Peripheral refraction: relationship to myopia, and manipulation using contact lenses

Author:
Kang, Pauline

Publication Date:
2012

DOI:
https://doi.org/10.26190/unsworks/15312

PERIPHERAL REFRACTION: RELATIONSHIP TO MYOPIA, AND MANIPULATION USING CONTACT LENSES

Pauline Kang *B.Optom (Hons)*

A thesis submitted in partial fulfilment of the requirements for admission to the degree of Doctor of Philosophy

School of Optometry and Vision Science
The University of New South Wales
Sydney, Australia

February 2012

PLEASE TYPE
THE UNIVERSITY OF NEW SOUTH WALES
Thesis/Dissertation Sheet

Surname or Family name: **Kang**

First name: **Pauline** Other name/s: **Heseon**

Abbreviation for degree as given in the University calendar: **PhD**

School: **Optometry and Vision Science** Faculty: **Science**

Title: **Peripheral refraction: relationship to myopia and manipulation using contact lenses**

Abstract 350 words maximum: (PLEASE TYPE)

The aims of this thesis were to investigate peripheral refraction in different refractive groups and verify the use of peripheral refraction as a measure of ocular shape. Furthermore, manipulation of peripheral refraction with orthokeratology (OK) and soft contact lenses (SCLs) for potential myopia control were explored.

Characteristic peripheral refraction profiles were measured using the Shin-Nippon NVision-K 5001 autorefractor in emmetropes (relative peripheral myopia) and myopes (relative peripheral hyperopia). East Asian moderate myopes had greater amounts of relative peripheral hyperopia compared to Caucasians with a similar central refractive error. This was interpreted to reflect a more prolate ocular shape in the myopic Asian eye.

Calculated axial length from peripheral refraction was found to comparable to direct axial length measurements with the IOLMaster in the nasal retina and to underestimate axial length in the temporal retina. Although not entirely comparable, peripheral refraction is still able to give information on the shape of eyes with different refractive errors.

Conventional corrections of central myopia induce hyperopia onto the peripheral retina. However, OK lenses were found to cause a hyperopic shift in the central visual field (VF) in both myopic children and adults. This caused peripheral refraction which was initially relatively hyperopic to become relatively myopic compared to the central refraction. Furthermore, changing the optic zone diameter or steepening the periphery of the OK lens was found to cause no significant effect.

Relative hyperopic peripheral refraction was measured along the horizontal VF with under (+0.75DS), full, over (-0.75DS) SCL correction and multifocal SCLs with a distance centre and plus power (+2.00) periphery were found to induce less peripheral hyperopia compared to single vision (SV) SCL correction.

OK allows the peripheral retina to experience myopic defocus while central myopia is corrected, and multifocal SCLs are able to reduce the amount of relative peripheral hyperopia compared to SV SCLs. This may explain the reduced myopia progression reported with OK and multifocal SCLs. The effects of manipulating other OK lens parameters for potential customised myopia control are yet to be explored, and the impact of myopic peripheral defocus on myopia progression in children is yet to be ascertained.

FOR OFFICE USE ONLY Date of completion of requirements for Award:

THIS SHEET IS TO BE GLUED TO THE INSIDE FRONT COVER OF THE THESIS

ORIGINALITY STATEMENT

'I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at UNSW or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked at UNSW or elsewhere, is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.'

Signed .....

Date .....

COPYRIGHT STATEMENT

Signed .....

Date .....

AUTHENTICITY STATEMENT

'I certify that the Library deposit digital copy is a direct equivalent of the final officially approved version of my thesis. No emendation of content has occurred and if there are any minor variations in formatting, they are the result of the conversion to digital format.'

Signed .....

Date .....

ABSTRACT

Recent human and animal studies have demonstrated the potential large influence of the peripheral retina on the development of central refractive error. Thus, it is currently hypothesised that inducing myopia onto the peripheral retina of myopes could possibly stop or slow down the progression of central myopia. The aims of this thesis were to investigate peripheral refraction in different refractive groups and verify the use of peripheral refraction as a measure of ocular shape. Furthermore, manipulation of peripheral refraction with orthokeratology (OK) and soft contact lenses (SCLs) for potential myopia control were explored.

In the research reported in this thesis, peripheral refraction profiles in emmetropic and myopic young adults were measured with the Shin-Nippon NVision-K5001 autorefractor and characteristic peripheral refraction profiles were found, confirming previous reports. Relative peripheral myopia was measured in emmetropes while relative peripheral hyperopia was found in low myopes and to a greater degree in moderate myopes. Furthermore, differences in peripheral refraction profiles were found between moderate myopes of different ethnic groups. East Asian moderate myopes had greater amounts of relative peripheral hyperopia compared to Caucasians with a similar central refractive error ($p=0.014$). This was interpreted as potentially reflecting a more prolate ocular shape in the myopic Asian eye, based on inferences from peripheral refraction.

To verify the use of peripheral refraction to describe ocular shape, peripheral axial lengths were calculated from peripheral refraction data and compared to direct measurements of peripheral axial lengths using the IOLMaster. Calculated axial length from peripheral refraction was comparable to direct axial length measurements in the nasal retina. Calculated axial length in the temporal retina tended to underestimate direct measurements by 0.29 ± 0.45mm. Both techniques indicated prolate ocular shapes in all refractive groups with myopes showing the most

and hyperopes the least prolate shape. Inferring ocular shape from peripheral refraction may not be an oversimplification.

Conventional corrections of central myopia induce hyperopia onto the peripheral retina of myopic individuals and it has been proposed that this peripheral hyperopia may drive the development of central myopia. Thus changes in peripheral refraction were investigated with OK lenses in both myopic adults and children. OK lenses were found to cause a hyperopic shift between 30° in the temporal visual field (VF) and 20° in the nasal VF in myopic children, and between 30° in the temporal VF and 10° in the nasal VF in myopic adults. This caused peripheral refraction which was initially relatively hyperopic to become relatively myopic compared to the central refraction.

To explore the possibility of inducing specified changes in peripheral defocus, the effects of changes in OK lens parameters were investigated. Changing the optic zone diameter (OZD) of an OK lens from a standard 6mm diameter to 5mm diameter was found to cause no significant changes in peripheral refraction profiles ($p>0.05$) or corneal topography ($p>0.05$). Furthermore, steepening the periphery of the OK lens by changing the tangent from a ¼ to a ½ was also found to cause no significant effect ($p>0.05$).

To determine if SCLs are a more predictable means of manipulating peripheral refraction, the effects of under (+0.75DS), full, over (-0.75DS) and multifocal SCL correction (distance centre and +2.00D peripheral add) on peripheral refraction were explored. Relative hyperopic peripheral refraction along the horizontal VF was found at all different levels of single vision (SV) SCL correction, and multifocal SCLs with a plus power periphery were found to induce less peripheral hyperopia compared to SV SCL correction.

From the results of the research reported in this thesis, we were able to determine that OK allows the peripheral retina to experience myopic defocus while central myopia is corrected, and that multifocal SCLs are able to reduce the amount of relative peripheral hyperopia compared to SV SCL correction. This may explain the reduced myopia progression reported with OK and multifocal SCL wear. The possibility of peripheral refraction manipulation for potential customised myopia

control is still unclear as only two OK lens parameters were investigated and changes in the OZD and tangent were found to have little effect on peripheral refraction. The effects of manipulating other OK lens parameters are yet to be explored, and the impact of myopic peripheral defocus on myopia progression in children is yet to be ascertained.

ACKNOWLEDGEMENTS

My thesis would not have been possible without the encouragement and support from family, friends and colleagues.

First and foremost I would like to sincerely thank my supervisor, Professor Helen Swarbrick, who is an inspirational woman and teacher with a tremendous amount of wisdom. Without Helen's guidance, ideas and support, I would not have accomplished my achievements. I consider myself very fortunate to have had you to mentor and supervise me and I hope that we continue to work together in the future. I am also grateful to my co-supervisor Associate Professor David Pye for his constant support and encouragement.

I have also had the privilege to be a part of the Research in Orthokeratology (ROK) group where I have been fortunate enough to work with Dr Paul Gifford, Dr Ahmed Alharbi, Arzu Demir, Helen O'Shea, Edward Lum, Vinod Maseedupally and Kathleen Watt. Particular mention goes to Paul Gifford for his tremendous help and advice, and Arzu Demir and Helen O'Shea who provided constant encouragement and friendship.

The research presented in this thesis would not have been possible without financial support from the APAI scholarship, which was funded through an Australian Government ARC Linkage Project scheme grant supported by industry partners Boston Products Group of Bausch & Lomb (USA), BE Enterprises and Capricornia Contact Lens (Australia). I give my sincere thanks to Don Noack for his time in designing and manufacturing all the lenses used in this thesis and to John Mountford for his advice on lens designs.

