that near work and myopia are associated (reviewed in Sherwin and Mackey (2013)) has led to investigations into the effect of accommodation on on-axis ocular biometry. During accommodation, there are well described changes to the crystalline lens: the central thickness increases, the equatorial diameter decreases. The posterior eye structure seems to change with accommodation. Using the Stiles–Crawford function, Hollins (1974) inferred that the central retina stretches by 4.5% during high accommodation demand (9 D) and Enoch et al. (1983) determined an average retinal stretch of 0.07 mm/D. However Singh et al. (2009) found only small changes in on-axis direction in the Stiles–Crawford effect with accommodation, which indicates little retinal change.

Studies using partial coherence interferometry (PCI) have found small on-axis axial length elongations during accommodation. Drexler et al. (1998) used the custom built system with 11 emmetropic and 12 myopic adults (mean accommodation response emmetropes 5.1 ± 1.2 D and myopes 4.1 ± 2.0 D). The emmetropic group had greater changes (mean elongation 13 ± 3 µm) than the myopic group (mean 5 ± 2 µm), but the average accommodation response was stated to be 1

D greater in the emmetropes. Conversely, Mallen et al. (2006) who used the Zeiss IOLMaster, found greater axial length elongation in myopes (60 ± 40 µm) than in emmetropes (40 ± 30 µm) for a 6 D stimulus.

It is likely that the reported changes in axial length during accommodation in Mallen et al. (2006) and Suzuki et al. (2003) are overestimates. During accommodation the lens thickening and the anterior chamber depth shallowing will increase optical path length, but no allowances are made for this in geometric axial length calculations used by the IOLMaster and Lenstar. More recent studies have reported corrected values based on the studies by Atchison and Smith (2004) and Atchison and Charman (2011). The corrected data of Read et al. (2010) gave mean axial length increases of 7 ± 15 µm in young adults for a 6 D stimulus, with means of 8 µm and 6 µm for emmetropes and myopes subgroups; group difference was not statistically significant ($p = 0.88$). The data of Woodman et al. (2012) showed mean axial length increases of 6 ± 22 µm for emmetropes and 22 ± 34 µm for myopes in response to a 4 D stimulus ($p = 0.14$). There is thus conflicting data as to whether axial length increases with accommodation are greater in emmetropes or myopes.

No studies have considered the effect of accommodation on peripheral axial length. Peripheral measurements of refraction have been made due to the recent interest in the possible role of the peripheral retina in myopia development (Verkicharla et al., 2012). Many studies since Rempt et al. (1971) have reported that the peripheral optics, relative to the centre, tends to relative peripheral hyperopia in myopes and relative peripheral myopia in emmetropes (e.g. Chen et al., 2010; Kang et al., 2010; Millodot, 1981; Mutti et al., 2000), at least for the horizontal visual field (Atchison et al., 2005; Berntsen et al., 2010). However, longitudinal studies in children have not shown a predictive effect of peripheral refraction pattern on myopia development (Atchison et al., 2015; Lee and Cho, 2013; Sng et al., 2011).

Studies involving animal models support the hypothesis that peripheral retina can stimulate eye growth even in the presence of on-axis myopia (reviewed in Wallman and Winawer (2004)). Young rhesus monkeys raised with ring-shaped diffusing filters developed axial refractive errors despite central apertures allowing 37° of unrestricted central vision (Smith et al., 2005). Similarly, lens-induced hyperopic defocus applied to the periphery, excluding the central 10° of field, resulted in myopia (Smith et al., 2009). Furthermore, when hypermetropic defocus was applied to selected parts of the visual field, myopic changes to the refraction and corresponding shape changes occurred in the corresponding parts of the retina (Smith et al., 2010). These data highlight the importance of both the central and peripheral retina in myopia development and progression.

The aim of this chapter is to investigate the effect 0 D and 6 D of accommodation demands on both on-axis and peripheral axial lengths in young adult emmetropes and myopes. A partial coherence interference instrument was modified using an external attachment to allow measurement at different visual field positions. The hypothesis to be tested is that the peripheral axial length, like the central axial length, would also increase with accommodation and that the increase would be greater in myopes than in emmetropes.

4.2. MATERIALS AND METHODS

Axial length was measured in 5° steps to ±30° across the horizontal visual field when the eye was unaccommodated (0 D accommodation demand; baseline) and accommodated (6 D stimulus). Young adult myopes and emmetropes with good accommodation responses were recruited. The project followed the Tenets of the Declaration of Helsinki and was approved by the Queensland University of Technology Human Research Ethics Committee. Written informed consent was obtained from all participants.

4.2.1 Participants

Ninety healthy adult participants aged from 18 to 25 years were recruited from the student population of the Queensland University of Technology. Each participant underwent a comprehensive ophthalmic examination that included subjective refraction and ocular health status. Contact lens wearers (n = 37) were asked to refrain from contact lens wear for the 24 hours before participation. Individuals with refractive errors greater than −5.50 D were excluded from the study due to limitations of the Badal system. Inclusion criteria included: no past or present ocular disease, normal logMAR visual acuity of 0.00 or better, no more than 1.00 D of cylinder or anisometropia, and good accommodative responses assessed with a COAS-HD Hartmann–Shack aberrometer. Seven potential participants were excluded from participation, two emmetropes with high cylinder (> 1.00 D) and five higher myopes with unsustained accommodation responses, leaving 83 participants.

Refractive errors for the right eye were measured using a Shin-Nippon-SRW-5000 autorefractor (Grand-Seiko, Osaka, Japan). Based on the mean spherical equivalent refraction (SER), the participants were classified as emmetropes (SER +1.00 to ‑0.25 D), low myopes (SER ‑0.50 to ‑3.00D) and higher myopes (SER < −3.00D). Table 4.1 summarises age, gender and refractive distribution for each refraction group.

The initial accommodation responses for the 6 D accommodation demand were 5.6 ± 0.4 D for emmetropes, 5.4 ± 0.7 D for low myopes and 5.2 ± 0.6 D for higher myopes (Chapter 3, section 3.3). One way ANOVA, with refractive group (emmetropes, low myopes and higher myopes) as the between-subject factor was performed to investigate the differences in accommodation response between refractive groups. Post hoc testing did not show significant differences in the accommodation response between groups ($p = 0.10$). Axial length was measured 20 min following the instillation of one drop of phenylephrine (1 drop, 2.5%, Chauvin Pharmaceuticals Ltd., UK). Sixty minutes after the first measurement with the Lenstar, accommodation responses were 5.5 ± 0.5 D for emmetropes, 5.3 ± 0.3 D for low myopes and 5.1 ± 0.5 D for higher myopes. To investigate the effect of phenylephrine on the accommodation response between refractive groups, one way ANOVA, with refractive group (emmetropes, low myopes and higher myopes) as the between-subject factor was also performed. Post hoc testing showed that there was no significant difference in accommodation response between refractive groups ($p = 0.73$).

Table 4.1: Group characteristics

Group	Number	Age (yr)	Gender (male: female)	Race (East Asian: South Asian: Caucasian)	SER (D)
Emmetropes	29	22.1±2.4	17:12	13: 3 : 13	+0.35 ± 0.35
Low myopes	32	21.6±2.3	14:18	20: 1: 11	−1.55 ± 0.80
Higher myopes	22	21.5±2.2	8:14	11: 2: 9	−4.47 ± 0.78

SER = spherical equivalent refraction. Data are mean ± SD.

4.2.2 Procedure

After a comprehensive ophthalmic examination, axial length was measured for all participants using the Lenstar LS 900 (Haag-Streit, Bern, Switzerland) under two accommodation demands (0 D and 6 D). The Lenstar measures central corneal thickness, anterior chamber depth, crystalline lens thickness, retinal thickness and axial length (the distance from the anterior corneal surface to the inner surface of the retinal pigment epithelium). This instrument uses the principle of optical low coherence refractometry and provides ocular biometric measurements that are similar to other biometers such as the IOLMaster (Buckhurst et al., 2009; Cruysberg et al., 2010; Rohrer et al., 2009; Shammas and Hoffer, 2012; Verkicharla et al., 2013). After dilating the pupil with one drop of phenylephrine (2.5%), eye lengths were determined in 5° steps to ±30° across the horizontal visual field. Measurements at more peripheral locations were not possible because the edge of the pupil (iris boundary) blocked the passage of the beam, especially with the 6 D stimulus.

To obtain peripheral eye length, the Lenstar was modified using an external attachment consisting of a goniometer, a beam splitter (Pellicle, Edmund Optics, USA; 72% transmission), a Maltese cross fixation target, a 13 D Badal lens and a light emitting diode source (Mallen and Kashyap, 2007; see Chapter 3, Figure 3.5). The goniometer was attached to the top of the Lenstar frame using a pair of right-angle retort clamps allowed measurements of eye length at different eccentricities and accommodative demands (0 D and 6 D). The goniometer was moved along the base rail until the target could be seen at all positions of goniometer rotation to ensure that the target rotation corresponded to the eye’s centre of rotation.

When the goniometer attachment was at its central position, the beam splitter was adjusted so that the Lenstar beam was aligned with the fixation target. The participant was asked to keep the target clear during measurements. For measurement along the horizontal visual field, participants were required to turn their eye without head movement to the fixation target at each eccentric location. Participants were asked to blink before each measurement to ensure a smooth tear film that would allow the alignment mires of the instrument to be clearly imaged on the corneal surface. All measurements were taken by the same examiner and were collected from the right eye while the left eye was occluded. The 0 D accommodation demand measurement was recorded as the baseline, and the longitudinal position of the fixation target was adjusted to produce a 6 D accommodation stimulus. Mean axial lengths were determined from four measurements for each accommodation demand and position.

Before measurements were taken, a pilot study was performed to examine the effect of a beam splitter in biometric measures on five participants. The mean differences in measurements with and without the beam splitter were 0.00 ± 0.01 mm for axial length, 0.00 ± 0.02 mm for central corneal thickness, 0.02 ± 0.07 mm for anterior chamber depth and 0.02 ± 0.08 mm for crystalline lens thickness. The beam splitter did not significantly affect measurements.

4.2.3 Analysis

The Lenstar instrument measures axial length by converting optical path lengths to geometric lengths. With accommodation, change in the crystalline lens shape increase the optical path length measurement and leads to an overestimate of eye length (Atchison and Smith, 2004). The previous studies that used the Lenstar to measure the on-axis axial length during accommodation, corrected the axial length measurements based on a method outlined by Atchison and Smith (2004).

Suheimat et al. (2015) investigated the Lenstar's conversion of the air thickness to geometrical path lengths for the different optical media of the eye. The refractive indices utilised were 1.415, 1.341, 1.340, and 1.354 for the crystalline lens, aqueous, cornea and overall eye, respectively. As mentioned in chapter 3, the error in change in axial length during accommodation was estimated using six theoretical model eyes with Zemax optical design software (Radiant Zemax, Redmond, USA). These models include the Le Grand model eye without and with 7.05 D of accommodation, the variable accommodating Navarro model (Navarro et al., 1985), and the Gullstrand No.1 model eye without and with 10.9 D of accommodation. Ray tracing was performed at normal incidence to the cornea at seven eccentricities (0° to 30°, in 5° steps) and geometrical and optical path lengths determined. These errors are subtracted from the axial length measured by Lenstar to provide the corrected axial length measurement for each participant, and it is these corrected results that are used in this and the following chapters. Our result for the Gullstrand No.1 accommodated model of an error of 19.2 μm are similar to those of Atchison and Smith (2004) of 18 μm. Table 3.4 in Chapter 3 shows the errors in the Lenstar due to accommodation as estimated using all 6 different model eyes. These errors were subtracted from the measured axial length (6 D) at each angle for each participant across the retina to provide the corrected axial length measurements.

To investigate changes in axial length with accommodation and differences of these changes between refractive groups, one way analysis of variance (ANOVA) was performed for each visual field position, with refractive group (emmetropes, low myopes and higher myopes) as the between-subject factor. These ANOVAs were done for 0 D accommodation, for 6 D accommodation, and for the differences between the two accommodation levels. Where refractive group was a significant factor in axial length, post hoc pair-wise comparisons were made with *t*-tests incorporating a Bonferroni correction.

Independent sample t-tests were performed to investigate the effects of race and gender on axial length. Linear regression was used to investigate the correlation of changes in axial length with spherical equivalent refraction in refractive groups. The significance level for all tests was set to $p < 0.05$.

4.3. RESULTS

The mean ages of the emmetropic and myopic groups were similar (emmetropes: 22.1 ± 2.4 yr, low myopes 21.6 ± 2.3 yr, higher myopes 21.5 ± 2.2 yr). There were no significant effects of race or gender on axial length changes at any visual field position ($p > 0.05$).

Table 4.2 and Figure 4.1 show axial lengths along the horizontal field for different visual field positions in the unaccommodated and accommodated states. There were significant differences between groups (ANOVA, $p < 0.001$) for unaccommodated state, with means of 23.3 ± 0.6 mm for emmetropes, 24.2 ± 0.9 mm for low myopes and 25.4 ± 0.9 mm for higher myopes. Significant differences occurred at all visual field positions ($p < 0.001$); the differences between groups decreased as eccentricity increased.

Correction of the measurement errors reduced the changes in axial length caused by accommodation, but the elongation in axial length caused by accommodation remained significant along the horizontal meridian both on-axis and in the periphery (ANOVA, $p < 0.001$).

Table 4.3 and Figure 4.2 show changes in axial length at all locations. All groups showed increases in axial length with accommodation at all field positions (means ranging from 17 to 41 µm). There were only four positions at which this was affected significantly by refractive group: on-axis where higher myopes elongated more than emmetropes (mean ± SE: 41 ± 29 µm for higher myopes; 30 ± 2 µm for emmetropes), at 20° nasal where higher myopes elongated more than other groups (mean ± SE: 31 ± 32 µm for higher myopes; 22 ± 22 µm for emmetropes; 21 ± 22 µm for low myopes), at 25° nasal (no significant post hoc pairwise comparisons) and at 30° nasal visual field where higher myopes elongated more than low myopes (mean ± SE: 29 ± 42 µm for higher myopes; 18 ± 24 µm for low myopes). Frequency histograms of increase in axial length as a function of refractive group also show that myopes had larger changes than emmetropes on axis and in the periphery (Figure 4.3).

Table 4.4 and Table 4.5 show correlations of accommodation-induced axial length change with spherical equivalent refraction and with unaccommodated axial length at the visual field positions in emmetropes and combined myopic groups. There was no significant correlation between axial length and spherical equivalent refraction in emmetropic groups at any position, but there were significant correlations in myopes at all positions with the highest correlation on-axis ($R^2 = 0.30$, $p < 0.001$) (Figure 4.4A) and with slopes between –1.4 and –5.2 µm/D. There were no significant correlations between axial length and unaccommodated axial length in emmetropic groups at any position, but there were significant correlations in myopes with the highest correlation on-axis ($R^2 = 0.15$, $p < 0.004$) (Figure 4.4B) and with slopes between +2.76 and +4.75 μm/D.

Table 4.2: Axial lengths (mm) in the unaccommodated and accommodated states along the horizontal field meridian for the three refractive groups.

Visual field position (°)	**Emmetropes**	**Low myopes**	**Higher myopes**	***p* value**
Unaccommodated				
−30 T	23.13±0.57	23.83±0.87	24.95±0.97	< **0.001**
−25 T	23.18±0.57	23.88±0.88	25.07±0.98	< **0.001**
−20 T	23.23±0.58	23.93±0.88	25.15±0.96	< **0.001**
−10 T	23.29±0.62	24.05±0.88	25.22±0.92	< **0.001**
−5 T	23.30±0.60	24.12±0.89	25.31±0.91	< **0.001**
0 (Centre)	23.33±0.60	24.15±0.89	25.31±0.91	< **0.001**
5 N	23.26±0.58	24.15±0.89	25.38±0.89	< **0.001**
10 N	23.23±0.59	24.04±0.90	25.30±87	< **0.001**
15 N	23.20±0.57	23.93±0.87	25.22±88	< **0.001**
20 N	23.15±0.57	23.86±0.86	25.09±0.92	< **0.001**
25 N	23.09±0.55	23.79±0.86	24.96±0.95	< **0.001**
30 N	23.04±0.56	23.67±0.85	24.8±0.95	< **0.001**
Accommodated state				
−30 T	23.15±0.57	23.85±0.88	24.97±0.98	< **0.001**
−25 T	23.20±0.57	23.91±0.98	25.10±0.98	< **0.001**
−20 T	23.25±0.85	23.96±0.88	25.18±0.96	< **0.001**
−10 T	23.32±0.62	24.07±0.88	25.26±0.92	< **0.001**
−5 T	23.33±0.59	24.15±0.88	25.35±0.91	< **0.001**
0 (Centre)	23.36±0.60	24.18±0.89	25.41±0.89	< **0.001**
5 N	23.29±0.58	24.09±0.88	25.37±0.89	< **0.001**
10 N	23.26±0.59	24.07±0.90	25.34±0.87	< **0.001**
15 N	23.22±0.57	23.95±0.87	25.25±0.88	< **0.001**
20 N	23.18±0.58	23.88±0.86	25.12±0.92	< **0.001**
25 N	23.11±0.55	23.81±0.86	24.99±0.95	< **0.001**
30 N	23.06±0.56	23.69±0.85	24.84±0.93	< **0.001**

Table 4.3: Changes in axial length (µm) with accommodation for the refractive error groups.

Visual field position (°)	Emmetropes	Low myopes	Higher myopes	*p* value	Post-hoc Bonferroni where significant
−30 T	21±25	17±20	26±31	0.067	
−25 T	22±33	21±63	26±33	0.727	
−20 T	22±23	21±23	33±85	0.144	
−10 T	24±29	25±30	34±58	0.211	
−5 T	25±37	29±57	38±71	0.237	
0 (Centre)	30±22	34±20	41±29	**0.005**	Higher myopia vs Emmetropia : 0.004
5 N	26±30	27±36	33±47	0.392	
10 N	25±27	22±29	32±66	0.212	
15 N	24±26	24±26	32±40	0.106	
20 N	22±20	21±22	31±32	**0.010**	Higher myopia vs Emmetropia: 0.037 Higher myopia vs Low myopia: 0.012
25 N	21±23	19±31	30±37	**0.049**	
30 N	20±23	18±24	29±42	**0.030**	Higher myopia vs Low myopia: 0.028

T = temporal visual field, N = nasal visual field.