I would like to also thank Drs Chitralekha and Kodikullam Avudainayagam for their help in ray tracing, Brett Davis for his help in corneal topography analysis and Edward Lum for producing the peripheral fixation device.

I sincerely thank Dr Lisa Asper and Dr Mei Boon, and in particular Associate Professor Barbara Junghans and my supervisor Professor Helen Swarbrick, who have given me the opportunity to be a part of academic teaching. Without this opportunity, I would not have developed my interest in academia and I am very grateful for this experience. Additionally, I would like to thank all the postgraduate students who have helped me with my studies and given me advice with my work, in particular to Brian Cheng for all his IT help.

Furthermore, I would like to thank the undergraduate students who were a part of many of the studies presented in this thesis, including Lindsay Bloch, Yvonne Fan, Sarah Gosling, Doug Grimson, Philomena McNamara, Kelly Oh, Jenna Owen, Kevin Trac, Bonney Vong, Jenny Wu, Stephanie Yeo and Frank Zhang. I also thank all the subjects who participated in the studies presented in this thesis.

Last but not least, my family and friends have given me the motivation and courage to undertake a PhD and provided unyielding support and encouragement throughout my candidature. My mum has supported me in any decision I have made and she has always gone above and beyond to take care of me. I am forever grateful for all the opportunities that have been made possible because of you and sincerely appreciate all that you have done for me. My sister Helen and my brother in law Owen are two inspiring and admirable people who have never hesitated to provide help or advice. Thank you for all your assistance not only in my PhD, but in all other aspects of my life. Dad, I hope you are proud of me.

My dearest friends Sun, Susan, Jenny, Mihyun, Thu, Kim, Yumi, Nisha and Dru. I am sincerely grateful for the invaluable friendships we have and thank you for all the support you have given me throughout my candidature.

THIS THESIS IS DEDICATED

TO MY LOVING PARENTS, HELEN AND OWEN

'The love of a family is life's greatest blessing'

Unknown

TABLE OF CONTENTS

FIGURES

TABLES

ABBREVIATIONS

BFS – best fit sphere

COAS – Complete Ophthalmic Analysis System

CL – contact lens

CRT – corneal refractive therapy

CT – computed tomography

EOM – extraocular muscle

LCA – longitudinal chromatic aberrations

MRI – magnetic resonance imaging

OK – orthokeratology

OZD – optic zone diameter

OZR – optic zone radius

PAL – progressive addition lens

PCI – partial coherence interferometry

RGP – rigid gas-permeable

RPR – relative peripheral refraction

SCL – soft contact lens

SD – standard deviation

SV – single vision

TD – total lens diameter

TZD – treatment zone diameter

VA – visual acuity

VF – visual field

CHAPTER 1

LITERATURE REVIEW

1.1 MYOPIA

1.1.1 DEFINITION

Myopia, more commonly known as short-sightedness, is a condition where parallel rays of light entering the unaccommodating eye converge and focus in front of rather than on the retina (Rabbetts, 2007b).

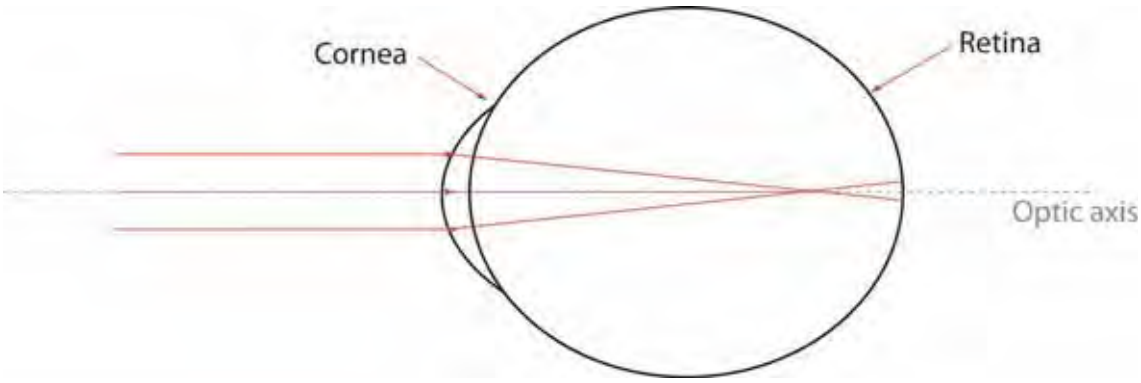


Figure 1.1 Simple ray tracing demonstrating parallel light rays converging in front of the retina in a myopic eye.

1.1.2 CLASSIFICATION

Myopia can be classified by a plethora of criteria which tend to reflect either the cause or course of the ocular condition.

Myopia can be a result of a single or combination of ocular refractive elements having too high a power and this is termed refractive myopia. Ocular parameters include the anterior and posterior curvature of the cornea and crystalline lens as well as the

refractive indices of the anterior chamber, crystalline lens and vitreous. The second and most common cause of myopia is axial elongation, whereby the axial length of the eye exceeds the focal length formed by the refractive components of the eye. This is termed axial myopia (Edwards, 1998). Elongation of the eye is usually due to increase in length of the vitreous chamber (McBrien and Adams, 1997, Xie et al., 2009). This elongation can occur through equatorial (peripheral) stretching, elongation of the central posterior pole or through global expansion as illustrated in Figure 1.2 a, b and c, respectively.

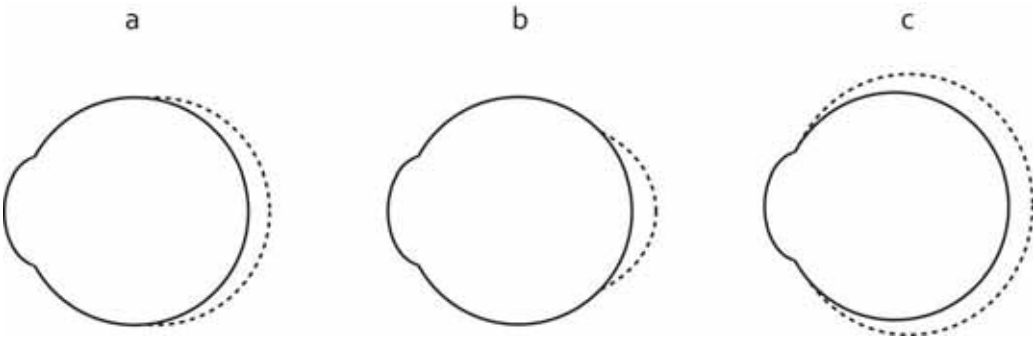


Figure 1.2. Classification of myopia by type of ocular expansion a) equatorial stretching b) posterior pole elongation and c) global expansion (adapted from Atchison et al, 2004).

Myopic eyes are typically longest axially (z-dimension), then vertically (y-dimension) and then horizontally (x-dimension) compared with emmetropic eyes (Atchison et al., 2004). Approximately 0.35mm increase in axial length is associated with 1 dioptre of myopic refraction (Atchison et al., 2004, Atchison et al., 2005a).

Myopia can also be classified by the degree of refractive error. Myopia of less than -3D is generally classified as low myopia, between -3D to -6D typically as moderate myopia and greater than -6D as high myopia (Edwards, 1998).

Myopia can be further classified by onset. Children who are born with myopia are classified as having congenital myopia. Myopia which manifests between approximately 6 years of age and teenage years is termed youth onset myopia and myopia which becomes apparent between the ages of 20-40 years is classified as

adult-onset myopia. Moreover, development of myopia after 40 years of age is termed late adult-onset myopia (Grosvenor, 1987).

1.1.3 PREVALENCE

The prevalence of myopia has increased at an alarming rate, particularly in the last generation. Although prevalence figures differ depending on region, the general trend is an increase in prevalence worldwide (Edwards and Lam, 2004, Lin et al., 2004, Rose et al., 2001, Saw, 2003).

In the United States, approximately 33% of all individuals over the age of twelve have been reported to be myopic (Vitale et al., 2008). In Australia, average prevalence rates of 8.4% (Junghans and Crewther, 2005) and 10% (Martinez, 2007) were found across several studies investigating the epidemiology of myopia in children, one of the lowest prevalence rates reported in Western countries.