Data are mean ± SD. Significant *p* values are bolded.

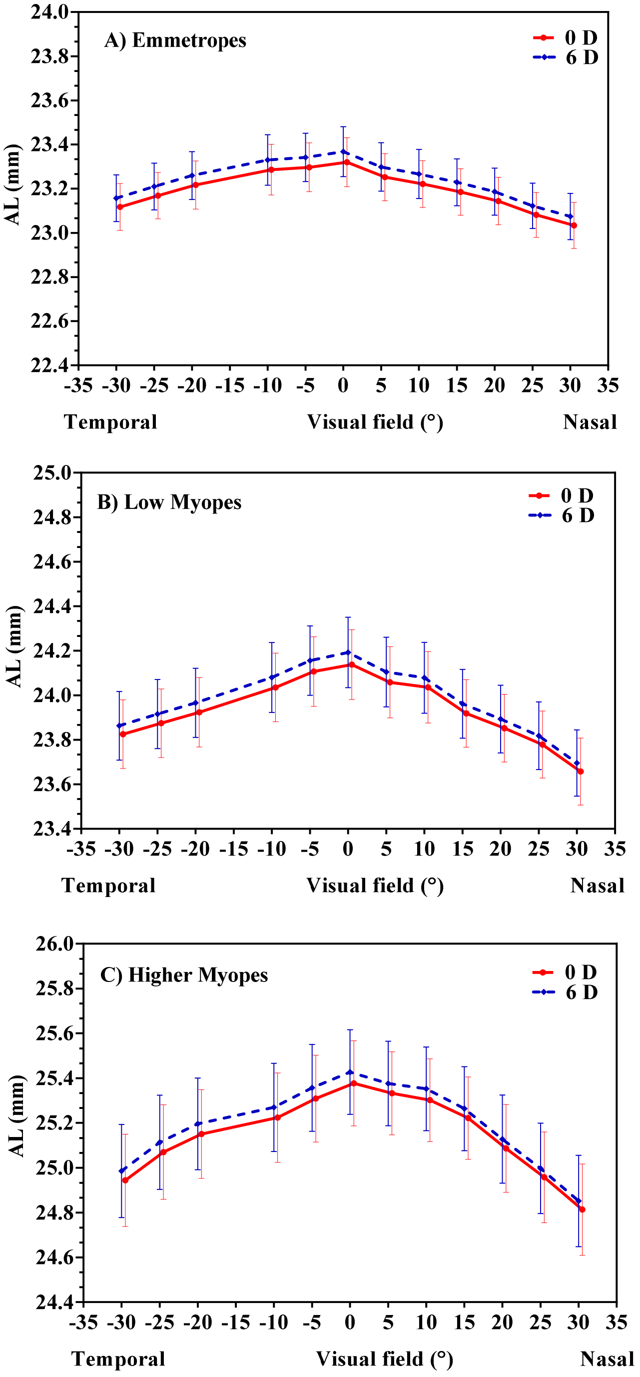


Figure 4.1: Axial length of eye (AL) for 0 D and 6 D accommodation stimuli along the horizontal meridian in (A) emmetropes, (B) low myopes and (C) higher myopes. The blind spot (−15°) was not tested. The error bars represent standard errors of means. For clarity, the plots for 0 D have been shifted slightly horizontally.

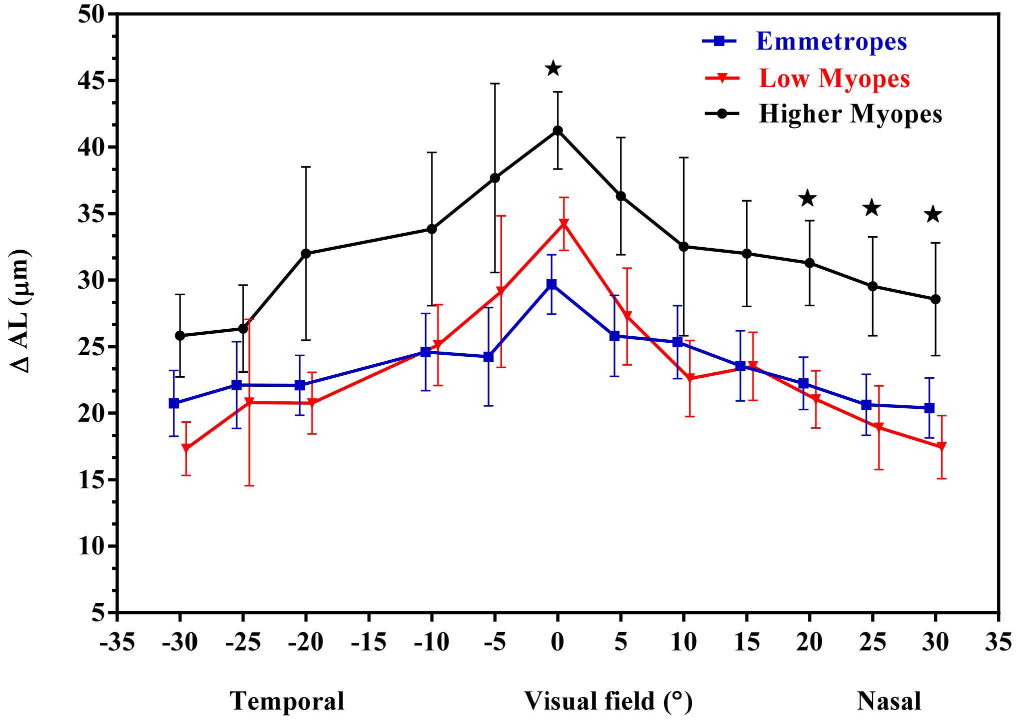


Figure 4.2: The mean changes in axial length (ΔAL) with accommodation along the horizontal meridianin emmetropes, low myopes and higher myopes. Error bars represent standard errors of means. For clarity, the plots for low myopes and emmetropes have been shifted slightly horizontally. Locations with significant effect of refractive groups are marked with asterisk.

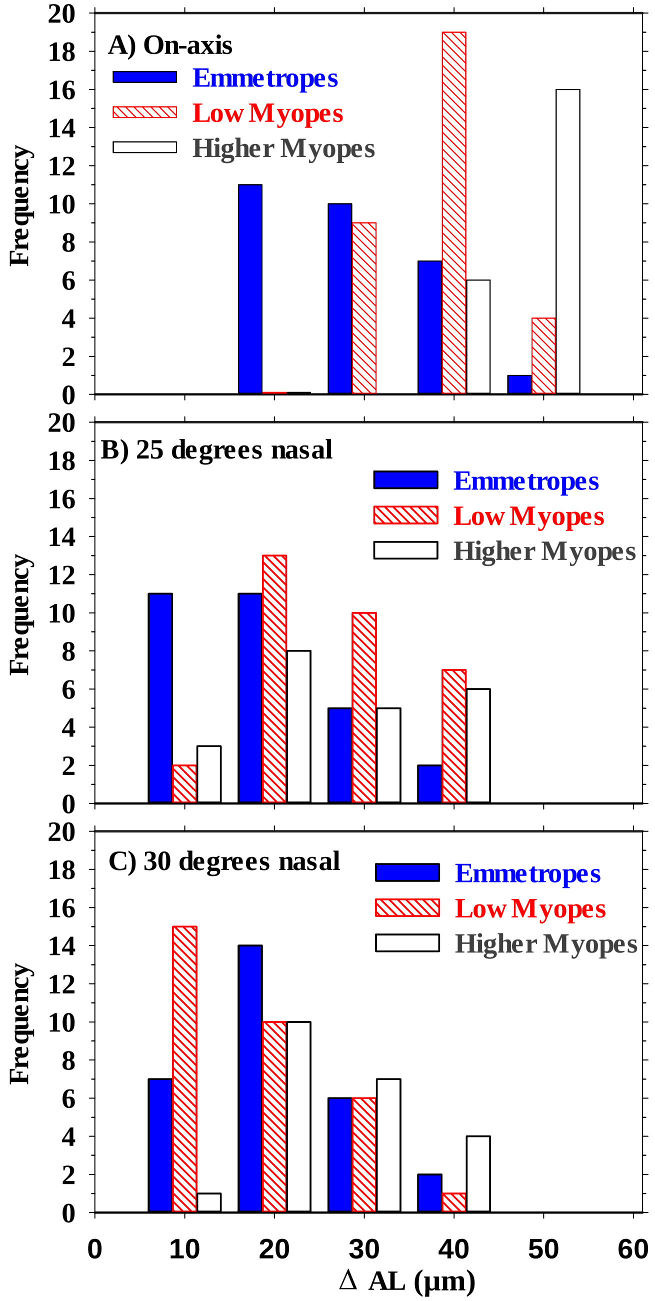


Figure 4.3: Frequency histograms of change in axial length (Δ AL) in emmetropes, low myopes and higher myopes at (A) on-axis, (B) 20° nasal, and (C) 30° nasal field. Bin widths of 10 µm are centred at 10, 20, 30, 40 and 50 µm.

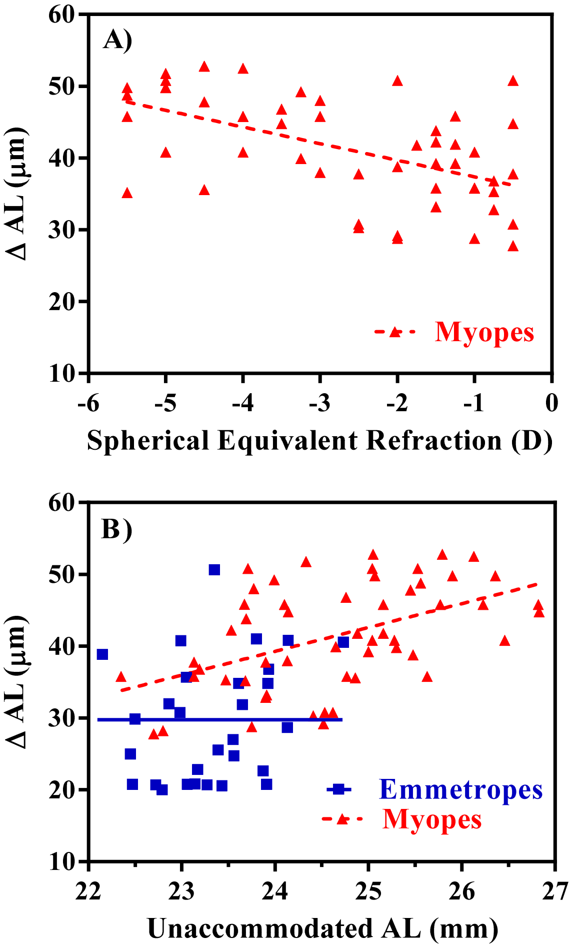


Figure 4.4: Correlation between the accommodation-induced change in axial length (ΔAL) and (A) spherical equivalent refraction along the optical axis for myopes (n = 54) and (B) the unaccommodated axial length of emmetropes and myopes. The linear regression in (A) is $y = -2.316x + 35.05$, $R^2 = 0.30$, $p < 0.001$. In (B) the linear regressions are $y = 3.688x - 56.37$, $R^2 = 0.07$, $p = 0.17$ for emmetropes and $y = 2.585x - 22.37$, $R^2 = 0.15$, $p = 0.004$ for myopes; as the slope for the former is not significant, the mean of 30 µm is plotted.

Table 4.4: Correlation between accommodation-induced changes in axial length and spherical equivalent refraction in emmetropes and myopes at different visual field positions.

Visual field position (°)	Slope (μm/D)	R^2	*p*-value
Emmetropes			
−30 T	5.36	0.02	0.444
−25 T	5.52	0.06	0.201
−20 T	10.19	0.09	0.112
−10 T	-5.98	0.04	0.284
−5 T	8.44	0.07	0.147
0 (centre)	2.13	0.02	0.396
5 N	0.66	0.02	0.424
10 N	10.66	0.08	0.118
15 N	7.74	0.05	0.239
20 N	-2.44	0.01	0.597
25 N	1.25	0.001	0.848
30 N	1.40	0.001	0.826
Myopes			
−30 T	-1.49	0.08	0.035
−25 T	-1.40	0.08	0.038
−20 T	-2.13	0.09	0.020
−10 T	-2.22	0.09	0.032
−5 T	-4.24	0.08	0.038
0 (centre)	-2.32	0.30	<0.001
5 N	-2.40	0.17	0.001
10 N	-2.42	0.20	0.001
15 N	-1.66	0.10	0.018
20 N	-1.29	0.08	0.037
25 N	-5.18	0.09	0.022
30 N	-3.10	0.08	0.042

T = temporal visual field, N = nasal visual field.

Table 4.5: Correlation between accommodation-induced changes in axial length and baseline axial length in emmetropes and myopes at different visual field positions.

Visual field position (°)	**Slope (μm/D)**	R^2	***p*-value**
Emmetropes			
−30 T	4.9	0.044	0.274
−25 T	1.59	0.003	0.716
−20 T	-4.39	0.05	0.266
−10 T	2.27	0.01	0.643
−5 T	-9.04	0.07	0.155
0 (centre)	3.41	0.02	0.377
5 N	-2.77	0.01	0.563
10 N	4.39	0.03	0.377
15 N	0.52	0.01	0.914
20 N	1.12	0.004	0.751
25 N	1.54	0.004	0.726
30 N	5.04	0.05	0.223
Myopes			
−30 T	2.76	0.08	0.041
−25 T	3.11	0.09	0.023
−20 T	2.98	0.09	0.023
−10 T	4.65	0.11	0.011
−5 T	3.79	0.15	0.004
0 (centre)	3.32	0.15	0.004
5 N	4.48	0.15	0.004
10 N	4.75	0.09	0.021
15 N	3.07	0.09	0.021
20 N	3.35	0.07	0.043
25 N	4.41	0.08	0.033
30 N	2.80	0.07	0.048

4.4 DISCUSSION

The aim was to determine the effect of accommodation and refractive error on peripheral eye length. The axial length during accommodation was corrected for Lenstar measurement error (the correction acts to reduce the effect of accommodation). A statistically significant increase in axial length with accommodation was observed at all eccentricities across the horizontal field meridian. Significant differences between refractive groups in the magnitude of the accommodation-induced axial elongation were observed at the fovea, with higher myopes elongated more than emmetropes. The axial length was elongated more in higher myopes than in emmetropes at 20° nasal field and more in higher myopes than in low myopes at 20° and 30° nasal fields (Table 4.3). Thus the data supported the hypothesis that the peripheral axial length, like the central axial length, increases with accommodation and that the increase is greater in myopes than emmetropes.

There were significant negative correlations between the changes in axial length along the horizontal meridian and the degree of myopia and the base-line axial length, i.e. the greater the myopia the greater axial length increase with accommodation. However, there were no significant correlations in emmetropes. These increases in axial length could provide the underlying reason for the association between near work and myopia. These small changes induced in the eye's periphery may also provide further evidence for the importance of the peripheral retina in myopia development.

The findings of this study, that accommodation results in axial length elongation are consistent with previous studies limited to on-axis (Drexler et al., 1998; Mallen et al., 2006; Read et al., 2010c; Suzuki et al., 2003; Woodman et al., 2012). However, the magnitude differs between studies. The mean axial length increase was 30 µm for the 6 D stimulus in emmetropic participants, which is substantially higher than 8 µm for a 6 D stimulus reported by Read et al. (2010c) and the 13 µm for a mean 5 D stimulus reported by Drexler et al. (1998). Similarly the mean increase in this study of 38 µm for myopes were much higher than 6 µm (Read et al., 2010c) and 5 µm (Drexler et al., 1998). In contrast, Mallen et al. (2006) reported greater increases of 37 µm and 58 µm for a 6 D stimulus in emmetropes and myopes, respectively, than in this study. After applying a correction, the data of Mallen et al. (2006) are similar to this study at 26 µm for emmetropes and 47 µm for myopes.

Read et al. (2010c) reported corrected values of axial length changes using measurements from the Lenstar instrument and the methods outlined by Atchison and Smith (2004) These corrections were "individualised", with a mean correction of 16.8 µm. Using our correction of 10.6 µm instead gives higher axial length changes of 15 µm and 13 µm for emmetropes and myopes, respectively, which are still considerably less than our mean changes of 30 µm and 38 µm, respectively.

The differences between myopes in the present study and the findings of Read et al. (2010c) may be related to the sample size of the populations, the amount of myopia and the age distribution of the participants. Read et al. (2010c) measured the axial length in 40 participants (aged 18 to 33 years, mean 25 ± 4 years), whereas this study examined the axial length during accommodation in 83 participants (aged from 18 to 25 years, mean 21.7 ± 2.3 years). The Read et al. study did not report the proportion of participants over 25 years. Read et al. used a subjective method (push-up test) to assess the amplitude of accommodation for the participants, but they measured the accommodation response for only five participants. Additionally, the myopic participants of Read et al. (2010c) showed substantially smaller myopia than myopic participants in the present study; the mean SER of myopes in the present study was −2.7 ± 1.6 DS compared with −1.8 ± 0.8 DS from Read et al. (2010c).

Drexler et al. (1998) used a custom PCI that used individual refractive index to measure corrected values of the axial length changes during accommodation and reported much smaller eye length elongation than the present study. A possible explanation for the differences in axial length change during accommodation between this study and Drexler et al.'s (1998) study is that Drexler et al. measured axial length at the near point for each participant and this led to different accommodative responses between the refractive groups (myopic participants accommodated 1.0 D less than emmetropic participants). The present study used the Badal system to correct the refractive errors of myopic participants and to provide equal levels of accommodation demand for all three refractive groups.