Significantly high prevalence rates have been documented in Asia (Edwards, 1999, Fan et al., 2004, He et al., 2007, He et al., 2004, Lam et al., 2004, Lin et al., 1999). Lin et al (1999) reported an alarming myopia prevalence rate of 84% in Taiwanese school children aged between 16 to 18 years while Lam et al (2004) reported a rate of 82.8% in 13 to 15 year old Chinese children. It appears that East Asians have the greatest myopia prevalence rate irrespectively of location (Ip et al., 2008, Kleinstein et al., 2003, Rose et al., 2008b). Additionally, the prevalence rate of myopia is increasing (Lin et al., 2004). The age of onset of myopia is becoming younger (Lin et al., 2004) which is of great concern as faster progression rates have been associated with earlier age of myopia onset (Edwards, 1999, Saw et al., 2000). This is likely to contribute to not only an increased severity of myopia within the population, but also an increased prevalence.

High prevalence rates (38.7%) continue to be reported in the older Asian population, 40 years and older (Wong et al., 2000), compared to Western countries such as the United States (26.2%) (Kempen et al., 2004) and Australia (15%) (Attebo et al., 1999).

Higher prevalence rates are also reported in urban areas compared to rural areas and this discrepancy has been attributed to differences in lifestyle (He et al., 2009, Saw, 2003, Saw et al., 2001a).

1.1.4 ASSOCIATED RISKS

Research into myopia control continues due to risks of pathological changes and the economical burden associated with myopia.

1.1.4.1 PATHOLOGICAL CHANGES

Excessive ocular elongation evident in high myopes (at least -6D) increases the risk of development of a number of sight threatening pathologies. These include glaucoma (Grodum et al., 2001, Mitchell et al., 1999, Saw et al., 2005a) and maculopathies (Hsu et al., 2004, Iwase et al., 2006, Xu et al., 2006) as well as various pathological vitreal and retinal changes (Grossniklaus and Green, 1992, Lai et al., 2008, Lam et al., 2005, Saw et al., 2005a, Yura, 1998). Retinal changes include staphylomas, lacquer cracks, chorioretinal atrophies (Vongphanit et al., 2002) and retinal detachments (Grossniklaus and Green, 1992). High myopia is also associated with cataracts (Lim et al., 1999, Wong et al., 2001). This makes myopia one of the most important causes of blindness, particularly in regions of the world with high myopia prevalence rates (Hsu et al., 2004, Iwase et al., 2006, Liang et al., 2008, Michon et al., 2002, Xu et al., 2006).

Malignant, degenerative or pathological myopia are terms coined to describe myopia accompanied by degenerative ocular changes.

1.1.4.2 SOCIAL AND FINANCIAL BURDEN

Myopia not only increases the risk of development of ocular pathology as described in Section 1.1.4.1, but it is also a social and financial burden on the individual (Berdeaux et al., 2002, Javitt and Chiang, 1994, Lim et al., 2009). It has been estimated that $8.1 billion dollars was spent in the United States in 1990 on optical devices and approximately $3.2 billion dollars spent on professional services for refractive error (Javitt and Chiang, 1994). In Singapore, the average annual direct cost of myopia was calculated to be approximately US$147.8 (Lim et al., 2009).

It has also been estimated that 3 hours is spent on travelling, waiting and receiving eye care while another 2 hours is spent on selecting frames and travelling back for final dispensing. Thus indirect costs of refractive error were estimated to be $1.5 billion dollars in the United States in 1990 (Javitt and Chiang, 1994).

1.1.5 CAUSES

There is much debate on the etiology of myopia and hence there are numerous proposed causes and treatment options. Myopia is a complex trait and many would argue more than one contributing factor is likely to be involved in the etiology of myopia and that both nature and nurture play a role in its development and progression.

1.1.5.1 GENETICS

Evidence for the involvement of genetics in myopia development is demonstrated through the high prevalence of myopia in children with one or two myopic parents. Studies have reported that children with one or two myopic parents are at greater risk of development of myopia (Lam et al., 2008, Mutti et al., 2002, Saw et al., 2001b, Zadnik, 1997, Zadnik et al., 1994). Longest axial lengths and deepest vitreous chamber depths were measured in children with two myopic parents followed by

children with one myopic parent and then by children with no myopic parents (Lam et al., 2008). Even before the progression of myopia, children with two myopic parents have been found to have longer anterior and vitreous chambers (Zadnik et al., 1994).

Saw et al (2001b) have reported an apparent association between parental myopia and progression. They found that children with one or two myopic parents had significantly higher myopia progression rates compared to children who had no myopic parents (0.63D compared to 0.42D per year). Lam et al (2008) reported similar findings with children with two myopic parents presenting the greatest annual myopia progression and axial length growth (-0.22D and 0.37mm, respectively) followed by children with one myopic parent (-0.07D and 0.26mm) and then by children with no myopic parents (-0.02D and 0.20mm). Parental myopia was ascertained through interview rather than through direct measurements in the two mentioned studies. Kurtz et al (2007) who reported similar findings overcame this issue by taking actual measurements of the parent's refractive error.

One of the strongest pieces of evidence for the role of inheritance of myopia arises from twin studies. Monozygotic or identical twins appear to be more likely to possess similar refractive states as well as ocular components compared to dizygotic or non-identical twins (Guggenheim et al., 2000, Hammond et al., 2001, Tsai et al., 2009).

1.1.5.2 ENVIRONMENT

1.1.5.2.1 HUMAN STUDIES

Support for the influence of the environment on the development of myopia arises from the positive relationship between increase in prevalence of myopia and increase in near work, in particular school work. Hence the term 'school myopia' was developed to reflect the apparent association between school work and myopia development. Moreover, the dramatic increase in prevalence of myopia (Section 1.1.3) in a single generation is too great to be explained by genetics alone.

Rigorous schooling systems in Asia, and thus the long hours spent on near work, have been suggested as a possible cause of high rates of myopia reported in Asia (Edwards, 1999, Fan et al., 2004, He et al., 2007, He et al., 2004, Lam et al., 2004, Lin et al., 1999). Higher education levels, which are often used as a surrogate for greater close work, have been found to be associated with high myopia prevalence (He et al., 2009, Saw et al., 2001c, Wu et al., 2001). Performing more than 20.5 hours of reading and writing per week was found to be associated with myopia in Singapore high school students (Quek et al., 2004). Children aged between 7 to 9 years who read more than two books per week were more likely to be myopic (Saw et al., 2002b). Longer axial lengths and vitreous chamber depths were associated with reading more than two books per week (Saw et al., 2002a). Faster rates of myopia progression have been reported during times of intense studying and lower rates during school holidays (Fulk et al., 2002, Tan et al., 2000), reinforcing the proposal that greater near work contributes to myopia onset and progression. Slower myopia progression rates during school holidays may also be associated with higher than average ambient illuminance levels (Rose et al., 2008a). Evidence of illuminance effects on myopia development have been demonstrated in chicks whereby high ambient illuminance levels retarded the development of form deprivation myopia (Ashby et al., 2009).

However, not all studies have identified the association between near work and myopia development. Mutti et al (2002) detected a small contribution of near work to myopia prevalence and Wu et al (2001) found that differences in education level could not fully explain the differences in myopia prevalence rates between ethnicities apparent in the 15095 Singaporean military conscripts who were recruited for the study. Moreover, Saw et al (2001b) found no association between near work and myopia progression.

However, it must be noted that the measurement of near work varies between studies whereby some have measured the number of hours spent on near work (Mutti et al., 2002, Saw et al., 2001a, Tan et al., 2000) while others have used the number of books read per week as a measure of near work (Saw et al., 2002a, Saw et al., 2002b).

Differences in myopia prevalence rates between urban and rural areas in the same country also provide evidence for the influence of the environment on myopia development (He et al., 2009, Saw, 2003, Saw et al., 2001a). Saw et al (2001a) suggested that the greater amount of time spent on near work by children in urban compared to rural China could contribute to the higher myopia prevalence rates.

Due to the apparent association between near work and myopia, studies have investigated accommodation and convergence in myopic individuals. Higher AC/A ratios, which are associated with reduced accommodation, have been detected in myopic children (Gwiazda et al., 1999, Mutti et al., 2000a). Children who become myopic have been found to have elevated response AC/A ratios up to 2 years before myopia onset compared to children who remain emmetropic (Gwiazda et al., 2005) and similarly in young emmetropic adults who later developed myopia (Jiang, 1995). Higher AC/A ratio has been found to be a risk factor for the development of myopia in children (Mutti et al., 2000a).

Reduced accommodation or increased lag of accommodation have also been detected in myopic children compared to emmetropic (Berntsen et al., 2011, Gwiazda et al., 1995, Gwiazda et al., 1993, Gwiazda et al., 2005) and hyperopic children (McBrien and Millodot, 1986). The increased lag of accommodation appears to be evident even before the onset of myopia (Goss, 1991, Gwiazda et al., 2005). It has been suggested that this increased lag of accommodation could be a potential myopiogenic factor, as animal studies across numerous species have demonstrated that imposed hyperopic retinal defocus encouraged axial length elongation while myopic defocus inhibited axial elongation (Irving et al., 1992, Smith and Hung, 1999, Wallman et al., 1995, Wallman and Winawer, 2004, Wildsoet and Wallman, 1995). This will be discussed in further detail in Section 1.1.5.2.2. The results from these numerous studies suggest that myopes appear to possess abnormal accommodative function which may lead to myopia development. However, conflicting results were reported by Mutti et al (2006) who found that although a higher accommodative lag was evident after the onset of myopia, there was no significant difference in accommodative lag until the year after the onset of myopia between children who

became myopic compared to those children who remained emmetropic. Accommodative lag appeared to not play a significant role in myopia development. Furthermore Weizhong et al (2008) and very recently Berntsen et al (2011) disclosed no association between accommodative lag and myopia progression in children who participated in the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study.

Support for environmental influence on myopia development is also reflected through the positive association of myopia with individuals in occupations that require high demands on near work. 49% of the 251 adult clinical microscopists investigated were found to have an onset of myopia progression after entering their profession (Adams and McBrien, 1992). Myopic shift in central refraction in this group of clinical microscopists was found to be caused predominantly by vitreous chamber elongation (McBrien and Adams, 1997). Higher myopia prevalence rates and higher rates of adult-onset myopia were also found in Singaporean women who worked compared to those who did not work (Saw et al., 1999).

The amount of time spent outdoors also has an apparent link with risk of myopia development. Jones et al (2007) found that more time spent on sporting or outdoor activities reduced the odds of developing myopia by the eighth grade. Dirani et al (2009) reported that the total time spent outdoors was negatively associated with myopia and positively associated with shorter axial length. The Sydney Myopia Study suggested a protective role for outdoor activity (Rose et al., 2008b), and not sports alone (Rose et al., 2008a), from myopia development. Outdoor activity may be related to higher than average ambient illuminance levels which, as previously mentioned, has been associated with slower myopia progression rates in children (Rose et al., 2008a) and shown to retard the development of form deprivation myopia in chicks (Ashby et al., 2009).

1.1.5.2.2 ANIMAL STUDIES

Animal studies provide further evidence of the influence of the environment or visual input on the development of refractive error. Obscuring or degrading images on the retina through either diffusers or lid suture results in elongation of the eye and hence myopia, termed form deprivation myopia. As there is no point of focus, the eye continues to elongate as demonstrated in marmosets (Troilo et al., 2000), tree shrews (Marsh-Tootle and Norton, 1989, McBrien and Norton, 1992), monkeys (Hung et al., 1995, Smith et al., 1987), chicks (Schaeffel et al., 1988, Wallman and Adams, 1987, Wallman et al., 1978) and mice (Tejedor and de la Villa, 2003). Brief periods of unrestricted vision are able to counterbalance the effects of form deprivation (Napper et al., 1995, Smith et al., 2002).

Animals have also been found to respond to a range of refractive defocus (Figure 1.3). Both choroidal and scleral responses to induced defocus have been reported. A minus lens will create a hyperopic defocus to which the retina responds by either increasing in axial length and/or thinning of the choroid (Hung et al., 1995, Hung et al., 2000, Irving et al., 1992, Schaeffel et al., 1988, Shaikh et al., 1999, Wallman et al., 1995, Wildsoet and Wallman, 1995, Wildsoet, 1997) in order to bring the image in focus on the retina. Positive lenses which create myopic defocus on the retina have been found to reduce axial length growth or increase the thickness of the choroid (Hung et al., 2000, Irving et al., 1995, Irving et al., 1992, Schaeffel et al., 1988, Wildsoet and Wallman, 1995, Wildsoet, 1997).

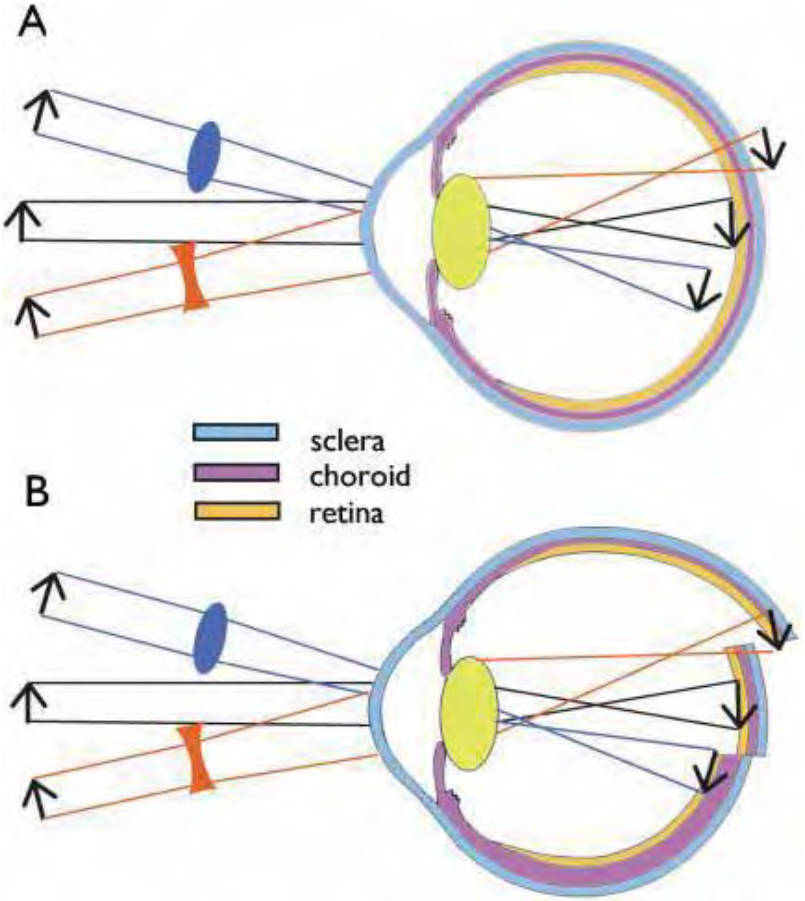


Figure 1.3 Schematic diagram of choroidal and scleral response to myopic and hyperopic defocus imposed on the retina (Reproduced from Wallman, J. & Winawer, J. Homeostasis of eye growth and the question of myopia. *Neuron*, 43, 447-68. Copyright (2004), with permission from Elsevier).

Studies have found that the response of the eye to imposed defocus is locally mediated. Optic nerve sectioning or blockage of its action potentials did not impede lens compensation (Norton et al., 1994, Troilo et al., 1987, Wildsoet and Pettigrew, 1988, Wildsoet and Wallman, 1995). Furthermore, lenses or diffusers placed to cover only part of the retina caused only the corresponding posterior region to respond (Diether and Schaeffel, 1997, Hodos and Kuenzel, 1984, Smith et al., 2009a, Wallman et al., 1987) (Figure 1.4).

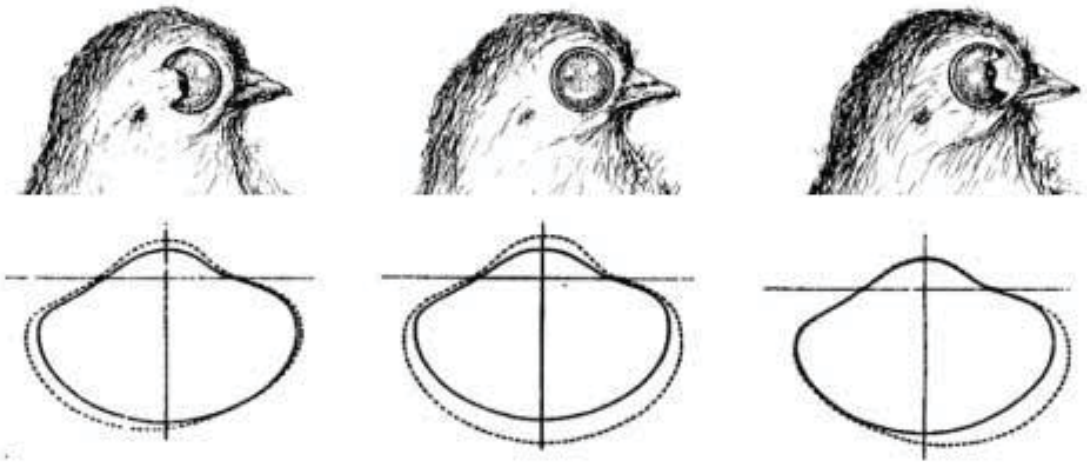


Figure 1.4 Traces from photographs of the right eye of chicks which experienced form deprivation over temporal retina (left) the entire eye (centre) and nasal retina (right) viewed from above. The dashed lines represent the experimental eye while the solid lines represent the contra-lateral control or untreated eye (Reproduced from Wallman, J. & Winawer, J. Homeostasis of eye growth and the question of myopia. *Neuron,* 43, 447-68. Copyright (2004), with permission from Elsevier).