The underlying mechanisms causing the increase in axial length with accommodation are not well understood. It has been suggested that eye elongation during accommodation is due to the contraction of the ciliary smooth muscle decreasing the circumference of the sclera and choroid, causing axial elongation of the eye (Drexler et al., 1998; Mallen et al., 2006). The greater axial elongation observed in myopes could be due to the enlarged eye having being subject to greater biomechanical effects of the ciliary muscle contraction. The thickness of the ciliary muscles has been reported to be thicker in myopes than emmetropes (Buckhurst et al., 2013; Kuchem et al., 2013; Pucker et al., 2013), with the thickness related to the degree of myopia. These differences in ciliary muscle thickness could transmit greater mechanical force.

Ciliary muscle tendons have been found to be connected with the peripheral choroid in the rhesus monkey (Tamm et al., 1991) and the ciliary muscle contracting during accommodation leads to thinning of choroid. Croft et al. (2013) reported that substantial anterior movement of the peripheral choroid accompanying the inward and forward movement of the ciliary muscle in monkey eyes. If with accommodation the myopes had greater choroidal thinning than emmetropes, this could explain the observed difference in refractive groups. The higher myopes showed greater accommodation induced axial elongation on-axis and in the nasal field. This pattern could be cause by differences in choroidal thinning at different locations.

4.5 CONCLUSION

The axial length of the eye was measured with 0 D and 6 D of accommodation in different refractive groups along the horizontal visual field out to ±30°. Accommodation (6 D stimulus) induced axial length increases across this visual field. Increase in axial length was greater in myopes than emmetropes and was correlated with the degree of myopia. The findings provide evidence for the link between near work and axial length elongation of the eye. Over time the accommodation induced increase in axial length may lead to permanent axial elongation.

Chapter 5: Change in Peripheral Eye Length During an Extended Period of Accommodation in Emmetropes and Myopes

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ABSTRACT

Purpose: To investigate the time course of peripheral axial length elongation during and following an extended period of accommodation in young adult emmetropes and myopes.

Methods: Axial length was measured in 51 young, healthy, adult participants using the Lenstar LS 900 (Haag-Streit, Bern, Switzerland) at 0°, 20° nasal and 20° temporal visual field positions during an 8 min accommodation task (6 D demand) and then for the following 8 min with no accommodation (0 D demand). A Badal system was used to both correct refractive errors and induce accommodation. The measurements were made at the following time intervals: 45 s, 2 min, 4 min, 6 min and 8 min. Participants were classified as emmetropes (n = 23, spherical equivalent refraction mean ± standard deviation, 0.23 ± 0.37 D) and myopes (n = 28, −2.94 ± 1.52 D). Pupils were dilated with 2.5 % phenylephrine to allow a large field to be measured when maintaining active accommodation. Mean axial length was calculated at each location and demand from three measurements.

Results: There were axial length elongations at all three visual field positions immediately following the start of the accommodation session (6 D) which were sustained for the duration of the accommodation task. The elongations were greater for the myopes than for the emmetropes at the three locations ($p < 0.05$). For

emmetropes, the mean elongations ± SD were 26 ± 10 µm on-axis, 24 ± 9 µm at 20° temporal field and 23 ± 11 µm at 20° nasal field. For myopes, the corresponding elongations were 37 ± 9 µm, 35 ± 10 µm, and 36 ± 11 µm. The elongation decreased gradually following cessation of the accommodation task at all three locations for both refractive groups, but recovery was not complete after 8 minutes. The percentage rate recovery was similar for emmetropes and myopes in all positions.

Conclusions: The axial length was significantly greater in myopes than in emmetropes at all time intervals during accommodation at three positions. This may be due to differences in the biomechanical properties of the globe which are associated with the degree of myopia. The recovery after removing accommodation stimulus was not complete after 8 min for both groups.

5.1. INTRODUCTION

An association between near work and the development of myopia has been described in several studies (Jacobsen et al., 2008; McBrien and Adams, 1997; Morgan and Rose, 2013; Pan et al., 2011; You et al., 2014; Zadnik, 1997); although a few report only a weak association (Goldschmidt et al., 2001; Saw et al., 2000). This association may be related to the accommodation that occurs during near work (Chen et al., 2003; Fernandez-Montero et al., 2015; Goss, 2000; Ip et al., 2008). The mechanisms by which accommodation might lead to eye elongation are not well understood, prompting investigation of the relationship between on-axis axial length changes and accommodation (Drexler et al., 1998; Mallen et al., 2006; Read et al., 2010c; Woodman et al., 2012; Woodman et al., 2011).

Studies have reported different findings regarding the magnitude of axial elongation during accommodation (Drexler et al., 1998; Mallen et al., 2006; Read et al., 2010c; Woodman et al., 2012). Drexler et al. (1998) reported that the axial length change with accommodation (mean of 4 to 5 D demand) was greater for emmetropic participants than for myopic participants (13 µm vs 5 µm). Two studies reported that myopes had the greater axial length change with accommodation: 58 ± 37 µm for myopes vs 37 ± 27 µm for emmetropes at 6 D task (Mallen et al., 2006); 22 ± 34 µm for myopes vs 6 ± 22 µm for emmetropes at 4 D task (Woodman et al., 2012). Another study reported that the change in axial length during accommodation was similar between refractive groups: 6 µm for myopes vs 8 µm for emmetropes at 6 D task (Read et al., 2010c). There thus appears no consensus on whether the degree of axial elongation does or does not vary with refractive errors.

The study designs differ in terms of the duration of time spent performing the accommodation task and the timing of the measurements. Mallen et al. (2006) and Read et al. (2010c) examined the effect of accommodation on axial length by collecting data at a single time point during accommodation for twenty seconds of accommodation, and similarly Drexler et al. (1998) collected data at a single time point during accommodation but did not report the duration of the accommodation task. Woodman et al. (2011) investigated the effect of a much longer accommodation duration, 30 min, on the axial length of the eye, but took measurements immediately before and after, but not during, the accommodation task. Woodman et al. (2012) measured the on-axis axial length every five min during 30 min of 4 D demand accommodation. The length of time may play an important role in the magnitude of axial elongation associated with near work. However, this time may alter the accommodation response for the participant which may affect axial length measurements induced by accommodation. Understating how the length of the time cause changes in axial length with accommodation may explain different results in previous studies.

Another difference in study design and hence impact on the findings relates to errors in the axial length measurements during accommodation (Atchison and Smith, 2004). Atchison and Smith (2004) suggested that because of the biometric changes with accommodation, the measurement collected with these techniques (IOLMaster) during accommodation may overestimate the on-axis axial length of the eye.

The previous studies finding that the axial length of the eye increases during accommodation were limited to on-axis. This chapter aims to investigate the change and recovery in both on-axis and peripheral axial length of the eye due to accommodation.

The association between near work and myopia is thought to be due to accommodation induced on-axis retinal defocus since animal studies have shown that hyperopic defocus disrupt the process of emmetropisation and thus development of myopia (Goss, 2000; Hung and Ciuffreda, 2007; Ong and Ciuffreda, 1995). The peripheral retina is also influenced by optical defocus (reviewed in Wallman and Winawer (2004)). Smith et al. (2005) found that young rhesus monkeys with ring-shaped diffusing filters developed axial refractive errors despite central apertures allowing 37° of unrestricted central vision. Other study by the same groups (Smith et al., 2009) used negative lenses (hyperopic defocus) applied only to the periphery resulted in myopia. When hyperopic defocus was applied to selected parts of the visual field, myopic changes to the refraction and corresponding shape changes occurred only in the corresponding parts of the retina (Smith et al., 2010). Huang et al. (2011) found that foveal ablation did not alter both central and peripheral refraction out to ±45° along the horizontal meridian with form deprivation in rhesus monkeys. This could be because the peripheral retina has more neurons than the fovea and thus has a potential stronger defocus signal than the fovea (Wallman and Winawer, 2004). Wallman and Winawer (2004) indicated that optical defocus in the peripheral retina can affect myopia by stimulating the eye growth even if the centre of the eye is myopic.

Short periods of on-axis hyperopic defocus (negative lenses) or myopic defocus (positive lenses) produce changes in axial length (shortening axial length with myopic defocus or increasing axial length with hyperopic defocus) in humans

(Chiang et al., 2015; Read et al., 2010b). These data indicates that the human visual system is able to detect the defocus signal and altering the retinal position.

The aim of this chapter is to investigate changes in axial length along the horizontal visual field during and after an 8 minute accommodation task in healthy young emmetropic and myopic adults. The hypothesis was that peripheral axial length will increase with an extended period of accommodation like central axial length will increase (similar to some of the previous studies observations) and that the increase will be greater in myopes than emmetropes.

5.2 MATERIALS AND METHODS

The axial length was measured at 0°, 20° nasal and 20° temporal visual field when the eye was unaccommodated (0 D accommodation demand) and accommodated (6 D accommodation stimulus). Young adult participants (both emmetropes and myopes) with good accommodation were recruited. The project followed the Tenets of the Declaration of Helsinki and was approved by the Queensland University of Technology Human Research Ethics Committee. Written informed consent was obtained from all participants.

5.2.1 Participants

Fifty-one healthy young adults participated; these included 40 of the 83 participants recruited for the first experiment (Chapter 4) and an additional 11 participants recruited from the student population of the Queensland University of Technology.

All participants underwent the comprehensive ophthalmic examination described in Chapter 3. Refractive errors were measured using a Shin-Nippon-SRW-5000 autorefractor (Grand-Seiko, Osaka, Japan). Based on the mean spherical equivalent refraction (SER), the participants were classified as emmetropes (+1.00 to −0.25 D) or myopes (≤ −0.50 D). The mean SER ± SD was +0.23 ± 0.37 D for emmetropes and −2.94 ± 1.52 D for myopes. Participants with refractive errors greater than −5.50 D were excluded from the study due to the limitations of the +13 D Badal system.

Accommodation responses were assessed using a COAS-HD Hartmann–Shack aberrometer. The mean accommodative response for the 6 D accommodation demand was 5.54 ± 0.34 D for emmetropes and 5.18 ± 0.51 D for myopes. This difference was statistically significant (*p* = 0.004). Many studies have shown that myopes tend to have poorer accommodation response at near than emmetropes, particularly for accommodation induced using negative lenses (Chen et al., 2003). Measurement of the accommodation response 60 min after instillation of phenylephrine 2.5% was 5.53 ± 0.33 D for emmetropes and 5.16 ± 0.51 D for myopes. The phenylephrine 2.5% dose had no significant effect on the accommodation response (*p* = 0.12 for emmetropes and *p* = 0.20 for myopes).

The emmetropes consisted of 15 males and 8 females, and the myopes consisted of 13 males and 15 females. The mean ages of the emmetropic and myopic participants were similar (emmetropes 21.9 ± 2.5 years and myopes 22.3 ± 2.0 years). The racial background of participants were Caucasian (11 emmetropes and 15 myopes), East Asian (9 emmetropes and 12 myopes) and Indian (3 emmetropes and 2 myopes).

5.2.2 Procedure

As in Experiment 1 (Chapter 4), the Lenstar LS 900 was used with the external attachment, but with the fixation target replaced by a white organic light-emitting diode microdisplay (eMagin Corporation, New York, USA; screen resolution 800 × 600 pixel with luminance ~21 cd/m^2) connected to a computer. The previous studies have shown that the Lenstar LS 900 provides accurate ocular biometric measurements that are comparable with other biometers such as the IOLMaster (Verkicharla et al., 2013; Shammas and Hoffer, 2012; Cruysberg et al., 2010; Buckhurst et al., 2009; Rohrer et al., 2009).

After dilating the pupil with a drop of phenylephrine 2.5%, the axial length for the right eye was measured at 0°, 20° nasal and 20° temporal along the horizontal meridian of the visual field under 0 D and 6 D of accommodation demand. To eliminate convergence effects (Bayramlar et al., 1999; Pärssinen et al., 1989), the left eye was occluded.

The participants were asked to look at the video through the Badal system and to keep it clear at all times (both during measurements and between measurements). To reduce any systematic error, the order in which the measurements were conducted was pseudo-randomised between participants. One-third of participants had the measures taken in each of the following orders: i) 0°, 20° nasal, 20° temporal; ii) 20° nasal, 20° temporal, 0°; and iii) 20° temporal, 0°, 20° nasal (i.e. first participant for order I, second participant for order ii and the third participant for the order iii, and so on).

Baseline measurements were made at the selected location under the 0 D accommodation demand. The accommodation demand was increased to 6 D and measurements were made at that location at the following time intervals: 45 s, 2 min, 4 min, 6 min and 8 min. As it takes approximately 45 s to complete three measurements, measurements commenced 45 s before the indicated time (therefore, the time indicated is the end point of the measurement period). The accommodation demand was reduced to 0 D at the end of 8 min and measurements were made at the further time intervals: 45 s, 2 min, 4 min, 6 min and 8 min. After completion of a location run, participants had a 5 min break before the next location run commenced.

5.3 DATA ANALYSIS

Axial length errors due to changes in the crystalline lens thickness during accommodation at the three visual field angles were corrected using the methods described in Chapter 2 and Section 3.4.3. The SPSS statistical software (Version 21, SPSS Incorporated, IBM Company, Chicago, USA) was used to perform one way ANOVA to compare axial lengths between groups (emmetropes and myopes) at baseline, separately for each position. One way ANOVAs were also conducted to compare changes in axial length (relative to baseline) at each point of time and visual field position combination. To investigate the changes (relative to baseline) over time in the axial length of the eye with accommodation between refractive groups, two-way ANOVAs were performed, with time as a within-subject factor and refractive group (emmetropes and myopes) as the between-subject factor for each visual position. All at these ANOVAs were completed for 6 D accommodation and for 0 D accommodation demands separately. Linear regression was used to estimate the correlation between axial length change and spherical equivalent refraction for three positions. The significance level was set to $p < 0.05$.

5.4 RESULTS

There were statistically significant differences in baseline axial length between the refractive groups for all three positions, with myopic participants exhibiting longer axial lengths (emmetropes: on axis 23.7 ± 0.8 mm, 20° temporal 23.5 ± 0.7 mm, 20° nasal 23.5 ± 0.8 mm; myopes: on axis 24.8 ± 1.2 mm, 20° temporal 24.4 ± 1.0 mm, 20° nasal 24.4 ± 1.1 mm; $p < 0.001$, ANOVA).

Figure 5.1a–c shows the mean changes in the axial length from the baseline measurement at the three visual field positions. For 6 D accommodation, the ANOVA showed no significant effect of time on on-axial length for both refractive groups at all three positions ($p = 0.67$). By 45 s, the axial length had increased by 26 ± 21 µm and 38 ± 14 µm for emmetropes and myopes, respectively ($p < 0.001$), and remained elongated at all points of time.

A similar pattern was observed in the periphery by 45 s, with the axial length increasing significantly at 20° nasal by 23 ± 15 µm for emmetropes and by 36 ± 7 µm for myopes, and significantly increasing at 20° temporal by 24 ± 16 µm for emmetropes and by 37 ± 8 µm for myopes compared with the baseline ($p < 0.001$). At all points in time during accommodation, the axial length for both angles remained elongated compared with baseline for both groups ($p < 0.05$).

There was a significant effect of refractive group for the change in axial length during accommodation at all three angles between myopes and emmetropes. Across all time points, the axial elongation during accommodation for myopes (mean ± SD, 37 ± 9 µm at 0°, 35 ± 10 µm at 20° temporal and, 36 ± 11µm at 20° nasal) was greater than the elongation for emmetropes (26 ± 10 µm at 0°, 24 ± 9 µm at 20° temporal and 23 ± 11 µm at 20° nasal).

Figure 5.2a-c shows the recovery of axial length by percentage over time measurement at the three visual field positions. A statistically significant effect of time on axial length was observed at all three positions ($p < 0.001$) (Figure 5.1). The recovery was slow and not quite complete after 8 minutes on axis (mean ± SD, 3 ± 1 µm for emmetropes; 4 ± 1 µm for myopes), at 20° temporal (mean ± SD, 4 ± 1 µm for emmetropes; 7 ± 1 µm for myopes), and at 20° nasal (mean ± SD, 4 ± 1 µm for emmetropes; 6 ± 1 µm for myopes). The recovery was similar for emmetropes and myopes in terms of percentage of the maximum elongations at all positions (Figure 5.2).

Figure 5.3a–c and Figure 5.4 a-c show the correlations of accommodation induced change in axial length with spherical equivalent and with baseline axial length were significant for the three positions in myopes. There were no correlations at any positions in emmetropes (Figure 5.5 a-c).

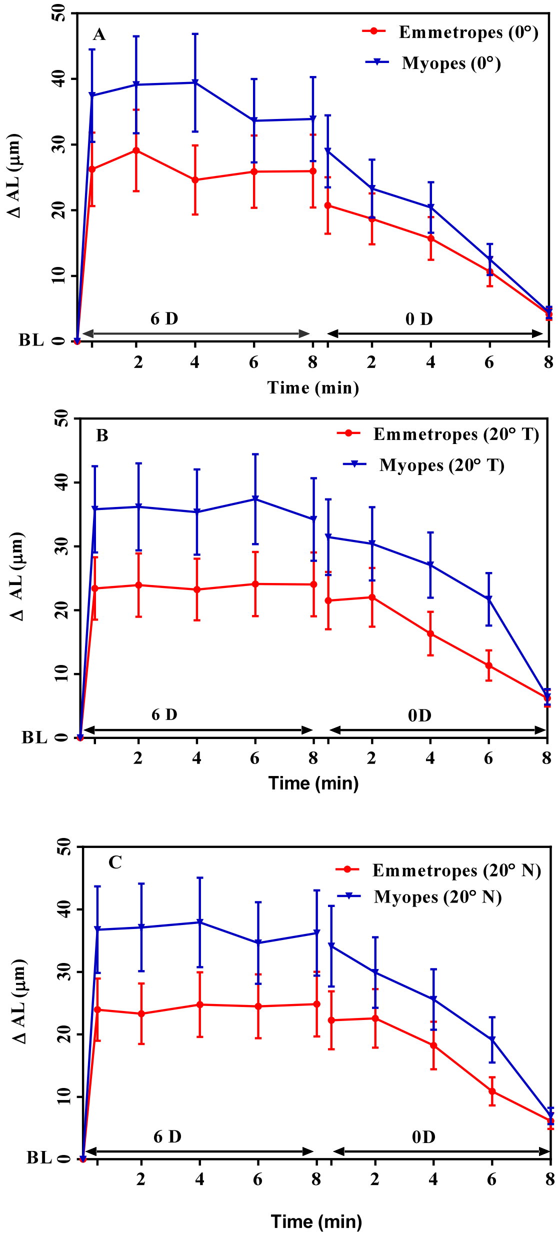

Figure 5.1: Mean change in axial length (ΔAL) over time from the baseline at 6 D and 0 D accommodation demand for emmetropes and myopes at (A) 0°, (B) 20° temporal field and (C) 20° nasal visual field. The error bars represent the standard errors of means.