Due to similar responses in lens compensating ocular growth with plus and minus lenses across a range of species, it is likely that human ocular growth may also be controlled by visual feedback.

1.1.6 TREATMENT

1.1.6.1 SPECTACLES

1.1.6.1.1 SINGLE VISION LENSES

Single vision (SV) lenses are one of the most routinely prescribed forms of refractive correction. However, there are limited studies on the effects of SV lens correction on myopia progression. Ong et al (1999) investigated the effects of different corrective lens wear patterns on myopia progression. Although statistically similar progression

rates were found in children with no correction compared to full or part time correction, children with no correction had the smallest myopia progression rate. Conversely, a more recent study (Chung et al., 2002) found that under-correcting myopic children aged 9-14 years by +0.75D produced faster myopia progression rates compared to full correction (-1.00D compared to -0.77D) over 2 years. The myopic defocus imposed by under-correction was anticipated to stimulate reduced axial length elongation reflecting animal studies which have shown that positive lenses appeared to reduce axial length growth or increase the thickness of the choroid (Hung et al., 2000, Irving et al., 1995, Irving et al., 1992, Wildsoet and Wallman, 1995, Wildsoet, 1997) to bring the image into focus on the retina (Section 1.1.5.2.2). Chung et al (2002) suggested that myopes may have an abnormal mechanism for detecting the direction of retinal image defocus which resulted in axial elongation despite under-correction.

1.1.6.1.2 MULTIFOCAL LENSES

Reduced accommodation has been found in myopes as described in Section 1.1.5.2.1, and the extended periods of retinal defocus consequent on the increased lag of accommodation is believed to potentially lead to axial elongation as suggested by animal studies (Section 1.1.5.2.2). The rationale behind multifocal or bifocal lenses with a near add is to reduce the amount of retinal defocus during near work which may potentially slow down the progression of myopia. There have been a few studies which have investigated the effects of either progressive addition lenses (PALs) or bifocal lenses on myopia progression in children.

The Correction of Myopia Evaluation Trial (COMET) was a multi-centre, double masked, randomised clinical trial comparing the effects of conventional SV lenses and PALs on myopia progression (Gwiazda et al., 2003). 462 myopic children completed the study and it was found that after 3 years of treatment, those with PALs had slower myopia progression rates (-1.28 ± 0.06D) compared to SV lens correction (-1.48 ± 0.06D). However, the difference in effect between the two types of correction was clinically insignificant (0.20 ± 0.08D).

A cross-over design study (Hasebe et al., 2008) was conducted in Japan similarly investigating the effect of PALs compared to SV lens correction on myopia progression in 6 to 12 year old children. The 92 children participants were randomly allocated to either wear PALs for 18 months followed by SV lenses for the next 18 months, or to initially wear SV lenses for 18 months followed by PALs for the second 18 month period. PALs produced less myopia progression by a statistically significant mean amount of 0.17 ± 0.05D compared to SV lenses at the end of the first 18 month phase (-0.89 ± 0.06D compared to -1.20 ± 0.08D, respectively). During the second 18 month period, the myopia progression rates between PALs and SV lenses were similar (-0.92 ± 0.07D compared to -0.94 ± 0.07D, respectively). The group of children who initially wore SV lenses however had an overall higher rate of myopia progression by -0.29D. It was suggested that early intervention with PAL correction may have a greater effect on myopia progression. Both the studies described (Gwiazda et al., 2003, Hasebe et al., 2008) found children with larger lags of accommodation or children with esophoria or orthophoria had larger treatment effects than those with small lags of accommodation or exophoria.

Conversely, another study conducted in Hong Kong (Edwards et al., 2002) found no difference in myopia progression and axial lengths in a group of children who wore PALs compared to another group wearing SV lenses over a two year period. Fulk et al (2000) found a mean myopia progression of -0.99D ± 0.68D with bifocals and -1.24D ± 0.65D with SV lenses over 30 months. Although statistically significant differences in myopia progression between PALs and SV lenses were evident, the mean difference in myopia progression demonstrated was clinically insignificant.

The Correction of Myopia Evaluation Trial 2 (COMET2) study (Gwiazda et al., 2011) recently reported that over a 3 year period, myopic children with at least 2 prism dioptres of esophoria had less overall myopia progression (-0.87 ± 0.82D) with PALs compared with SV lenses (-1.15 ± 0.75D). Thus PALs appear to reduce myopia progression by a clinically significant amount compared to SV lenses in children with esophoria.

1.1.6.2 CONTACT LENSES

Contact lenses (CLs) are another popular means of myopia correction. Earlier studies investigated the effects of SV CLs on the progression of myopia. Recently multifocal lenses have also gained attention as a possible means of myopia correction and control.

1.1.6.2.1 SINGLE VISION CONTACT LENSES

1.1.6.2.1.1 Rigid gas-permeable contact lenses

One of the earliest studies investigating the effect of rigid gas-permeable (RGP) lenses was by Stone (1976). Annual myopia progression of -0.08D was reported compared to -0.37D in spectacle lens wearers. It was concluded that about half of the control of myopia was due to corneal flattening. More recent studies such as that by Khoo et al (1999) found a significant difference in annual axial length increase between children wearing RGP lenses compared to SV spectacle lenses (0.22mm compared to 0.31mm, respectively). Additionally, a statistically significant difference in corneal curvature was detected with RGP lens wearers having flatter corneas compared to spectacle wearers by a mean of 0.08D. Due to poor RGP adaptation there was a very high dropout rate of nearly 50% in addition to large inter-subject variation. Perrigin et al (1990) determined that the difference in myopia progression between RGP lenses (-0.48 ± 0.70D) compared to SV spectacles (-1.53 ± 0.81D) could be explained in part by flattening of the cornea with RGP lens wear. Similar to Khoo et al (1999), this study suffered a high dropout rate.

More recently, Katz et al (2003) measured no significant difference in myopia progression and axial length increase over a 2 year period between children wearing RGP lenses and SV spectacle lenses. A recent clinical trial, the Contact Lens and Myopia Progression (CLAMP) study (Walline et al., 2001), recruited 116 children and found that myopia progression was -1.56 ± 0.95D in RGP wearers and -2.19 ± 0.89D for SCLs worn over a 3 year period. Although myopia progression was significantly

different between the two types of CL correction, at the end of the 3 years no significant difference in axial length growth was evident. Furthermore, there was reduced corneal steepening in RGP wearers (0.62 ± 0.60D) compared to SCL wearers (0.88 ± 0.57D) during the 3 years. It was suggested that the difference in corneal steepening (corneal flattening with RGP lenses) could account for the difference in myopia progression apparent between the two types of CLs.

From these studies, it appears that reduction in myopia progression detected with RGP lens wear is due in part to corneal flattening subsequent to lens wear. No change in axial length growth with RGP lens wear compared to SCL (Walline et al., 2001) or spectacle lenses (Katz et al., 2003, Khoo et al., 1999) indicates that conventional RGP lenses have a minimal impact on myopia progression.

1.1.6.2.1.2 Soft contact lenses

Earliest reports on myopia progression with full correction SCLs appeared in the early 1970s whereby increased myopia progression was reported to be associated with SCL wear (Barnett and Rengstorff, 1977, Grosvenor, 1975, Harris et al., 1975). However recent studies have shown no significant difference in myopia progression between daily SCL wear compared to SV spectacle lens wear (Andreo, 1990) even over a three year period (Horner et al., 1999). Walline et al (2008) recently published a study comparing 247 SCL and 237 SV spectacle lens wearers and confirmed no significant difference in corneal curvature or axial length increase between the two types of correction.

Higher myopia progression rates have been reported in children who switched from spectacles to SCLs. Average rates of -0.74D and -0.76D of myopia progression in one year were found in 19 adolescents who changed from SV and bifocal spectacles to SCLs respectively, compared to children who remained in SV (-0.23D) or bifocal lenses (-0.26D). Recently, Marsh-Tootle et al (2009) reported that children who switched from glasses to SCLs experienced a statistically significant but clinically insignificant

increase in myopia progression. Current studies appear to indicate that SCL wear has no significant effect on the progression of myopia.