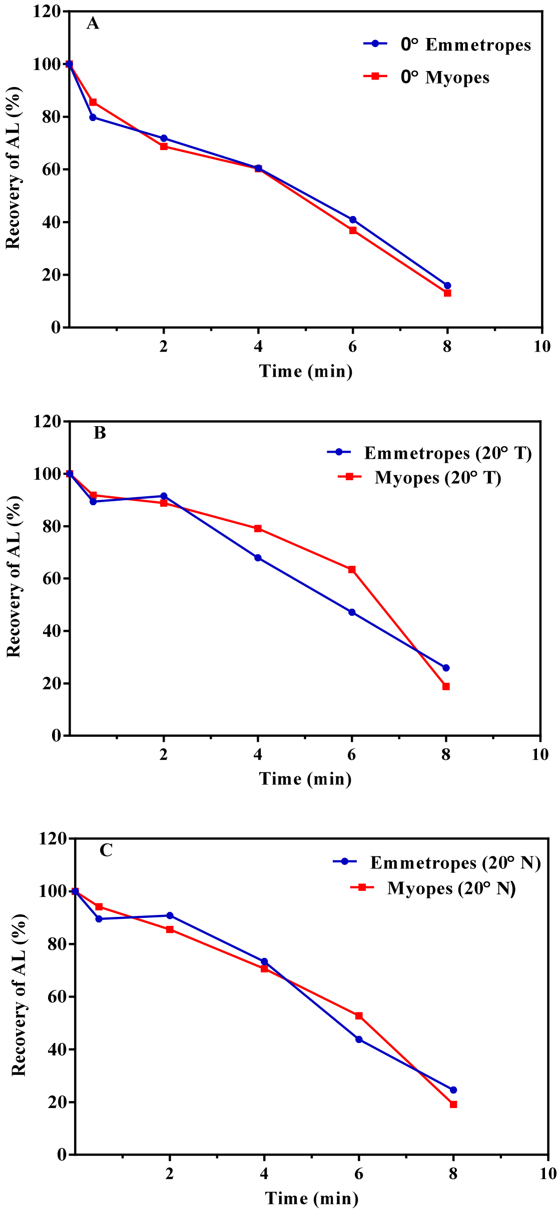

Figure: 5.2: The recovery of axial length (AL) to baseline by percentage over time (% = the average of each time point at 0 D for each participants divided by the average of the last time point (8 min) at 6 D X 100) at three visual field positions for (A) central, (B) 20° temporal and (C) 20° nasal visual field.

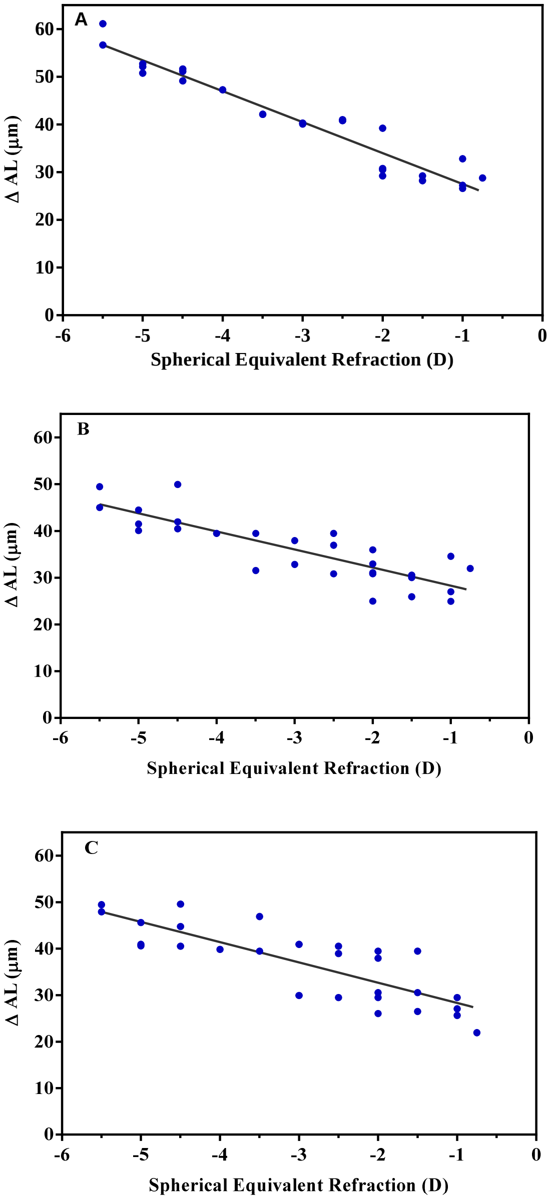

Figure 5.3: Correlation between spherical equivalent refraction and changes in axial length (ΔAL) at 45 s in myopes at (A) 0°, (B) 20° temporal and (C) 20° nasal visual field. The linear regression lines and correlation coefficients are: $y = -6.49x + 21.03$, $R^2 = 0.93$, $p < 0.001$ for 0°; $y = -3.861x + 24.44$, $R^2 = 0.72$, $p < 0.001$ for 20° temporal; and $y = -4.36x + 23.97$, $R^2 = 0.67$, $p < 0.001$ for 20° nasal.

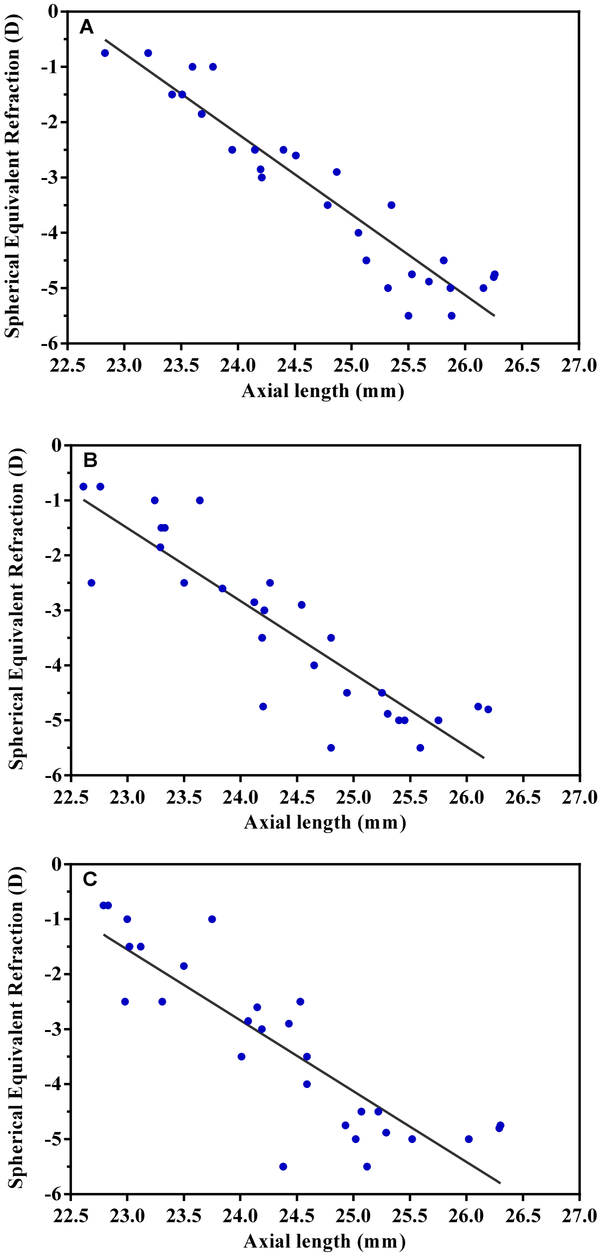

Figure 5.4: Correlation between baseline axial length (at 0s) and spherical equivalent refraction in myopes at (A) 0°, (B) 20° temporal and (C) 20° nasal visual field. The linear regression lines and correlation coefficients are: $y = -1.45x + 32.73$, $R^2 = 0.90$, $p < 0.001$ for 0°; $y = -1.33x + 28.98$, $R^2 = 0.78$, $p < 0.001$ for 20° temporal; and $y = -1.29x + 28.09$, $R^2 = 0.75$, $p < 0.001$ for 20° nasal.

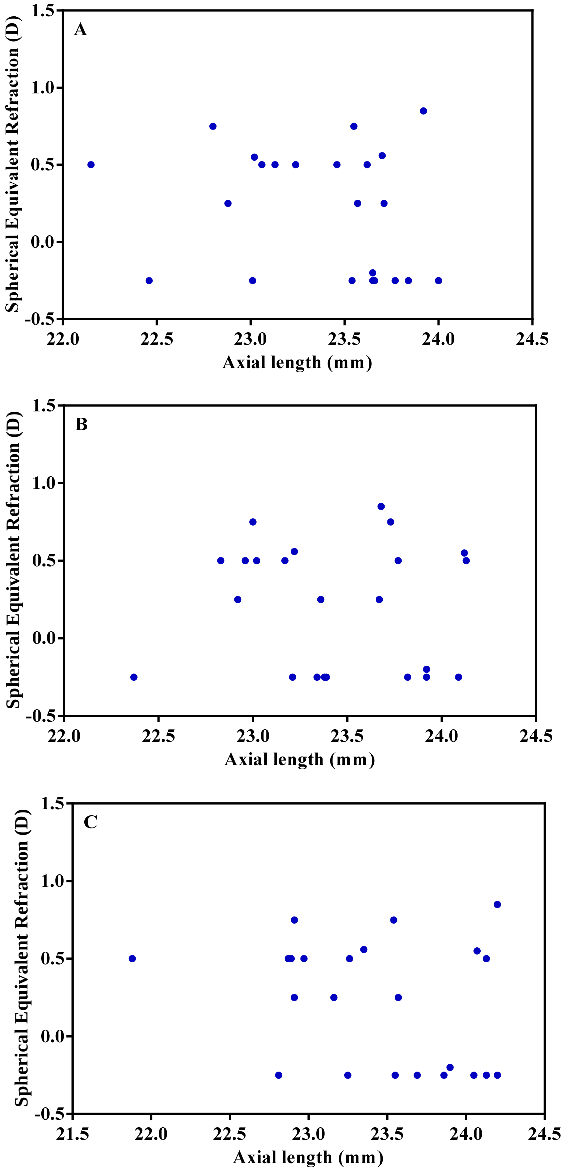

Figure 5.5: Correlation between baseline axial length and spherical equivalent refraction in emmetropes at (A) 0°, (B) 20° temporal and (C) 20° nasal visual field. The linear regression lines and correlation coefficients are: $y = -0.174x + 4.278$, $R^2 = 0.04$, $p = 0.35$ for 0°; $y = -0.042x + 1.205$, $R^2 = 0.002$, $p = 0.82$ for 20° temporal; and $y = -0.189x + 4.67$, $R^2 = 0.078$, $p = 0.19$ for 20° nasal. As the slopes are not significant, the regressions have not been plotted.

5.5 DISCUSSION

This study aimed to investigate the changes in axial length along the horizontal visual field during and after an accommodation task in young adult emmetropes and myopes. The hypothesis was that the axial length would increase during accommodation but the magnitude and/or timing and/or decay may differ in myopes and emmetropes.

Six dioptres of accommodation demand induced significant axial length elongation within 45 s at all three visual field angles and for both refractive groups. The axial length remained elongated for the 8 minutes for which the stimulus was presented, with myopes exhibited significantly greater elongation than emmetropes. The axial elongation decreased steadily following the cessation of the high accommodation demand but had not reached baseline after 8 min. The recovery was similar for both groups in terms of percentage of the maximum elongations at all positions.

The accommodation response was greater for emmetropes than myopes (about 0.36 D, $p = 0.04$); this cannot explain the differences in axial length elongation between groups as it works in the opposite direction.

The finding of this study that on-axis axial length elongates with accommodation is consistent with previous studies (Drexler et al., 1998; Mallen et al., 2006; Read et al., 2010c; Woodman et al., 2012; Woodman et al., 2011) and support the findings in chapter 4 regarding accommodation induced elongation in peripheral axial length.

As this study is cross-sectional and not longitudinal, it is not known whether the refractive group differences in the degree and time course of the axial elongation observed with accommodation are related to the cause of the myopia or are a consequence of the myopia. It is possible that near work at short distances (with high accommodation demands) would induce a large magnitude of axial elongation both on-axis and in the eye's periphery, which may lead to the development of myopia. On the other hand the differences may be due to changes in the eye's anatomy that occur after the development of myopia and are related to the degree of myopia (see the correlation graphs).

NITM is the hysteresis of accommodation that is measured after a period of sustained near work, i.e. the eye remains myopic for a period of time after the near work is ceased. The axial elongation seen in refractive group after task cessation could account for very low levels of NITM. The time is usually longer in myopes than in emmetropes, presumably due to a delay in relaxation of accommodation (Ong and Ciuffreda, 1995; Vasudevan and Ciuffreda, 2008; Wolffsohn et al., 2011). Although the increase in AL is too small to account for any of this initial slowness to recover, sometimes the eye remains slightly myopic; the average difference between the pre- and post-task distance refraction is 0.12 D in myopes and 0.09 D in emmetropes (Ciuffreda and Lee, 2002; Ciuffreda and Wallis, 1998). This change is small proportion and remains within the eye's depth of focus; hence the individual is asymptomatic. The average AL increase observed here of 40 µm would equate to approximately a 0.12 D myopic shift (40/1000 x 3D; using the approximation that a 1 mm increase in AL results in 3 D of myopia).

There are a number of possible mechanisms by which accommodation could induce axial length elongation. One of these mechanisms is that ciliary muscle tendons have been found to be connected with the peripheral choroid in the rhesus monkey (Tamm et al., 1991) and this may allow ciliary muscle contraction during accommodation which leads to thinning of the choroid. The experiment in Chapter 6 found that the choroid becomes thin with accommodation along the horizontal meridian of the visual field, and this change in the choroidal thickness is significantly negatively correlated with changes in the axial length. The thinning of the choroid during accommodation decreases with increased eccentricity. The results of this study predicted that the accommodation might induced thinning in the choroid very fast (within 45 s) which result in changes in axial length, but takes longer than 8 min for recovery, indicating that the force of ciliary muscle contraction influence of choroidal thickness mechanically since the animal studies have shown ciliary muscle tendons connect with the anterior choroid (Tamm et al., 1991). This experiment therefore supports the hypothesis of the previous studies (Drexler et al., 1998; Mallen et al., 2006) that the role of accommodation in development of myopia is of a mechanical origin.

The second possible mechanical mechanism arises from a number of studies that have hypothesised that eye elongation during accommodation is due to contraction of the ciliary smooth muscle decreasing the circumference of the sclera (Drexler et al., 1998; Mallen et al., 2006). Both animal and human studies have demonstrated that the sclera changes the eye’s shape in response to accommodation to ensure stable refraction of the eye (Croft et al., 2013; Harper and Summers, 2015). This mechanism is likely given that the sclera moves forward and backward due to contraction of the ciliary muscles, which cause overall elongation of the eye. Given that the thickness of sclera in myopic eyes is thinner and weaker after development of myopia (Elsheikh et al., 2010; Norman et al., 2010; Vurgese et al., 2012), the sclera thickness might respond differently to accommodation leading to differences in axial length between myopes and emmetropes. These changes in sclera thickness due to a high level of accommodation may cause long-term permanent stretching in the thickness of sclera in myopic eyes. It is possible that this greater elongation observed in myopic participants in this study might relate to changes in ocular rigidity (McBrien and Gentle, 2003). These weaknesses in the posterior pole allow the force of ciliary muscle contraction to be more effectively transmitted to sclera and choroid in these participants leading to increasing changes in axial length. Further studies are required to measure the scleral thickness and to investigate the effect of accommodation on sclera.

A third potential mechanism is the effect of optical defocus on the periphery. Animal studies have shown that introducing hyperopic defocus causes a thinning of the choroid, whereas myopic defocus causes a thickening of the choroid which resulted in alteration in axial length in response to the choroidal direction (Nickla and Wallman, 2010; Wildsoet and Wallman, 1995). Read et al. (2010) have also found changes in choroidal thickness in response to short duration defocus in human participants. Therefore, changes in the characteristics of the eye during accommodation may lead to defocus along the horizontal meridian, for example, due to increased lag of accommodation which could result in changes in the choroid thickness and hence an increase in axial length associated with near work. However, because the participants in this study were young healthy adults with robust accommodation, the changes in axial length due to a lag of accommodation are unlikely.

5.6 CONCLUSION

This study confirms the findings in Chapter 4 that the axial length along the horizontal meridian of the visual field increases with accommodation. The elongations were greater for the myopes than for the emmetropes at the three locations and remained for the entire 8 min response duration. It lessens following the cessation of accommodation, but is not quite complete after 8 min. Recovery was similar for both groups in terms of percentage of the maximum elongations at all positions.

Chapter 6: Peripheral Choroidal Thickness Changes with Accommodation in Emmetropic and Myopic Eyes

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ABSTRACT

Purpose: To investigate peripheral choroidal thickness profile changes along the horizontal field meridian during accommodation in young adult emmetropes and myopes.

Methods: Central and peripheral choroidal thickness was measured with the Optical Coherence Tomographer RS-3000 Advance in 69 young adult participants out to ±35° along the horizontal visual field meridian for 0 D and 6 D accommodation demands. Participants were classified as emmetropes (n = 24, spherical equivalent refraction mean ± standard deviation +0.28 ± 0.34 D), low myopes (n = 23, −1.34 ± 0.87 D) and higher myopes (n = 22, −4.47 ± 0.78 D). Pupils were dilated with 2.5% phenylephrine to allow a large field to be measured when maintaining active accommodation. Accommodation induced changes in choroidal thickness and axial length (see chapter 4) were compared.

Results: Choroidal thickness was greatest at the fovea, with reduction in thickness with increasing eccentricity for all three refractive groups. For both the unaccommodated and accommodated states, refractive group affected choroidal thickness significantly at most angles. For the 22 out of 28 accommodation/visual field combinations at which significance occurred, emmetropes and low myopes had significantly thicker choroids than the higher myopes for 21 and 11 combinations,

respectively. Choroids thinned with accommodation, with the amount of thinning decreasing away from the fovea. There were only two positions at which this thinning was affected significantly by refractive group, at the fovea where the higher myopes thinned more than the emmetropes (mean ± SE: 9.0 ± 2.4 µm) and at 30° temporal where the emmetropes thinned more than low myopes (4.6 ± 1.8 µm) and higher myopes (7.1 ±1.9 µm).

There were significant negative correlations between accommodation-induced changes in choroidal thickness and axial eye length for all refractive groups at all eccentricities. Changes in axial length were –45% to –165% of the changes in choroidal thickness across the field (mean ± SD: –83 ± 29%).

Conclusions: Across the horizontal visual field meridian to at least ±35°, young adult myopes had thinner choroids than young adult emmetropes and there was choroidal thinning in response to accommodation. Changes in the choroidal thickness were responsible for most of the accommodation-induced changes in axial length.

6.1 INTRODUCTION

There is considerable evidence that changes in choroidal structure are attributable to development of refractive error (Ho et al., 2013; Tan et al., 2014; Wei et al., 2012). In higher myopia, excessive axial elongation leads to visual complications such as choroidal neovascularisation, retinal detachment, glaucoma and cataracts (Lim et al., 2009; Saw et al., 2005). As found in Chapters 4 and 5, accommodation caused increases in axial length of the eye across the horizontal meridian. Since the axial length is estimated as the distance from the anterior surface of the cornea to the retinal pigment epithelium, it is possible that changes in axial length could be due to changes in choroidal thickness. The effect of accommodation on peripheral choroidal thickness has not been investigated previously.

Evidence from avian (Irving et al., 1992; Priolo et al., 2000) and primate (Hung et al., 1995; Smith et al., 2010) models shows that eye growth development can be modulated in response to optical defocus. Defocus can cause change in choroidal thickness (Hung et al., 2000; Wallman et al., 1995): positive lenses cause choroidal thickening and forward movement of the retina, whereas negative lenses cause choroidal thinning and backward movement of the retina. During optical defocus, there is also significant disruption to the natural diurnal rhythms that occur in axial length and choroidal thickness in chicks (Nickla, 2006), marmosets (Nickla et al., 2002), and primates (Troilo et al., 2000). The choroid is thought to regulate sclera growth by delivering a signal to the sclera in response to visual stimuli (Summers, 2013). For example, studies on both chicks and mammals demonstrated changes in protegoglycan synthesis, collagen synthesis, and extracellular matrix constituents in response to visual stimuli leading to remodelling of sclera (Nickla et al., 1997; Rada et al., 2000; 1999).

On-axis choroidal thickness changes in response to defocus have also been observed in young adults using partial coherence interferometry with significant thinning in response to hyperopic defocus (Chakraborty et al., 2013; Read et al., 2010b). These data suggest that continued hyperopic defocus during accommodation could lead to changes in the choroid.

Woodman et al. (2012) investigated the effect of accommodation on on-axis choroidal thickness in 59 healthy young participants (22 emmetropes and 37 myopes) using the Lenstar LS 900. Due to the poor signal quality of the A-scans from the choroidal–sclera interface, only 27 participants had valid choroidal data. During accommodation, choroidal thickness thinned by 7 ± 22 µm in emmetropes and by 9 ± 18 µm in myopes. This suggests that the choroid plays an important role in development of refractive status.

In recent years, several studies have used non-invasive Spectral domain optical coherence tomography (SD-OCT) techniques for imaging and measuring the retinal pigment epithelium and choroidal thicknesses (Li et al., 2014; Manjunath et al., 2010; Song et al., 2014; Tuncer et al., 2014). SD-OCT produces high-resolution images in people of all ages (Ikuno et al., 2010a; Manjunath et al., 2010; Tuncer et al., 2014). The good repeatability of choroidal thickness measurements has been demonstrated by several studies (Rahman et al., 2011; Spaide et al., 2008; Vujosevic et al., 2012; Yamashita et al., 2012). SD-OCT is the current optimal technique for imaging and measuring choroidal thickness and for providing a better understanding of the choroid response during accommodation.

The aim of this study was to investigate peripheral choroidal thickness profile changes during accommodation in emmetropic and myopic eyes. The Optical Coherence Tomography RS-3000 Advance (Nidek, Gamagori, Japan) was used to measure both on-axis and peripheiral choroidal thickness for 0 D and 6 D accommodation demands along the horizontal field. The hypothesis to be used is that peripheral choroidal thickness will thin during accommodation and this thinning will be greater in myopes than in emmetropes (as has been found centrally). This study may provide a better understanding of the underlying mechanisms that contribute to the development of myopia that is associated with near work.

6.2 MATERIALS AND METHODS

This research project followed the Tenets of the Declaration of Helsinki and was approved by the Queensland University of Technology, Human Research Ethics Committee. Written informed consent was obtained from all participants before taking measurements.

6.2.1 Choroidal thickness measurement – OCT image acquisition

The Optical Coherence Tomography RS-3000 Advance (Nidek, Gamagori, Japan) was used to measure choroidal thickness. It uses an 880 nm wavelength source with a scanning speed of 53,000 A-scans/second to provide cross-sectional posterior images of the eye at an axial resolution of 7 µm (Dag et al., 2013; Vujosevic et al., 2012).

Phenylephrine (2.5%, Chauvin Pharmaceuticals Ltd., UK) was used to dilate pupils. It has been shown that the 2.5% phenylephrine does not affect choroidal thickness (Bajenova et al., 2012; Sander et al., 2014). After dilating the pupil with one drop of phenylephrine, the choroidal thickness of the right eye was measured while the left eye was occluded by an eye patch. The participants were aligned to the instrument and instructed to focus on an internal cross target. The system was configured to take the image along the horizontal macula line. The scan pattern was a 12 mm line consisting of 1024 A-scans to measure the choroidal thickness with high definition 50 frame enhancement software to visualize the choroidal-sclera border. To obtain cross-sectional images of choroidal thickness horizontally participants were instructed to fixate the internal target. To obtain horizontal peripheral images, the internal target was moved to 17.25° from the centre to nasal/temporal positions (section 3.5). Refractive errors were corrected with the internal system of the OCT. After taking images with each participant in a relaxed state, the accommodative stimulus (6 D) was presented using the internal system. Three images were taken at each location for both accommodation levels and means were calculated using the OCT NAVIS-EX Software.

Given the variability in the axial length of the eyes among the participants, the actual transverse length for each participant varied. To achieve actual transversal resolution, the OCT NAVIS-EX software provides functions for measuring the actual scan length after taking the images by entering the real axial length and the refractive error in the input data dialog box for each participant (see section 3.5 for more detail). The OCT instrument converts the acquired image from field angle into a distance, taking into account the axial length of the eye. The formula used to convert is not given. The inbuilt software offers a ruler tool where distances can be measured on the retina in micrometres. To convert back into field angles, an approximation of 1° = 300 μm was used in this experiment. To quantify the error in choroidal thickness due to this approximation, two measurement of choroidal thickness where acquired at the extremes of axial length (22 – 26 mm), at the furthest point in the field where the approximation would yield maximum error. The choroid was 1.7% thinner with 22 mm than with 26 mm axial lengths. In addition, since the approximation under-estimates the angle, it over-estimates the choroidal thickness; its effect on correlations with change in axial length, if any, is reducing them. Therefore, this approximation is reasonable.

6.2.2 Participants

The study used data from 71 out of the 83 participants recruited for the experiment described in Chapter 4. As choroidal thinning is associated with cigarette smoking all participants were non-cigarette smokers (Sizmaz et al., 2013). Participants were aged between 18 to 25 years (mean ± SD, 21.4 ± 2.1 years). Two participants data were excluded due to poor OCT image resolution. The remaining 69 participants were deemed suitable for the project.

Refraction was measured using a Shin-Nippon SRW-5000 autorefractor (Grand-Seiko, Osaka, Japan). Based on the mean spherical equivalent refraction (SER), participants were classified as emmetropes (n = 24, SER 1.00 to −0.25 D), low myopes (n= 23, SER −0.50 D to −3.00 D) and higher myopes (n = 22, SER < −3.00 D). The mean ± SD SER was + 0.28 ± 0.34 D for emmetropes, −1.34 ± 0.87 D for low myopes and −4.47 ± 0.78 D for higher myopes.

Accommodation responses were assessed using a COAS-HD Hartmann–Shack aberrometer. The mean accommodation response for the 6 D accommodation demand was 5.6 ± 0.4 D for emmetropes, 5.4 ± 0.8 D for low myopes and 5.2 ± 0.6 D for higher myopes. There was no significant difference in accommodation response between refractive groups (ANOVA, $p = 0.14$). All participants had good accommodation responses.

Results for axial length as given in Chapter 4 are used for comparison with choroidal thickness.

6.3 DATA ANALYSIS

To examine choroidal thickness across the horizontal meridian, one-way ANOVAs for choroidal thickness were conducted at each visual field position with refractive group (emmetropes, low myopes and higher myopes) as the between-subject factor. These ANOVAs were done for 0 D accommodation, for 6 D accommodation, and for the differences at the two accommodation levels. Where refractive group was a significant factor in choroidal thickness, post hoc pair-wise comparisons were made with *t*-tests incorporating a Bonferroni correction.

Linear regressions of accommodation-induced changes in axial length with changes in choroidal thickness were conducted. Axial length measurements were restricted to within ±30° because the edge of the pupil blocked the beam of the Lenstar LS 900 at 35°.

6.4 RESULTS

Table 6.1 and Figure 6.1a-c show choroidal thickness along the horizontal field for different visual field positions for the three refractive groups at the unaccommodated and accommodated states. Table 6.2 and Figure 6.2 show changes in choroidal thickness that occurred with changes in accommodation at all visual peripheral locations. Figure 6.2 shows also the changes in axial length with change in accommodation.

Choroidal thickness was greatest at the fovea, with reduction in thickness with increasing eccentricity for all three refractive groups e.g. for the emmetropic group in the unaccommodated state, thickness decreased from 279 ± 48 μm (mean ± SD) at the fovea to 205 ± 48 μm at 35° nasal. For both the unaccommodated and accommodated states, refractive group affected choroidal thickness significantly at most angles – as a comparison to the emmetropic results just given, higher myopes had choroids thinner by 41 and 26 μm at the fovea and 35° nasal, respectively (Table 6.1). There were 22 out of 28 accommodation/visual field combinations at which refractive group affected thickness significantly, and of these emmetropes and low myopes had significantly thicker choroids than the higher myopes for 21 and 11 combinations, respectively (Table 6.1).

Choroids thinned with accommodation, with the amount of thinning decreasing away from the fovea (Table 6.2, Figure 6.2). There were only two positions at which this thinning was affected significantly by refractive group: at the fovea where the higher myopes thinned more than the emmetropes (mean ± SE: 9.0 ± 2.4 μm) and at 30° temporal where the emmetropes thinned more than low myopes (4.6 ±1.8 μm) and higher myopes (7.1 ±1.9 μm).

Table 6.3 show accommodation-induced changes in axial length as a function of changes in choroidal thickness. There are statistically significant correlations for all combinations of refractive group and visual position, with changes in axial length explained by changes in choroidal thickness varying between

17% and 37% and slopes varying between –0.45 and –1.66 (mean slope –0.83 ± 0.29). Figure 6.3 shows results on-axis (emmetropes R^2 = 0.29, p = 0.006; low myopes R^2 = 0.35, p = 0.003; higher myopes R^2 = 0.37, p = 0.003), Figure 6.4 shows results for 20° nasal (emmetropes R^2 = 0.18, p = 0.037; low myopes R^2 = 0.19, p = 0.041 for low myopes; higher myopes R^2 = 21, p = 0.032 for higher myopes) and Figure 6.5 shows results for 20° temporal (emmetropes R^2 = 0.23, p = 0.017; low myopes R^2 = 0.20, p = 0.031; higher myopes R^2 = 20, p = 0.036).

Table 6.4 show correlations between the accommodation-induced choroidal thickness measurements and spherical equivalent refraction at the visual field positions in emmetropes and all myopic groups. There was no significant correlation between choroidal thickness and spherical equivalent refraction at any position in the emmetropic group. There was significant correlation in myopic groups up to ±20°, with the highest correlation on-axis (R^2 = 0.15, p < 0.006) (Figure 6.6).

Table 6.1: Choroidal thickness (µm) in the unaccommodated and accommodated states for the three refractive groups

Visual field positions (°)	Emmetropes	Low myopes	Higher myopes	*p* value	Group differences	*p*-value (Bonferroni)
Unaccommodated state						
−35 T	211±59	207±37	179±45	0.058		
−30 T	219±78	221±39	182±50	**0.047**	Higher M vs Emm	0.100
					Higher M vs Low M	0.088
					Emm vs Low M	1.00
−25 T	224±32	223±44	189±41	**0.005**	Higher M vs Emm	**0.013**
					Higher M vs Low M	**0.016**
					Emm vs Low M	1.00
−20 T	226±50	232±50	198±46	**0.049**	Higher M vs Emm	0.158
					Higher M vs Low M	0.065
					Emm vs Low M	1.00
−10 T	248±46	247±41	213±51	**0.020**	Higher M vs Emm	**0.036**
					Higher M vs Low M	0..051
					Emm vs Low M	1.00
−5 T	271±52	255±60	219±53	**0.008**	Higher M vs Emm	**0.007**
					Higher M vs Low M	0.105
					Emm vs Low M	0.966
0 (Centre)	279±48	268±64	238±55	**0.048**	Higher M vs Emm	0.051
					Higher M vs Low M	0.247
					Emm vs Low M	1.00
5 N	266±62	265±46	223±40	**0.008**	Higher M vs Emm	**0.021**
					Higher M vs Low M	**0.020**
					Emm vs Low M	1.00
10 N	263±47	253±20	218±54	**0.002**	Higher M vs Emm	**0.002**
					Higher M vs Low M	**0.020**
					Emm vs Low M	1.00

15 N	255±46	241±23	207±37	**<0.001**	Higher M vs Emm Higher M vs Low M Emm vs Low M	**<0.001** **0.007** 0.644
20 N	245±44	233±35	203±43	**0.003**	Higher M vs Emm Higher M vs Low M Emm vs Low M	**0.002** **0.044** 0.940
25 N	236±43	223±46	197±50	**0.018**	Higher M vs Emm Higher M vs Low M Emm vs Low M	**0.016** 0.182 1.00
30 N	228±31	218±51	189±52	**0.014**	Higher M vs Emm Higher M vs Low M Emm vs Low M	**0.041** 0.110 1.00
35 N	205±48	205±46	176±47	0.060		
Accommodated state						
−35 T	200±58	200±38	173±43	0.084		
−30 T	204±79	210 ± 40	173 ± 47	0.089		
−25 T	211±33	212±44	178±40	**0.006**	Higher M vs Emm Higher M vs Low M Emm vs Low M	**0.019** **0.015** 1.00
−20 T	213±50	219 ±50	187±44	0.066		
−10 T	235±45	234±43	197±48	**0.009**	Higher M vs Emm Higher M vs Low M Emm vs Low M	**0.017** **0.027** 1.00
−5 T	255±50	240±62	200±53	**0.004**	Higher M vs Emm Higher M vs Low M Emm vs Low M	**0.004** 0.052 1.00
0 (Centre)	261±48	245±66	211±57	**0.015**	Higher M vs Emm Higher M vs Low M Emm M vs Low M	**0.014** 0.146 1.00
5 N	249±64	248±46	206±41	**0.008**	Higher M vs Emm Higher M vs Low M Emm vs Low M	**0.024** **0.016** 1.00

10 N	249±48	238±20	200±54	**0.001**	Higher M vs Emm	**0.013**
					Higher M vs Low M	**0.001**
					Emm vs Low M	1.00
15 N	241±44	228±22	193±43	**<0.001**	Higher M vs Emm	**<0.001**
					HigherM vs Low M	**0.004**
					Emm vs Low M	1.00
20 N	233±42	223±35	191±43	**0.002**	Higher M vs Emm	**0.002**
					Higher M vs Low M	**0.029**
					Emm vs Low M	1.00
25 N	225±44	213±46	185±49	**0.015**	Higher M vs Emm	**0.014**
					Higher M vs Low M	0.146
					Emm vs Low M	1.000
30 N	218±31	208±50	178±55	**0.013**	Higher M vs Emm	**0.013**
					Higher M vs Low M	0.100
					Emm vs Low M	1.00
35 N	196±47	199±44	169±45	0.053		

T = temporal visual field, N = nasal visual field.

Data are mean ± SD. Significant effect of refractive group are bolded.