1.1.6.2.2 MULTIFOCAL SOFT CONTACT LENSES

There has been a great surge of interest in the state of defocus on the peripheral retina with both animal and human studies suggesting a significant influence of the peripheral retina on the development of central refractive error (discussed later in Section 1.2.3). Two commercially available multifocal lenses have since been developed which are designed to induce a myopic defocus onto the peripheral retina through a plus peripheral power. The Anti-Myopia Contact Lens (AMCL; Ciba Vision; Australia) was developed by Holden et al (2010) and only preliminary results have been published. The exact design of this silicone hydrogel SCL is restricted under patent laws and thus the amount of myopic defocus induced onto the peripheral retina of children subjects involved in their study has not yet been published. A reported reduction in myopia progression of -0.26 ± 0.25D compared to -0.60 ± 0.29D and axial length elongation of 0.08 ± 0.11mm compared to 0.25 ± 0.12mm was reported over a 6 month period in 50 children subjects wearing the AMCL compared to SV spectacle lenses, respectively.

The Dual-Focus lens, commercially known as the MiSight lens (Coopervision; New York, USA), was developed and investigated by Anstice and Phillips (2011) who similarly demonstrated reduced myopia progression with these multifocal SCLs in a group of 40 myopic children aged between 11 and 14 years. The Dual-Focus lens consists of a central distance correction surrounded by two concentric +2.00 myopic treatment zones and another 2 concentric distance correction zones as shown in Figure 1.5.

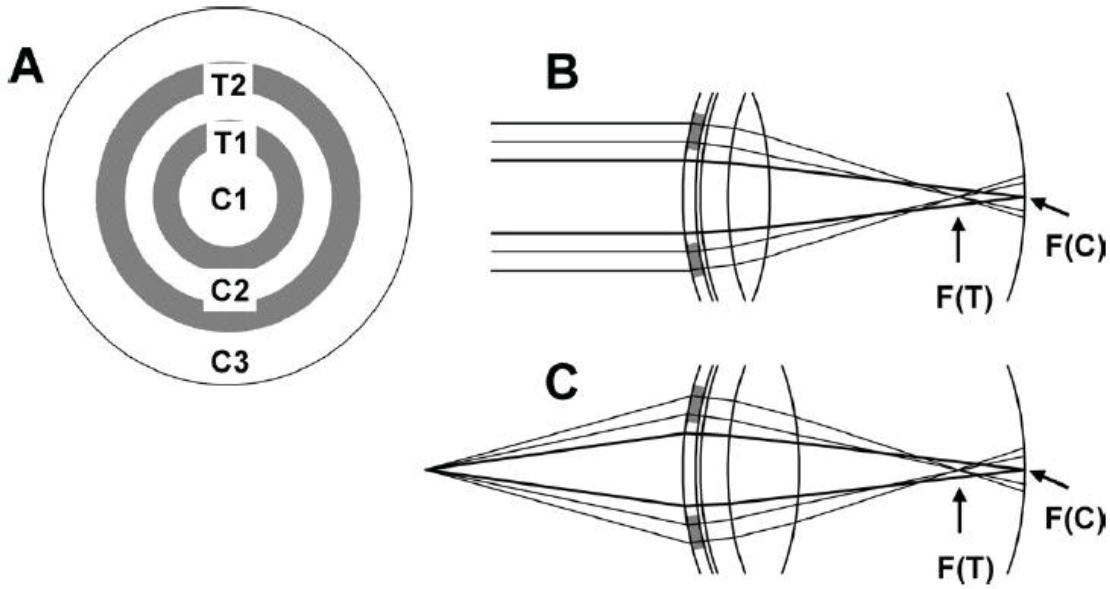


Figure 1.5 a) Concentric multifocal design of the Dual-Focus lens. The outer diameters of the central refractive error correction zones are C1 = 3.36mm, C2 = 6.75mm and C3 = 11.66mm. The treatment zones (+2.00DS) which induce a myopic defocus onto the retina have outer diameters of T1 = 4.78mm and T2 = 8.31mm. b) Distance viewing through Dual-Focus SCLs results in the focal planes of the correction zones lying on the retina while the focal planes of the treatment zones fall in front of the retinal plane resulting in myopic defocus on the retina. c) Accommodative near viewing similarly results in the focal planes of the correction zones lying on the retinal plane and the focal planes of the treatment zones falling anterior to the retinal plane consequently inducing myopic defocus onto the retina. (Reproduced from Anstice, N. S. & Phillips, J. R. Effects of Dual-Focus soft contact lens wear on axial myopia progression in children. *Ophthalmology*, 118, 1152-61. Copyright (2011), with permission from Elsevier).

The rationale behind this multifocal lens design was to induce myopic defocus onto the retina during both distance and near viewing. This approach was taken subsequent to a monovision study (Phillips, 2005) which found that children who apparently experienced sustained myopic defocus over the entire retina during both distance and near viewing had reduced myopia progression compared to the fully corrected contra-lateral eye. However this study (Phillips, 2005) consisted of only 13 subjects by the end of the 30 month study period.

In the study reported by Anstice and Phillips (2011), subjects were randomised to wear the Dual-Focus lens in one eye and a SV SCL in the contra-lateral eye for 10 months (period 1). Lens assignment was then swapped for the second 10 months (period 2). During period 1, myopia progression of -0.44 ± 0.33D compared to -0.69 ± 0.38D and axial length elongation of 0.11 ± 0.09mm compared to 0.22 ± 0.09mm was measured

in the eye wearing the Dual-Focus lens and SV SCL, respectively. After the cross-over period, the eye now wearing the Dual-Focus lens was reported to have myopia progression of -0.17 ± 0.35D and axial elongation of 0.03 ± 0.10mm compared to the eye now wearing SV SCLs which had myopia progression of -0.38 ± 0.38D and axial elongation of 0.14 ± 0.09mm. However both these studies fail to thoroughly explain the changes in peripheral refraction associated with wear of these novel multifocal SCLs and publication of more detailed results is highly anticipated.

1.1.6.2.3 ORTHOKERATOLOGY

Orthokeratology (OK), otherwise known as corneal refractive therapy (CRT), is a procedure which involves the overnight wear of RGP lenses with a reverse geometry design with no lens wear during the day. The lenses temporarily change corneal curvature overnight and the resultant central corneal flattening corrects mild to moderate degrees of myopia (Swarbrick, 2006). Although traditional daily-wear OK was developed almost 50 years ago, improvements in lens design and development of lens materials and instrumentation have resulted in OK becoming a predictable and stable form of myopia correction which has gained in popularity.

In 2005, the Longitudinal Orthokeratology Research in Children (LORIC) pilot study (Cho et al., 2005) monitored refractive error, axial length and vitreous chamber depth in 35 children fitted with OK lenses and 35 children wearing SV spectacle lenses, aged between 7-12 years of age, over a 2-year period. Due to changes in central refraction and corneal topography with OK, axial length was used as a measure of myopia progression. Axial elongation of 0.29 ± 0.27mm and 0.54 ± 0.27mm was measured in the OK and SV spectacle lens wearers, respectively. Although there was high variation in axial length measurements, it was proposed that OK lenses may have a potential anti-myopiogenic effect.

In 2009, Walline et al (2009) published data from the Corneal Reshaping and Yearly Observation of Nearsightedness (CRAYON) pilot study which also investigated the effects of OK on myopia progression in a group of 8-11 year old myopic children. At

baseline, axial length was 24.20 ± 0.69mm and 24.30 ± 0.73mm in SV SCL and OK lens wearers, respectively. After 2 years, axial length of 24.77 ± 0.80mm and 24.55 ± 0.72mm was measured in the SCL wearers and OK lens wear group, respectively. A statistically significant mean difference in axial length of 0.22 ± 1.12mm was measured at the end of 2 years. Furthermore a significant growth in both anterior chamber and vitreous chamber depths was detected with SCL wear compared to OK lens wearers. At the end of 2 years, the anterior and vitreous chambers were 0.08 ± 0.38mm and 0.11 ± 1.11mm deeper in SCL wearers compared to OK lens wearers, respectively.

Swarbrick et al (2010) published preliminary data from their 1-year cross-over study involving overnight OK lens wear in one eye and RGP daily lens wear in the contra-lateral eye. The study was cross-over in design whereby one eye was randomly selected to wear OK lenses and the other fitted with RGP lenses. OK lenses were worn overnight and RGP lenses worn throughout the day and after 6 months of treatment, the eye-lens wearing combination was swapped. In the eye wearing OK lenses during the first phase of the study, no change in axial length was detected from baseline whereas an increase in axial length was measured in the eye wearing RGP lenses (-0.01 ± 0.09mm compared to 0.05 ± 0.09mm). Once the lenses were swapped for the second phase of the study, the eye now wearing the OK lens similarly demonstrated no change in axial length while the eye wearing the RGP lens demonstrated axial length elongation (-0.04 ± 0.13mm compared to 0.09 ± 0.12mm). Axial length appeared to not elongate during the period of OK treatment, implying no progression of myopia.

The exact mechanisms behind reduced myopia progression with OK lenses are unknown. However, it has been suggested (Walline et al., 2009) that the corneal steepening which occurs in the para-central cornea may cause changes in the defocus experienced in the peripheral retina which may in turn slow down the rate of myopia progression. Cho et al (2005) proposed that higher order aberrations induced by OK lens wear may be a stimulus for the slowing of eye growth.

1.1.6.3 PHARMACEUTICAL AGENTS

There are some pharmaceutical agents which have been specifically investigated as a means of potential myopia treatment. Topical muscarinic antagonists have been used due to their cycloplegic effect as accommodative dysfunction has been associated with myopia. As described in Section 1.1.5.2.1. reduced accommodation or a large lag of accommodation typically found in myopes creates a hyperopic defocus on the retina which is believed to be potentially myopiogenic. The rationale behind muscarinic antagonist agents is to inhibit accommodation and provide clear near vision with the use of either PALs or bifocal lenses. This could eliminate the retinal defocus apparent in myopes during near tasks which could potentially eliminate the myopiogenic stimulus. On the other hand, some studies have argued that atropine may have an effect on myopia progression independent of its effects on accommodation (McBrien et al., 1993, Schaeffel et al., 1990), and may in fact act at a retinal level.

The most commonly used ocular muscarinic antagonists are atropine, pirenzipine and less commonly tropicamide and scopolamine. Atropine is a non-selective muscarinic antagonist causing mydriasis from 12 minutes after instillation and cycloplegic effects from within 12–18 minutes (Frazier and Jaanus, 2008). Atropine has been most readily investigated as a form of myopia control and will be discussed in more detail below. Pirenzepine is a selective M1 muscarinic receptor antagonist (Dorje et al., 1991) and less likely to cause mydriasis and cycloplegia compared to atropine (Bartlett et al,. 2003, Tan et al., 2005). Although initial results using 2% pirenzepine were promising (Siatkowski et al., 2004) with approximately 50% reduction in myopia progression compared to a placebo group, there have not been further studies which may be due to the reduced efficacy of myopia reduction compared to atropine (Ganeson and Wildsoet., 2010). Tropicamide is a fast onset and short acting muscarinic antagonist (Frazier and Jaanus, 2008). The shorter duration of action requires more frequent drop administration and this is a likely reason for minimal research into the effects of tropicamide on myopia progression. Scopolamine is also a non-selective muscarinic antagonist with similar effects to atropine. However central nervous system toxicity

is more common with scopolamine (Frazier and Jaanus, 2008) and thus this drug has been rarely used for myopia control.

Shih et al (2001) conducted a large study on the efficacy of atropine for myopia control involving 227 myopic children aged between 6 and 13 years. Myopic progression over 18 months was significantly less with 0.5% atropine and PAL correction (-0.42 ± 0.07D) compared to PAL (-1.19 ± 0.07D) or SV spectacle lenses (-1.40 ± 0.09D) alone. The mean increase in axial length was correspondingly smallest in the group treated with combined atropine and PALs, followed by PALs then SV lenses (0.22, 0.49 and 0.59mm, respectively). Chua et al (2006) also reported similar results of reduced myopia progression with 1% atropine. 400 children aged between 6 and 12 years old were assigned to receive atropine or placebo treatment in only 1 eye for 2 years. The eye receiving atropine progressed in myopia by only -0.28 ± 0.92D with no significant change in axial length compared to baseline (-0.02 ± 0.35mm). The eye receiving placebo treatment experienced myopia progression of -1.20 ± 0.69D and axial elongation of 0.38 ± 0.38mm after 2 years which was found to be similar to the control eyes within each treatment group. There are ethical issues of treating one eye for such a long period to be considered in studies such as the one reported by Chua et al (2006). If atropine does have an effect on myopia progression, children in this study are likely to develop anisometropia. At the end of the 2-year study period, there was nearly 1D difference in refractive error between eyes.

A rebound effect has been apparent after the cessation of atropine use. Tong et al (2009) followed subjects recruited in the Atropine in the Treatment of Myopia study (Chua et al., 2006). After cessation of 1% atropine instillation, myopia progression of -1.14 ± 0.80D was detected after one year. On the other hand, the placebo treated eyes only progressed by -0.38 ± 0.39D. However, the absolute overall myopia measured from the commencement of the 3 year Atropine in the Treatment of Myopia study was significantly lower in atropine-treated eyes compared to placebo-treated eyes (-4.29 ± 1.67D compared to -5.22 ± 1.38D) (Tong et al., 2009).

Although atropine may show one of the most promising effects on reducing myopia progression, side effects associated with atropine limit its use. These include

photophobia, glare, allergic reaction, increased UV exposure, increased risk of angle closure glaucoma and possible elevation in IOP (Frazier and Jaanus, 2008).

1.2 PERIPHERAL REFRACTION

1.2.1 INTRODUCTION

Research has typically focused on axial refraction as vision is most acute at the fovea and clear central vision is critical for daily functioning. Thomas Young proposed the concept of oblique astigmatism in the peripheral visual field (VF) and earliest measurements of peripheral refraction were reported in the late 19th and early 20th centuries. There was little further interest until research on peripheral refraction resurfaced in the 1960s and 1970s. During the past decade, it has been recognised that the significance of the peripheral retina may have been underestimated.

1.2.2 RETINAL ANATOMY

1.2.2.1 PHOTORECEPTOR MOSAIC IN THE HUMAN EYE

The photoreceptor layer in the retina is the first element in visual processing and consists of two photoreceptor cell types, cones and rods. These specialised neuron cells are capable of converting electromagnetic radiation into transmembrane receptor potentials in a process termed phototransduction. There is another newly discovered type of photoreceptor cell in the ganglion cell layer called the intrinsically photosensitive retinal ganglion cell which has functional roles fundamentally different from rods and cones (Berson, 2003). Intrinsically photosensitive retinal ganglion cells are able to encode ambient light intensity, playing a role in synchronising the body's circadian rhythms, regulating melatonin levels and activity released by the pineal gland as well as influencing pupil responses (Berson, 2003). On the other hand, cones and rods have an intrinsic role in image formation. These two fundamental neural cells are differentiated by response to kinetics and sensitivity, as well as by metabolic and morphological characteristics. Cones have a conical inner segment including three types of photopigment sensitive to different wavelengths in the visual spectrum

which give rise to our trichromatic colour vision. Little convergence of cones to ganglion cells, and in some cases a 1:1 ratio between cone cells and ganglion cells, underlies our high acuity photopic vision (Ahnelt, 1998, Remington, 2005). Rods have tubular inner and outer segments and contain a single pigment type. They are better motion sensors and incredibly sensitive. They are able to detect low levels of light and are responsible for scotopic vision (Ahnelt, 1998, Remington, 2005).

The foveal centre is characterised by an absence of rods and a high density of cones. The rod free area is estimated to have a diameter of 250-350μm (Figure 1.6). Taking into account significant individual variability, the density of cones in the fovea is estimated to be 150 000 – 180 000 cones/mm^2. Towards the periphery cone density declines rapidly, at a faster rate in the vertical than the horizontal retina and more rapidly in the nasal compared to the temporal retina (Azzopardi and Cowey, 1993, Curcio et al., 1990) (Figure 1.7). In the mid periphery, the density of cones appears to remain relatively stable with an approximate mean of 2000-4000 cones/mm^2 (Azzopardi and Cowey, 1993, Jonas et al., 1992). A little known phenomenon is the second zone of increased cone density at the extreme retinal periphery (Mollon et al., 1998). The number of cones is equal to that of rods at the very edge of the retina. At approximately 1.5mm from the ora serrata, the number of cones outnumbers rods with a ratio approaching 10:1. It is estimated that there are 250 000 cones in this outer rim compared to 75 000 in the fovea. This phenomenon is most apparent in the nasal and upper nasal rim of the retina which indicates a possible functional role of the cones in this particular area in detection of stimuli in the extreme lateral field where there is minimal obstruction of facial anatomy (Mollon et al., 1998). Although the function of this cone-rich rim is uncertain, it is believed the cones may integrate light scattered within the globe, or passing through the sclera. It may be a mechanism by which the eye is able to integrate information from the entire visual scene (Mollon et al., 1998, Smithson, 2005).