Table 6.2. Changes in choroidal thickness (µm) with accommodation for the three refractive groups

Visual field positions (°)	Emmetropes	Low myopes	Higher myopes	*p* value	Group differences	*p*-value (Bonferroni)
−35 T	−11±14	−6±11	−6±10	0.364	Higher M vs Emm	0.626
					Higher M vs Low M	1.00
					Emm vs Low M	0.707
−30 T	−15±9	−11±4	−8±5	**0.001**	Higher M vs Emm	**0.001**
					Higher M vs Low M	0.608
					Emm vs Low M	**0.040**
−25 T	−13±7	−11±7	−11±4	0.442	Higher M vs Emm	0.930
					Higher M vs Low M	1.00
					Emm vs Low M	0.732
−20 T	−13±6	−13±10	−11±9	0.622	Higher M vs Emm	1.00
					Higher M vs Low M	1.00
					Emm vs Low M	1.00
−10 T	−13±7	−13±8	−16±8	0.428	Higher M vs Emm	0.706
					Higher M vs Low M	0.859
					Emm vs Low M	1.00
−5 T	−16±11	−15±10	−19±8	0.320	Higher M vs Emm	0.872
					Higher M vs Low M	0.430
					Emm vs Low M	1.00
0 (Centre)	−18±7	−22±5	−27±11	**0.002**	Higher M vs Emm	**0.001**
					Higher M vs Low M	0.137
					Emm vs Low M	0.266
5 N	−17±10	−18±4	−18±8	0.845	Higher M vs Emm	1.00
					Higher M vs Low M	1.00
					Emm vs Low M	1.00
10 N	−14±9	−15±6	−17±5	0.171	Higher M vs Emm	0.192
					Higher M vs Low M	0.639
					Emm vs Low M	1.00

15 N	−14±7	−13±4	−14±4	0.830	Higher M vs Emm	1.00
					Higher M vs Low M	1.00
					Emm vs Low M	1.00
20 N	−12±7	−11±6	−12±5	0.662	Higher M vs Emm	1.00
					Higher M vs Low M	1.00
					Emm vs Low M	1.00
25 N	−11±3	−10±3	−11±5	0.537	Higher M vs Emm	1.00
					Higher M vs Low M	0.810
					Emm vs Low M	1.00
30 N	−10±5	−10±2	−11±6	0.848	Higher M vs Emm	1.00
					Higher M vs Low M	1.00
					Emm vs Low M	1.00
35 N	−10±6	−6±9	−7±5	0.156	Higher M vs Emm	0.743
					Higher M vs Low M	1.00
					Emm vs Low M	0.171

T = temporal visual field, N = nasal visual field.

Data are mean ± SD. Significant effect of refractive group are bolded.

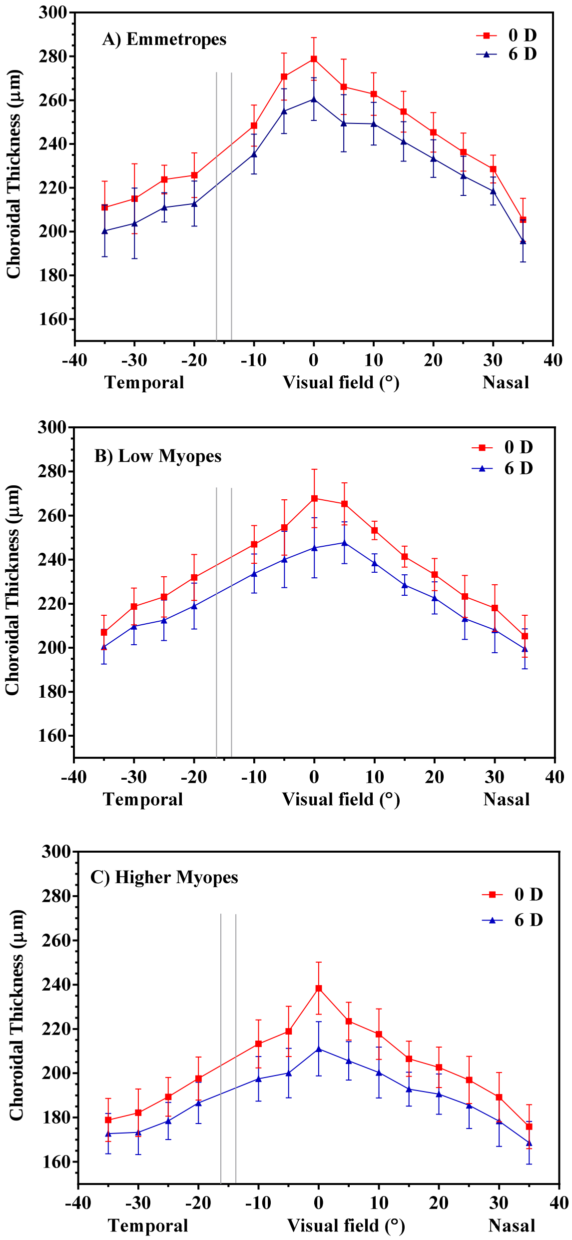

Figure 6.1: Choroidal thickness for 0 D and 6 D accommodation stimuli as a function of visual field angle in (A) emmetropes, (B) low myopes and (C) higher myopes. The grey lines correspond approximately to blind spot limits. Error bars represent the standard errors of means.

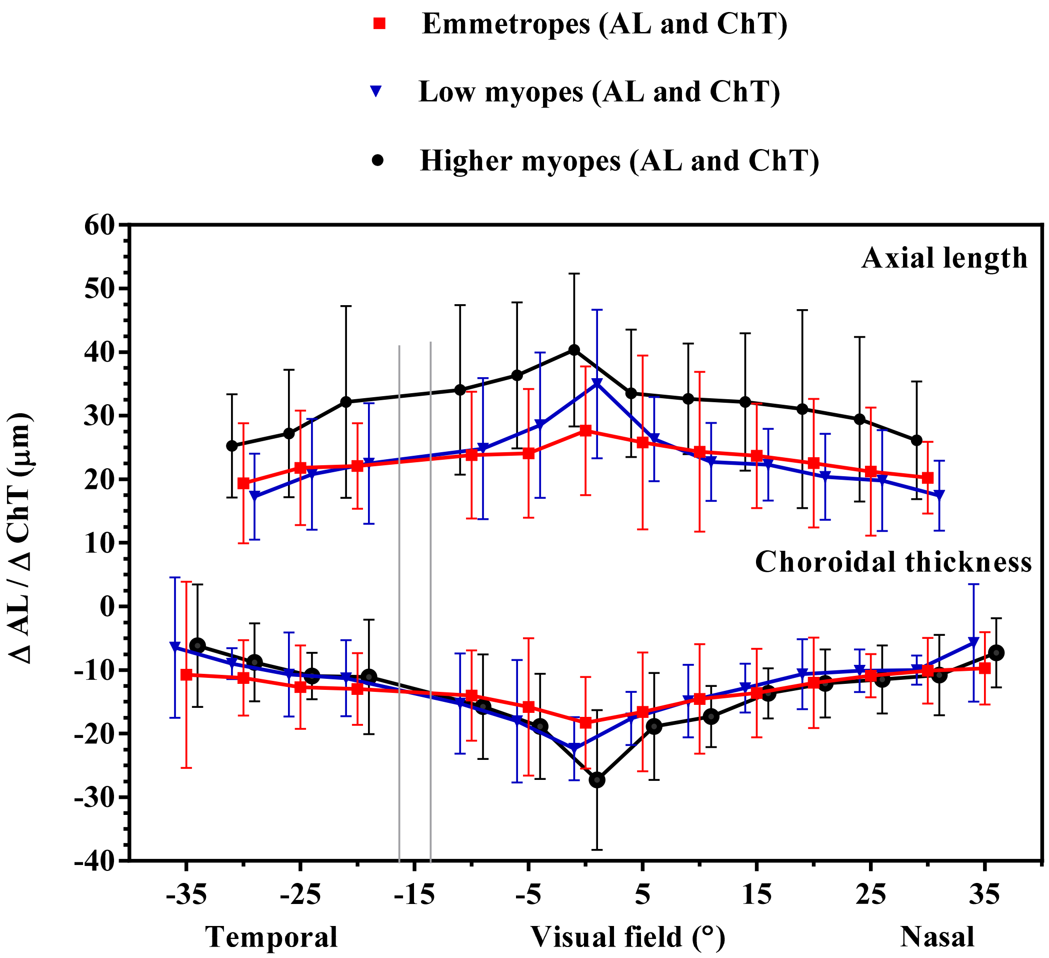

Figure 6.2: The mean changes in axial length (ΔAL) and choroidal thickness (ΔChT) with accommodation along the horizontal meridian in emmetropes, low myopes and higher myopes. The grey lines correspond approximately to the blind spot limits. Error bars represent standard errors of means. For clarity, the plots for low myopes and high myopes have been shifted slightly horizontally.

Table 6.3: Linear regression of accommodated-induced change in axial length on change in choroidal thickness for the refractive groups.

Group	Visual field positions (°)	Slope	R^2	*p*-value
	−30 T	−0.71	0.21	0.024
	−25 T	−0.78	0.21	0.022
	−20 T	−0.76	0.23	0.017
	−10 T	−0.63	0.24	0.015
	−5 T	−0.54	0.26	0.010
EMM	0 (Centre)	−1.35	0.29	0.006
	5 N	−0.76	0.28	0.007
	10 N	−0.76	0.28	0.008
	15 N	−0.59	0.26	0.011
	20 N	−0.73	0.18	0.037
	25 N	−1.39	0.23	0.017
	30 N	−0.68	0.20	0.027
	−30 T	−1.15	0.17	0.049
	−25 T	−0.61	0.21	0.026
	−20 T	−0.71	0.20	0.031
	−10 T	−0.66	0.22	0.023
	−5 T	−0.56	0.22	0.023
Low myopes	0 (Centre)	−1.37	0.35	0.003
	5 N	−0.77	0.24	0.017
	10 N	−0.53	0.24	0.017
	15 N	−0.71	0.24	0.018
	20 N	−0.60	0.19	0.041
	25 N	−1.06	0.21	0.029
	30 N	−1.01	0.17	0.045
	−30 T	−0.55	0.18	0.047
	−25 T	−1.18	0.18	0.045
	−20 T	−1.04	0.20	0.036
	−10 T	−0.72	0.19	0.038
	−5 T	−0.62	0.20	0.036
Higher myopes	0 (Centre)	−0.69	0.37	0.003
	5 N	−0.45	0.21	0.032
	10 N	−0.78	0.19	0.043
	15 N	−1.19	0.19	0.044
	20 N	−1.66	0.21	0.032
	25 N	−1.03	0.18	0.047
	30 N	−0.62	0.18	0.047

T = temporal visual field, N = nasal visual field.

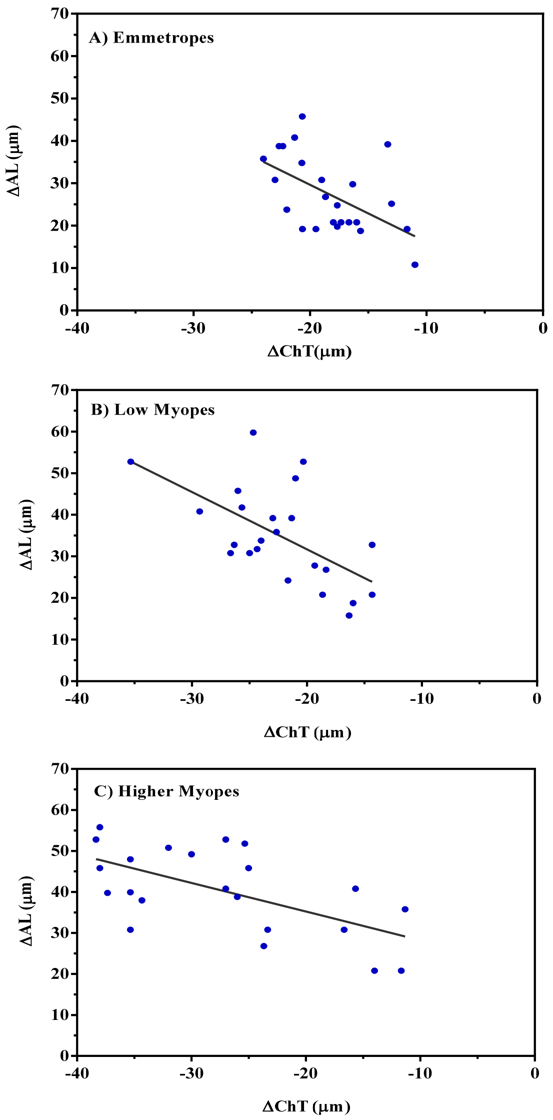

Figure 6.3: Relationship between accommodation-induced changes in axial length (ΔAL) and changes in choroidal thickness (ΔChT) in (A) emmetropes, (B) low myopes and (C) higher myopes on-axis. The linear regressions are $y = -1.35x + 2.65$, $R^2 = 0.29$, $p = 0.006$ for emmetropes; $y = -1.37x + 4.16$, $R^2 = 0.35$, $p = 0.003$ for low myopes; $y = -0.69x + 21.28$, $R^2 = 0.37$, $p = 0.003$ for higher myopes.

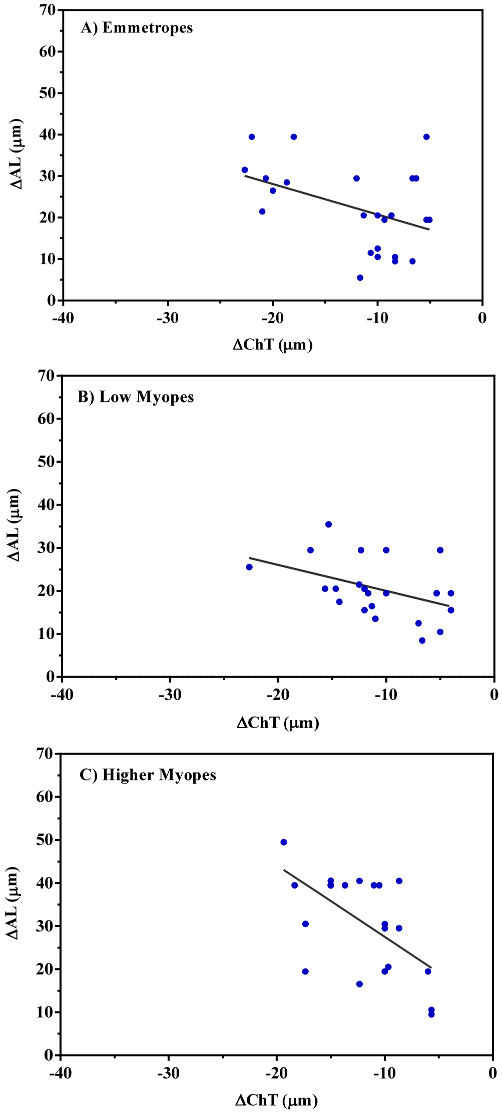

Figure 6.4: Relationship between accommodation-induced changes in axial length (ΔAL) and choroidal thickness (ΔChT) in (A) emmetropes, (B) low myopes and (C) higher myopes at 20° nasal field. The linear regressions are: $y = -0.735x + 13.40$, $R^2 = 0.18$, $p = 0.037$ for emmetropes; $y = -0.604x + 13.96$, $R^2 = 0.19$, $p = 0.041$ for low myopes; $y = -1.66x + 10.84$, $R^2 = 0.21$, $p = 0.032$ for higher myopes.

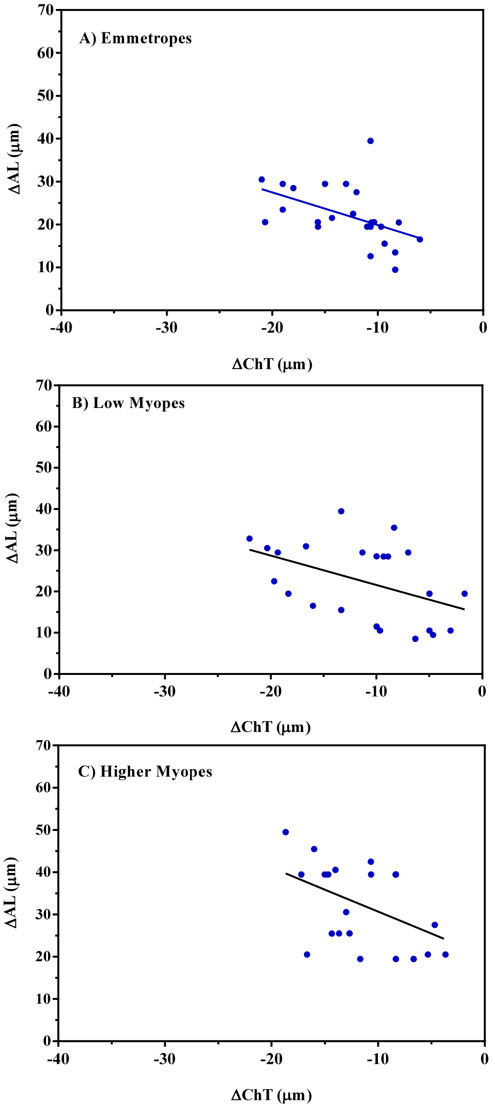

Figure 6.5: Relationship between accommodation-induced changes in axial length (ΔAL) and choroidal thickness (ΔChT) in (A) emmetropes, (B) low myopes and (C) higher myopes at 20° temporal field. The linear regressions are: $y = -0.760x + 12.27$, $R^2 = 0.23$, $p = 0.017$ for emmetropes; $y = -0.714x + 14.44$, $R^2 = 0.20$, $p = 0.031$ for low myopes; $y = -1.039x + 20.30$, $R^2 = 0.20$, $p = 0.036$ for higher myopes.

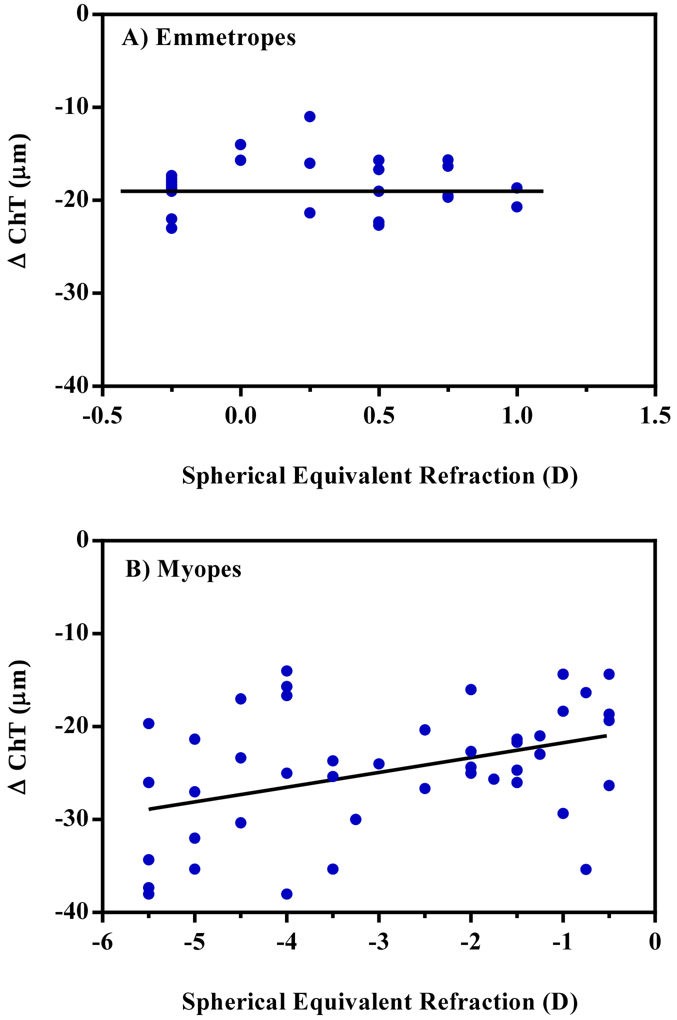

Figure 6.6: Correlation between the accommodation-induced change choroidal thickness (ΔChT) and spherical equivalent refraction on-axis in (A) emmetropes (n = 24) and (B) all myopes (n = 45). The linear regression line are emmetropes: $y = -0.045x - 18.27$, $R^2 < 0.001$, $p = 0.97$; myopes: $y = 1.42x - 10.36$, $R^2 = 0.16$, $p = 0.006$. As the slope for the former is not significant, the mean of –18.3 µm is plotted.

Table 6.4: Correlation between accommodation-induced changes in choroidal thickness and spherical equivalent refraction in emmetropes and myopes at different visual field positions.

Visual field position (°)	Slope (µm/D)	R^2	*p*-value
Emmetropes			
-35T	−3.01	0.02	0.512
−30 T	−4.24	0.09	0.139
−25 T	0.70	0.003	0.786
−20 T	2.07	0.03	0.454
−10 T	1.09	0.005	0.755
−5 T	4.08	0.04	0.377
0 (centre)	−0.05	< 0.001	0.974
5 N	−7.07	0.11	0.116
10 N	3.62	0.03	0.392
15 N	−0.85	0.003	0.806
20 N	2.35	0.03	0.407
25 N	0.14	< 0.001	0.932
30 N	0.18	< 0.001	0.920
35N	3.22	0.06	0.245
Myopes			
-35T	−0.20	0.004	0.667
−30 T	−0.53	0.04	0.215
−25 T	−0.07	0.01	0.799
−20 T	−0.89	0.09	**0.035**
−10 T	1.59	0.15	**0.008**
−5 T	1.26	0.09	**0.041**
0 (centre)	1.42	0.16	**0.006**
5 N	0.62	0.09	**0.034**
10 N	0.93	0.10	**0.034**
15 N	0.39	0.12	**0.020**
20 N	0.59	0.08	**0.046**
25 N	0.09	0.001	0.81
30 N	0.17	0.003	0.689
35N	0.94	0.04	0.165

T = temporal visual field, (N) = nasal visual field. Significant *p* values are bolded.

6.5 DISCUSSION

The aim of this study was to investigate peripheral choroidal thickness changes along the horizontal field meridian during accommodation in emmetropic and myopic eyes. Previous studies showed on-axis choroidal thinning during accommodation (Woodman et al., 2012). I hypothesised that peripheral choroidal thickness, like central choroidal thickness, would also thin with accommodation and this thinning would be greater in myopes than in emmetropes. This work involved 69 participants divided into 24 emmetropes, 23 low myopes and 22 high myopes. Investigation of the choroidal thickness along the horizontal visual meridian using non-invasive SD-OCT could help to explain the choroid response to accommodation as well as its correlation with the length of the eye in response to accommodation.

Choroidal thickness was greatest at the fovea, with reduction in thickness with increasing eccentricity for all three refractive groups. For both the unaccommodated and accommodated states, refractive group affected choroidal thickness significantly at most positions. As such, this study supports previous studies finding that the on-axis choroid is thinner in myopic than emmetropic eyes (Flores-Moreno et al., 2012; Fujiwara et al., 2009; Manjunath et al., 2010). For the 22 out of 28 accommodation/visual field combinations at which significance occurred, emmetropes and low myopes had significantly thicker choroids than the higher myopes for 21 and 11 combinations, respectively. Choroids thinned with accommodation, with the thinning decreasing away from the fovea. There were only two positions for which this thinning was affected significantly by refractive group, at the fovea where the higher myopes thinned more than the emmetropes (mean ± SE: 4.1 ± 2.4 μm) and at 30° temporal where the emmetropes thinned more than the higher myopes (7.1 ± 1.9 μm).

For all three refractive groups, there were statistically significant negative correlations between accommodation-induced changes in axial length and choroidal thickness at all visual field positions. Changes in axial length were –45% to –165% the change in choroidal thickness across the field (mean ± SD: –83 ± 29%), and as such changes in choroidal thickness can be considered to account for most of the accommodation-induced changes in axial length.

There were significant negative correlations between the changes in choroidal thickness along the horizontal meridian and spherical equivalent refraction of myopic eyes up to ±20° was found, with highs correlation at on-axis. However, there was no significant correlation was observed in emmetropic groups. The results of this study are consistent with previous studies regarding on-axis negative correlation between choroidal thickness and spherical equivalent refraction (Flores-Moreno et al., 2012; Ikuno and Tano, 2009; Nakakura et al., 2014; Nishida et al., 2012).

The hypothesis that the choroid will thin both on-axis and peripheral during accommodation and that this will be thinner in myopes than in emmetropes has been partially supported in that thinning was found out to 35° from fixation along the horizontal visual field. However, there was no systematic difference in response between emmetropes and myopes.

Woodman et al. (2012) have examined on-axis choroidal thickness during accommodation (4 D demand) for two refractive groups. The participants were classified as emmetropes (SER ± SD, +0.16 ± 0.28 D) and myopes (SER ± SD, –2.90 ± 1.57 D) without the range of myopia being reported. There were significant differences in choroidal thinning during accommodation between the refractive groups ($p < 0.05$). To compare the data of this study to that of Woodman et al.'s study, the participants' data were collapsed into two groups of emmetropes (SER ± SD, +0.28 ± 0.34 D) and myopes (SER ± SD, –2.91 ± 1.71 D). The mean ± SD thinning of choroidal thickness with accommodation was –18 ± 7 µm for emmetropes and –25 ± 9 µm for myopes, which is substantially higher than that reported by Woodman et al. (2012) of –9 ± 18 µm and –7 ± 22 µm for myopes and emmetropes, respectively. They found significant, but weak correlations between change in axial length and choroidal thickness ($R^2 = 0.077$, $p < 0.001$) whereas this study found significant and stronger correlations ($R^2 = 0.43$, $p < 0.001$).

The differences in the mean choroidal thickness change during accommodation between the present study and that of Woodman et al. (2012) which may be related to the level and duration of accommodation, the type of instrument, and sample size. The accommodation stimulus level used in the present study was 6 D during a short time of accommodation, whereas Woodman et al. used a lower 4 D demand and at the end of 30 minutes of sustained accommodation.

Woodman et al. (2012) used partial coherence interferometry (Lenstar LS 900), whereas the present study used SD-OCT. Poor signal quality from the choroidal–scleral interface, manual detection of the A-scan peaks (which need subjective judgment) and difficulty of taking measurements from thicker choroid are the major drawbacks of the Lenstar. Brown et al. (2009) and Read et al. (2010b) have reported difficulty in determining the choroidal thickness due to high variation in A-scan peaks during the measurement for some participants. Because of this limitation, Woodman et al. (2012) obtained measurements of choroidal thickness for only 37 of their 59 participants (12 emmetropes and 25 myopes), about half those in this study (n = 69, 24 emmetropes and 45 myopes). The Woodman et al. study has the advantage over ours of determining changes in choroidal thickness and axial length with a single instrument, but their weak correlations between changes in axial length and choroidal thickness may be attributable to the limitation of the Lenstar instrument in determine the A-Scan peaks. This study has a limitation as well: different instruments were used to measure the changes in axial length (Lenstar) and choroidal thickness (OCT) along the horizontal meridian. It is difficult to ensure that the axial length measured at a particular angle with the Lenstar corresponds to the same choroid angle measured with OCT. Another limitation is related to the different methods used to stimulate accommodation. This study does not use an external attachment to simulate accommodation in OCT which the Lenstar does, because of limited space between the eye of participant and the OCT. These differences between two methods might produce different accommodation response between the participants. These limitations may affect the correlation in this study.

Recently, Woodman et al. (2015) measured on-axis choroidal thickness in 20 emmetropes (SER ± SD, +0.38 ± 0.22 D) and 20 myopes (SER ± SD, –2.83 ± 1.50 D) using OCT. An external attachment was used to stimulate 6 D of accommodation demand. After excluding five participants (4 emmetropes and one myopes), the mean ± SD thinning of choroidal thickness with accommodation was 5 ± 6 µm for emmetropes and 4 ± 8 µm for myopes, which is substantially smaller than that reported in this study. Woodman et al. (2015) used the Heidelberg Spectralis-SD-OCT (Heidelberg Engineering, Heidelberg, Germany) whereas this study used the Nidek RS-3000 Advanced spectral domain optical coherence tomographer to measure the choroidal thickness during accommodation. Differences between instruments may explain the differences in the mean change of choroidal thickness between the studies. Several studies reported that choroidal thickness measurements may differ from instrument to another (reviewed in Chhablani et al. (2014)). Differences between Woodman et al.'s results and the current study could also be due to the different methods to stimulate accommodation.

The present study showed that accommodation alters choroidal thickness along the horizontal field meridian. The mechanism leading to choroidal thinning with accommodation and the greater response in myopia is not clear. Ciliary muscle tendons connect with the anterior choroid at the Bruch's membrane layer in the rhesus monkey and the choroid moves forwards as the ciliary muscle contracts during accommodation (Tamm et al., 1991), which may produce the thinning.

Another possible mechanism leading to changes in choroidal thickness during accommodation is that non-vascular smooth muscle cells in the choroid (Nickla and Wallman, 2010; Schrodl et al., 2001) contract because of parasympathetic input during accommodation that causes contraction of these cells. It has been reported that the non-vascular smooth muscle cells are distributed through choroid and in some eyes most of these cells are concentrated around the temporal region of the fovea whereas other eyes have less density within temporal quadrant of fovea (May, 2005). This indicates that while these cells might play some role in on-axis choroidal thickness, they are unlikely to affect peripheral choroidal thickness during accommodation.

Defocus might contribute to changes in choroidal thickness during accommodation. Animal studies have shown that introducing hyperopic defocus causes choroidal thinning and myopic defocus causes choroidal thickening (Nickla and Wallman, 2010; Wildsoet and Wallman, 1995). Read et al. (2010b) found similar changes in humans. It is possible that choroidal thinning and axial length could be influenced by lag of accommodation during accommodation. Since the participants in this study were healthy adults with good accommodation response, changes in choroidal thickness due to lag of accommodation is unlikely.

This finding of temporary effect of choroidal thinning during accommodation over a short time suggests that performing near work over extended periods of time may lead to permanent changes in the thickness of choroid which may cause eye growth. Other factors such as stretching of the sclera along the horizontal field with accommodation should be taken into account in future research as a causative factor for changing ocular structure.

6.6 CONCLUSIONS

The aim of this chapter was to investigate the influence of accommodation for both on-axis and off-axis choroidal thickness using a non-invasive SD-OCT technique. This study addressed the third hypothesis of this thesis: choroidal thickness will thin both on-axis and peripherally during accommodation and this will be different in emmetropes and myopes. Across the horizontal visual field meridian to ±35°, young adult myopes had thinner choroids than young adult emmetropes. There was choroidal thinning in response to accommodation, but this was not influenced by refractive status. The choroidal appears to be responsible for much of the accommodation-induced increases in axial length.

Chapter 7: Discussion and Conclusion

7.1 SUMMARY OF FINDINGS

When myopia occurs at an early age, it leads to a higher degree of myopia than later onset myopia, and on a population basis, results in significant public health concerns (Seet et al., 2001; Liu et al., 2010). Intensive near work is considered one of the most important environmental risk factors for myopia and is thought responsible for an increase in the prevalence of myopia around the world, particularly in developed countries (Lin et al., 2001; Morgan et al., 2012; Morgan and Rose, 2013). Accommodation has been found to increase the axial length and thin the choroid along the optical axis (Drexler et al., 1998; Mallen et al., 2006; Read et al., 2010c; Woodman et al., 2012; Zhong et al., 2014). Although it was thought that the centre of the retina (fovea) along the optic axis was the primary driver of myopia elongation, the peripheral retina has received recent prominence. For example, peripheral hyperopia can induce myopia in animal models (Smith et al., 2009) and peripheral relative hyperopia in myopes and peripheral relative myopia in emmetropes has been found in humans (Rempt et al., 1971). Thus understanding the relationship between near work and changes to the peripheral retina may be very important for the development of preventative strategies.

There is debate about whether the increases in axial length are caused by or are a consequence of the development of myopia. As several studies have shown that myopes tend to have greater lag of accommodation than emmetropes, and that poorer lags of accommodation are associated with the development of myopia (Abbott et al., 1998; Gwiazda et al., 1995a; 1993; 2005). Other studies, however, have posited that the poor lag of accommodation observed in myopes occurs after myopia onset rather than before it appears (Mutti et al., 2006; Rosenfield et al., 2002; Weizhong et al., 2008). Since this study is a cross-sectional study, it is not possible to draw firm conclusions as to whether the changes in axial length and thinning of the choroid are causes or consequences of developing myopia.

The objective of this thesis was to investigate the impact of accommodation on peripheral ocular biometry. Peripheral axial length and choroidal thickness were measured using the Lenstar LS 900 and SD-OCT, respectively. This study had three aims addressing three hypotheses.

7.2 THE EFFECT OF ACCOMMODATION ON THE PERIPHERAL AXIAL LENGTH OF THE EYE

The first aim of this study was to investigate the effect of accommodation on the peripheral axial length of the eye in young healthy adult participants (Experiment 1, Chapter 4). I hypothesised that the peripheral axial length, like the central axial length, would also increase with accommodation and that the increase would be greater in myopes than in emmetropes. A total of 83 participants were enrolled in this study and divided into three groups: 29 emmetropes, 32 low myopes and 22 high myopes.

To test the hypothesis for the first aim, the axial length of the eye was measured for 0 D and 6 D demands of accommodation ±30° along the horizontal meridian field in three different refractive groups. Before data analysis, axial length measurement errors due to changes in the shape of the crystalline lens with accommodation were corrected by methods described in Chapter 3 and Section 3.4.3. A statistically significant increase in axial length with accommodation was found at all eccentricities across the horizontal meridian of the visual field for all three refractive groups. These increases in axial length with accommodation might show the association between near work and peripheral elongation of axial length. Therefore, long-term changes in axial length with accommodation may play a role in the development of myopia. This study found significant elongation in on-axis axial length during accommodation that is similar to the results of previous studies (Drexler et al., 1998; Mallen et al., 2006; Read et al., 2010c; Woodman et al., 2012).

Differences in the magnitude of on-axis axial length changes during accommodation between the results of Chapter 4 of the present study and previous studies could be caused by different sample sizes, age groups, instruments and levels of accommodation (see Chapter 4, Section 4.4 for more detail). Differences may be also associated with the duration of the accommodation task. Some studies, such as Mallen et al. (2006) and Read et al. (2010), measured the on-axis axial length (e.g. single time point) with short periods of accommodation (20 seconds) whereas Woodman et al. (2012) measured axial length at different points of time, for example, every 5 min over 30 min for a 4 D accommodation demand. Although these studies have shown important findings regarding the role of accommodation along the on-axis, spending a long time performing an accommodation task at the periphery could also affect myopia.

7.3 TIME DYNAMICS OF THE EFFECT OF ACCOMMODATION ON THE PERIPHERAL AXIAL LENGTH OF THE EYE

The second aim was to examine time course and recovery of both on-axis and peripheral axial length elongation of the eye during accommodation (Experiment 2, Chapter 5). The hypothesis was that the axial length will increase with an extended period of accommodation and this will be different in emmetropes and myopes. Twenty-eight myopes and 23 emmetropes participated. Axial elongation was found to occur within 45s, of commencement of 6 D accommodation demand. This was sustained over the 8 min of the accommodation task. Following cessation of the accommodation task, axial elongation regressed slower and not complete after 8 min at all positions.

The differences between myopes and emmetropes in on-axis axial length during cessation of the accommodation task are consistent with previous findings (Mallen et al., 2006; Read et al., 2010c; Woodman et al., 2012). These differences between refractive groups in axial elongation induced by accommodation might reflect differences in the biochemical properties of components of the eye. Mallen et al. (2006) suggest that due to the difference of ocular rigidity between refractive groups, the transmission of forces to the choroid and sclera will be greater in myopes than in emmetropes. The anatomical relationship between choroid and ciliary muscle could explain the changes in axial length across the retina. Since anatomical relationship between sclera and ciliary muscle exists, it is possible the forces of ciliary muscle contraction during accommodation could affect the sclera thickness which might be responsible for unaccounted changes in axial length elongation. Both animal and human studies have demonstrated that during the development of refractive errors, both choroid and sclera becomes weak and thin

(Elsheikh et al., 2010; Ho et al., 2013; Nickla et al., 2013; Norman et al., 2010; Phillips et al., 2000; Tan et al., 2014; Vurgese et al., 2012).

I found that the axial length was greater in myopes than emmetropes at all time intervals during accommodation (Chapter 5), and the choroidal thinning was responsible for most of these axial length changes (Chapter 6). This suggests that the choroid may show different decay response in different refractive groups. Further study using spectral domain optical coherence tomography (SD-OCT) is needed to investigate accommodation induced changes and recovery over time of the choroidal thickness.

7.4 THE EFFECT OF ACCOMMODATION ON THE PERIPHERAL CHOROIDAL THICKNESS OF THE EYE

The third aim of this study was to investigate the change in peripheral choroidal thickness during accommodation in young healthy adults (Experiment 3, Chapter 6). Since thinning of the choroid has been found to be a causative factor in on-axis axial elongation during accommodation (Woodman et al., 2012), I hypothesised that peripheral choroidal thickness would also thin with accommodation and this thinning would be greater in myopes than in emmetropes. This work involved 69 participants divided into 24 emmetropes, 23 low myopes and 22 high myopes.

To test the hypothesis for third aim, the choroidal thickness profile was measured for 0 D and 6 D accommodation demands over ±35° along the horizontal meridian of the visual field. The SD-OCT technique allowed accurate imaging and mapping of the changes in choroidal thickness along the horizontal field during accommodation. A significantly thinner choroid with accommodation was found at all eccentricities. There was significant negative correlation between change in choroidal thickness and change in axial length along the horizontal meridian of the visual field, and this correlation accounted for most of the change in axial length with accommodation. This study provides evidence that part of the change in axial length during accommodation is due to change in choroidal thickness. The portion of choroidal thickness changes which contributed to the changes in axial length varied between 17% and 37% across the horizontal meridian.

Significant different thinning was found between different refractive groups during accommodation. There were only two positions at which this thinning was affected significantly by refractive group, at the fovea where the higher myopes thinned more than the emmetropes (mean ± SE: 9.0 ± 2.4 µm) and at 30° temporal where the emmetropes thinned more than low myopes (4.6 ±1.8 µm) and higher myopes (7.1 ±1.9 µm).

Thinning of choroid has been reported to be associated with development of refractive errors in humans (Fujiwara et al., 2009; Ho et al., 2013). This suggests that changes in ocular structure could indicate early signs of the development of myopia. Therefore, the findings of the present study where changes in choroidal thickness across the horizontal meridian of the visual field occur with short-term accommodation have implications for the role of near work at the periphery in the development of myopia. In individuals who perform near work for a long time, the choroid might be permanently thinned along the horizontal meridian of the visual field which, in turn, causes long-term eye growth changes.

7.5 ROLE OF CHOROID IN AXIAL ELONGATION

This study has found accommodation-induced changes in the biometry of eye (Figure 7.1). There was thinning of choroid along the horizontal meridian that coincided with axial length elongation. It is possible that contraction of ciliary muscle during accommodation is one of the mechanisms leading to peripheral choroidal thinning along the horizontal meridian of the visual field. Ciliary muscle tendons have been found connected with peripheral choroid in the rhesus monkey (Tamm et al., 1991) and the ciliary muscle contracting during accommodation leads to thinning of choroid. Croft et al. (2013) reported that substantial anterior movement of the peripheral choroid accompanying the inward and forward movement of the ciliary muscle in monkey eyes. The thickness of the ciliary muscles has been reported to be thicker in myopes than emmetropes (Buckhurst et al., 2013; Kuchem et al., 2013; Pucker et al., 2013). Other studies found that thickness of the ciliary muscles increases with increased myopia. These differences in ciliary muscle thickness could transmit greater mechanical force on the choroid of myopes compared to that of emmetropes during accommodation. This could explain the differences in axial elongation during accommodation between myopes and emmetropes.

The changes in axial length during accommodation could involve autonomic inputs. Nickla and Wallman (2010) reported that blood vessels of choroid receive parasympathetic input during accommodation and possibly the neural signal could alter the blood flow of choroid leading to changes in the thickness of the choroid across the horizontal visual field which results in changes in the axial length. Differences in the underlying autonomic tone (reviewed in Chen et al. (2003)) of emmetropes and myopes may therefore also be involved in the observed differences.

Given that the choroid has non-vascular smooth muscle cells (Nickla and Wallman, 2010; Poukens et al., 1998; Schrodl et al., 2001), it is probably affected by parasympathetic input during accommodation causing contraction of these muscles and thinning of the choroid. However, it is unlikely that these non-vascular smooth muscles cells are able to modulate the peripheral choroidal thickness during accommodation because it has been reported that most of non-vascular smooth muscles cells concentrate around fovea (May, 2005). Therefore, these cells might only have a role on-axis choroidal thickness during accommodation. The results of this experiments, overall, suggest that mechanical stretching of the choroid due to contraction of the ciliary muscles with accommodation was likely to cause changes in choroidal thickness which responsible for the accounted changes in axial length elongation.

7.6 OTHER MECHANISMS WHICH MIGHT BE CAUSING AXIAL ELONGATION

Another possible mechanism causing changes in axial length during accommodation is that both animal models and human studies have shown that sclera changes in response to the accommodation due to the ciliary muscles fibres connected to the both scleral spur and ora serrata (Croft et al., 2013; Harper and Summers, 2015). This anatomical relationship may make the sclera move backward and forward along the horizontal meridian due to the ciliary muscle contraction during accommodation which results in elongation of the eye. It is possible that changes in axial length could due to alterations in the scleral position or thickness during accommodation.

The influence of optical defocus could also lead to changes in choroidal thickness during accommodation along the horizontal meridian of the visual field. Animal models have shown that introducing hyperopic defocus causes a thinning of the choroid, whereas myopic defocus causes a thickening of the choroid (Nickla and Wallman, 2010; Wildsoet and Wallman, 1995). Read et al. (2010b) and Chakraborty et al. (2013) have found changes in choroidal thickness and axial length in response to optical defocus in human participants. Accommodation can lead to defocus as a result of lag of accommodation and thus have an effect on the biometry of the eye.

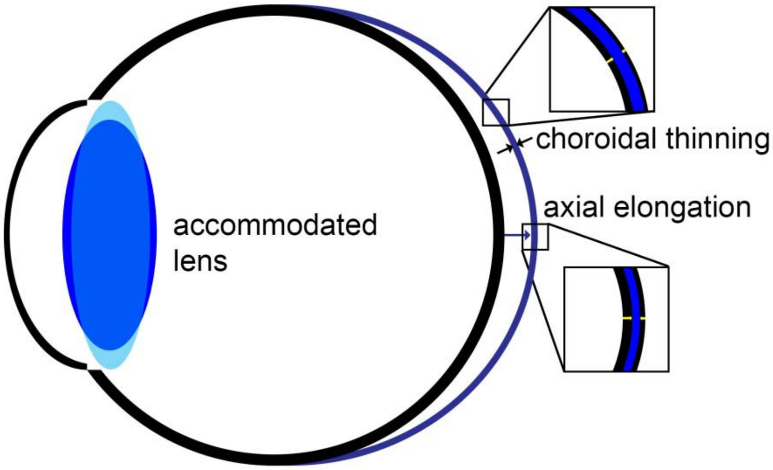

Figure 7.1: Model of changes in accommodated eye (not to scale). During accommodation the lens thickness changes and the choroid thins which leads to axial elongation. Changes in the choroidal thickness were responsible for most changes in axial length during accommodation across the horizontal field.

7.7 CLINICAL RELEVANCE

This research investigates the effect of accommodation on the peripheral ocular biometry of the eye. It found that a high level of accommodation induces changes in axial length in both on-axis and peripheral vision. These changes differed significantly between myopes and emmetropes. Several studies have shown that progressive multifocal lenses or bifocals slow the progression of myopia in children (Cheng et al., 2011; Gwiazda et al., 2004; Hasebe et al., 2008). It has been shown that hyperopic defocus occurs due to lag of accommodation at near distances, which is considered a potential risk factor for developing myopia (Gwiazda et al., 2005). However, the optical intervention designs reported in these studies focus solely on on-axis vision. Newly available lenses dubbed "anti-myopia" lenses have been designed to reduce peripheral defocus effects in myopia (Elliott, 2011). In clinical studies, reduction in myopia progression was observed when these lenses were used in young children (Sankaridurg et al., 2010).

The findings of this study also indicate that short-term accommodation-induced changes in axial elongation across the retina take longer time to recovery for both groups. This important finding should be taken into account when designing optical interventions for the peripheral retina.

I propose that reading for a long time without intermittent vision breaks could contribute to the development of myopia. Since these changes in axial length were seen at a high level of accommodation that is outside the normal distance for reading or other activities, the risk of developing myopia will not be displayed to a significant degree in adults. However, children usually perform their tasks at closer distances than adults. Therefore, children should be encouraged to take breaks between their near-focus activities to help reduce signals of hyperopic defocus at the retina; this behaviour may slow the development of myopia.

7.8 FUTURE WORK

Although there is considerable evidence of an association between near work and development of myopia, the underlying mechanisms that explain how the accommodation affect the biometry of eye is not well understood. The outcomes of this study show that accommodation induces changes in choroidal thickness and axial length and these changes differ between myopic and emmetropic eyes along the horizontal meridian of the visual field during accommodation. There are some potential avenues of research arising from the findings of this thesis that may help to develop an increased understanding of mechanisms that lead to the development of myopia.

All experiments in this project involved young adult participants and were cross-sectional. Because the myopia develops in early stage, longitudinal studies are required to examine these changes in children on whether these changes in axial length and choroidal thickness are causes or consequences of myopia development. The external attachment to measure the peripheral axial length (see section 3.4) requires manual adjustment. It would be better to use automation, especially in children, to reduce the testing time.

On-axis choroidal thickness has been reported to thin with age (Ikuno et al., 2010a; Manjunath et al., 2010; Wei et al., 2012). While the present study investigated the effect of accommodation on the choroidal thickness across the horizontal field in young adults, further research using an appropriate technique such as SD-OCT using eye tracking feature to ensure measuring the same location is needed to measure the profile of choroidal thickness in children.

This study reported that the choroid causes part of the increase in axial length along the horizontal visual meridian during short-term accommodation, but the choroid may recover differently after a longer period of accommodation. It would be interesting to investigate the peripheral choroidal thickness changes among refractive groups during an extended period of accommodation using SD-OCT similar to the method used in Chapter 6.

As discussed in Section 7.6, the sclera stretch mechanism might be responsible for the unaccounted changes in the length of the eye during accommodation. Previous studies have reported that the sclera changes in response to accommodation along the visual axis (Croft et al., 2013; Harper and Summers, 2015). Since the sclera has been reported to be thinner and weaker in myopic eyes than emmetropic eyes (Elsheikh et al., 2010; Norman et al., 2010; Vurgese et al., 2012), the sclera might be reshaped over all of the eye during accommodation and lead to axial length elongation, with more thinning in myopic eyes during accommodation. Investigation of the effect of accommodation on sclera thickness along horizontal field using the SD-OCT technique between refractive groups may be of interest.

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Appendix 1 - Ethics approval forms

QUT Queensland University of Technology
Brisbane Australia

PARTICIPANT INFORMATION FOR QUT RESEARCH PROJECT

Accommodation effects on peripheral ocular biometry

QUT Ethics Approval Number 1300000162

RESEARCH TEAM

Principal Researcher:	A/Prof Katrina Schmid	3138 6150	k.schmid@qut.edu.au
Associate Researchers:	Prof David A Atchison	3138 6152	d.atchison@qut.edu.au
	Dr Marwan Suheimat	3138 6153	marwan.suheimat@qut.edu.au
	Mr Hussain AL Dossari	3138 6403	hussainmubarakd.aldossari@student.qut.edu.au

Vision Domain, Institute of Health and Biomedical Innovation (IHBI), Queensland University of Technology (QUT)

DESCRIPTION

This project is being undertaken as part of PhD research for student Hussain AL Dossari. In this study we will measure retinal shape, direction of the photoreceptors (light sensitive cells in the retina), and choroidal thickness (posterior outer layer of the eye) with accommodation (focussing). You are invited to participate in this project because you are aged between 18 and 23 years of age.

PARTICIPATION

Your participation will involve routine eye examination including eye and general medical history, refraction, distances between ocular components and biomicroscopy (viewing light reflected from the eye structures). It will also involve some specialist tests including ocular length, choroidal thickness (posterior outer layer of the eye) and direction of the photoreceptors (light sensitive cells in the retina). We will need to dilate the pupil of one eye with eye drops. Screening will be carried out before the experiment on the first visit. There are 3 visits and up to 5 hours of your time will be needed.

Your participation in this project is entirely voluntary. If you do agree to participate you can withdraw from the project without comment or penalty. If you withdraw, on request any identifiable information already obtained from you will be destroyed. Your decision to participate or not participate will in no way impact upon your current or future relationship with QUT (for example your grades).

EXPECTED BENEFITS

It is expected that this project will not benefit you directly; however, you may be interested in learning more about your eyes. In this study we will measure retinal shape, choroidal thickness (posterior outer layer of the eye) and direction of the photoreceptors (light sensitive cells in the retina) during accommodation (focussing). The results of this study will provide a better understanding of myopia (short-sightedness) development risk and likely optical treatment effectiveness. This study will eventually be of benefit to people at risk of myopia (short-sightedness) development.

To compensate you for your contribution should you choose to participate, the research team will provide you with out-of-pocket expenses in the form of a $15 supermarket voucher upon completion.

RISKS

There are minimal risks associated with your participation in this project. The eye drops that we use are used in clinical eye examinations, and there are low risks associated with using them. However, we will screen for the likelihood of possible side effects. The pupil dilating eye drop does not affect focusing ability, the eyes pupil will be enlarged for a few hours (~4 hours). As pupil dilation makes the eye more sensitive to bright light, we recommend that you bring your sunglasses to wear afterwards. Until the pupil size returns to normal, you should not drive or cycle, and take care with walking.

PRIVACY AND CONFIDENTIALITY

All comments and responses will be treated confidentially. The names of individual persons are not required in any of the responses.

CONSENT TO PARTICIPATE

We would like to ask you to sign a written consent form (enclosed) to confirm your agreement to participate.

QUESTIONS / FURTHER INFORMATION ABOUT THE PROJECT

Please contact any of the research team members named above to have any questions answered or if you require further information about project.

CONCERNS / COMPLAINTS REGARDING THE CONDUCT OF THE PROJECT

QUT is committed to research integrity and the ethical conduct of research projects. However, if you do have any concerns or complaints about the ethical conduct of the project you may contact the QUT Research Ethics Unit on 3138 5123 or email ethicscontact@qut.edu.au. The QUT Research Ethics Unit is not connected with the research project and can facilitate a resolution to your concern in an impartial manner.

Thank you for helping with this research project. Please keep this sheet for your information.

Queensland University of Technology Brisbane Australia	CONSENT FORM FOR QUT RESEARCH PROJECT

Accommodation effects on peripheral ocular biometry

QUT Ethics Approval Number 1300000162

RESEARCH TEAM CONTACTS

A/Prof Katrina Schmid	Mr Hussain AL Dossari
3138 6150	31386403
k.schmid@qut.edu.au	hussainmubarakd.aldossari@student.qut.edu.au

STATEMENT OF CONSENT

By signing below, you are indicating that you:

- Have read and understood the information document regarding this project.
- Have had any questions answered to your satisfaction.
- Understand that if you have any additional questions you can contact the research team.
- Understand that you are free to withdraw at any time, without comment or penalty.
- Understand that you can contact the Research Ethics Unit on 3138 5123 or email ethicscontact@qut.edu.au if you have concerns about the ethical conduct of the project.
- Agree to participate in the project.

Name ______________________________

Signature ______________________________

Date ______________________________

Please return this sheet to the investigator.

University Human Research Ethics Committee (UHREC)

HUMAN RESEARCH ETHICS APPROVAL CERTIFICATE

NHMRC Registered Committee Number EC00171

Date of Issue: 24/4/15 (supersedes all previously issued certificates)

Dear Mr Hussain Mubarak D Aldossari

This approval certificate serves as your written notice that the proposal has met the requirements of the *National Statement on Ethical Conduct in Human Research* and has been approved on that basis. You are therefore authorised to commence activities as outlined in your application, subject to any specific and standard conditions detailed in this document.

Project Details

Category of Approval: Human Negligible-Low Risk

Approved From: 16/04/2013

Approved Until: 16/04/2016 (subject to annual reports)

Approval Number: 1300000162

Project Title: Accommodation effects on peripheral ocular biometry

Investigator Details

Chief Investigator: Mr Hussain Mubarak D Aldossari

Other

Investigator Name	Type	Role
A/Prof Katrina	Internal	Supervisor
Prof David Atchison	Internal	Supervisor
Dr Marwan Suheimat	Internal	Supervisor

Conditions of Approval

Specific Conditions of Approval:

None apply

Standard Conditions of Approval:

1. Conduct the project in accordance with QUT policy, the ***National Statement on Ethical Conduct in Human Research*** (http://www.nhmrc.gov.au/guidelines/publications/e72), the ***Australian Code for the Responsible Conduct of Research*** (http://www.nhmrc.gov.au/guidelines/publications/r39), any associated legislation, guidelines or standards;
2. Gain UHREC approval for any proposed variation (http://www.orei.qut.edu.au/human/var/) to the project

prior to implementation;

3. Respond promptly to the requests and instructions of UHREC;
4. Immediately advise the Office of Research Ethics and Integrity (http://www.orei.qut.edu.au/human/adv/) if:
    - any unforeseen development or events occur that might affect the continued ethical acceptability of the project;
    - any complaints are made, or expressions of concern are raised, in relation to the project;
    - the project needs to be suspended or modified because the risks to participants now outweigh the benefits;
    - a participant can no longer be involved because the research may harm them; and
5. Report on the progress of the approved project at least annually, or at intervals determined by UHREC. The Committee may also choose to conduct a random audit of your project.

If any details within this Approval Certificate are incorrect please advise the Research Ethics Unit within 10 days of receipt of this certificate.

End of Document

Appendix 2 - Conference presentation

Aldossari, H, Atchison DA, Suheimat M, Schmid, KL. The effect of accommodation on peripheral eye lengths of myopes and emmetropes. Institute of Health and Biomedical Innovation (IHBI) Inspires postgraduate student conference, November, 2013, Gold Coast, Australia.