Rod cells start to appear from outside the rod free area in the foveal centre, and increase in number towards the periphery (Figure 1.6). There are similar numbers of rod and cone cells at 0.4-0.5mm outside the foveal centre. Increase in rod density is asymmetrical, increasing most rapidly in the superior meridian and least along the

nasal meridian (Azzopardi and Cowey, 1993, Curcio et al., 1990). At approximately 4-6mm from the fovea (20°-30°), there is a horizontal elliptical ring consisting of the highest density of rods. Further out towards the periphery of the retina the density of the rods, like cones, decreases. This occurs in a less abrupt manner with an average density of 30 000-40 000 rods/mm^2 (Azzopardi and Cowey, 1993, Curcio et al., 1990, Jonas et al., 1992). The total number of photoreceptor cells in the mid and outer peripheral retina significantly outnumbers the number of cells in the fovea (Azzopardi and Cowey, 1993).

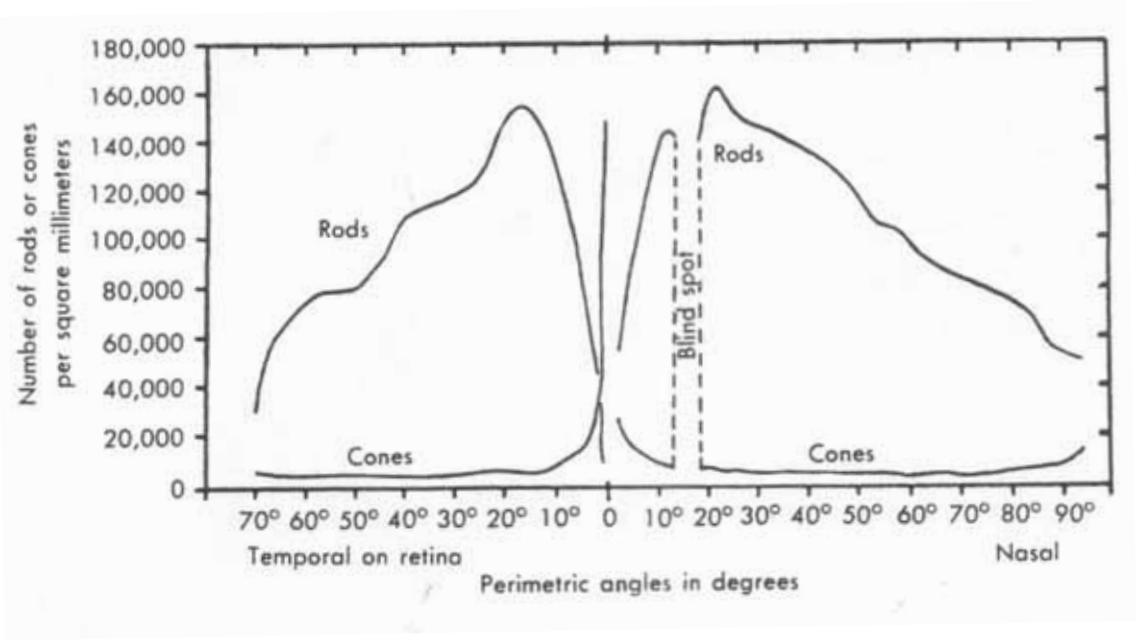


Figure 1.6 Graph of the distribution of cone and rods in the human retina across the horizontal meridian (Reproduced from Remington, L. The retina. *In:* Remington, L. (ed) *Clinical Anatomy of the Visual System,* Missouri, Butterworth Heinemann, 49-77. Copyright (2005), with permission from Elsevier).

1.2.2.2 GANGLION CELLS

Information from photoreceptors is relayed to bipolar cells which are second order neuron cells, then to ganglion cells in the retina and ultimately to the visual cortex through the visual pathway. Although photoreceptors set the limit on the spatial frequency able to be discerned by the retina, it is the ganglion cells that set the

absolute limit on the amount of information that is transferred to the brain, more specifically, the receptive fields of these cells. The ganglion cell layer is generally a single cell layer thick except at the macula where it can be up to 8-10 cells thick and on the temporal side of the optic disc where it is two cells thick (Remington, 2005). The highest ganglion cell densities and hence low convergence to ganglion cells are found at the fovea in the human eye and decline with eccentricity towards the ora serrata, more rapidly along the vertical than along the horizontal meridian. Ganglion cells are more abundant in the nasal than temporal retina and for much of the periphery, the nasal retina has 3 times more ganglion cells at corresponding eccentricities than the temporal retina (Curcio and Allen, 1990).

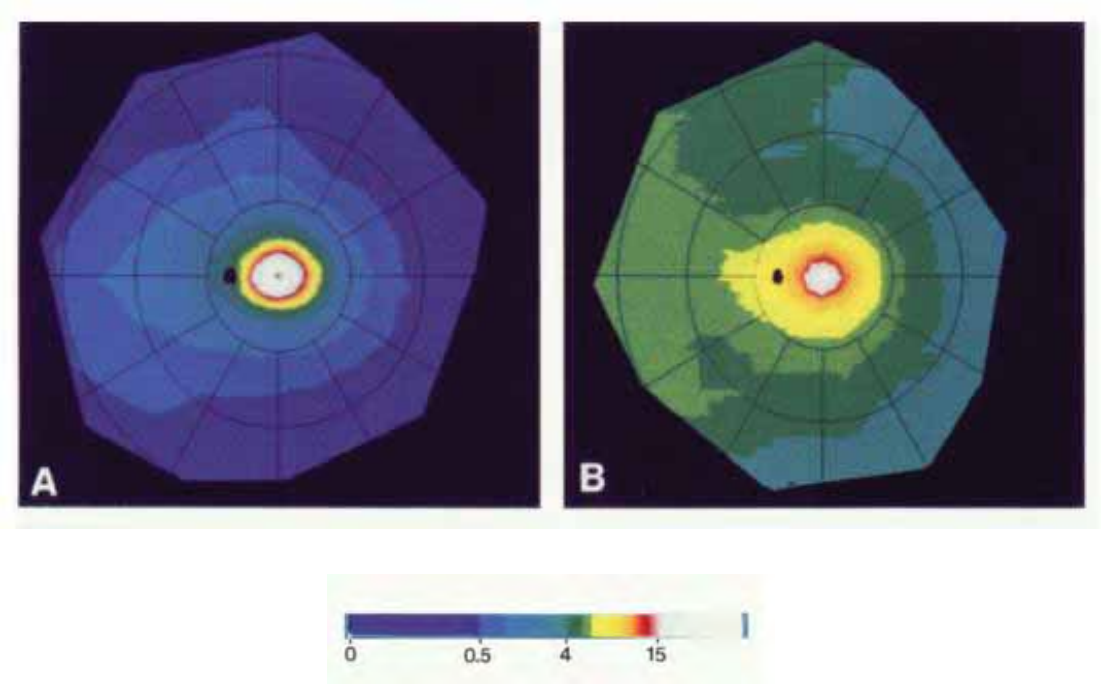


Figure 1.7 Computer-generated maps of a) ganglion cells and b) cones displayed on the fundus of a left eye (cells/mm^2). The values on the scales should be multiplied by 1000 cells/mm^2. Densities above 15,000 cells/mm^2 are represented by white (Reproduced from Curcio, C. A. & Allen, K. A. Topography of ganglion cells in human retina. *J Comp Neurol*, 300, 5-25. Copyright (1990), with permission from John Wiley and Sons).

1.2.2.3 HUMAN STRIATE CORTEX

The human cortex is the outermost layer of the grey matter of the brain. Each hemisphere of the cortex is 2-4mm thick and covers a surface area of approximately 1000cm^2. The entire human cortex contains about 25 billion neurons and 20% of this is dedicated to vision and termed the visual cortex. The visual cortex involves the occipital lobe and extends into the temporal and parietal lobes (Wandell et al., 2007). Advances in technology have permitted comprehensive investigation of the organisation of an intact human visual cortex.

In the early stages of visual processing, the sampling in the fovea is approximately 40 times greater than in the peripheral retina giving rise to visual acuity (VA) that is significantly better centrally than in the periphery. There are 3.3-5.9 times more lateral geniculate nucleus cells dedicated to each ganglion cell in the fovea compared to the peripheral retina (Azzopardi and Cowey, 1993). Furthermore, there are 10 times more primary visual cortex cells (striate cells) for every lateral geniculate nucleus cell relaying information from the fovea resulting in approximately 160 more striate cells dedicated to each cell in the fovea than in the periphery. This is reflected in the surface area of the human visual cortex dedicated to the central vision (Duncan and Boynton, 2003) (Figure 1.8). When observing a representation of the VF map on the human visual cortex as modified by Horton and Hoyt (1991) (McFadzean et al., 1994) (Figure 1.8) it can be seen that approximately 50-60% of the surface area of the human visual cortex is dedicated to the central 10° of vision. The human visual cortex assigns a disproportionately large surface area to information relayed from the fovea.

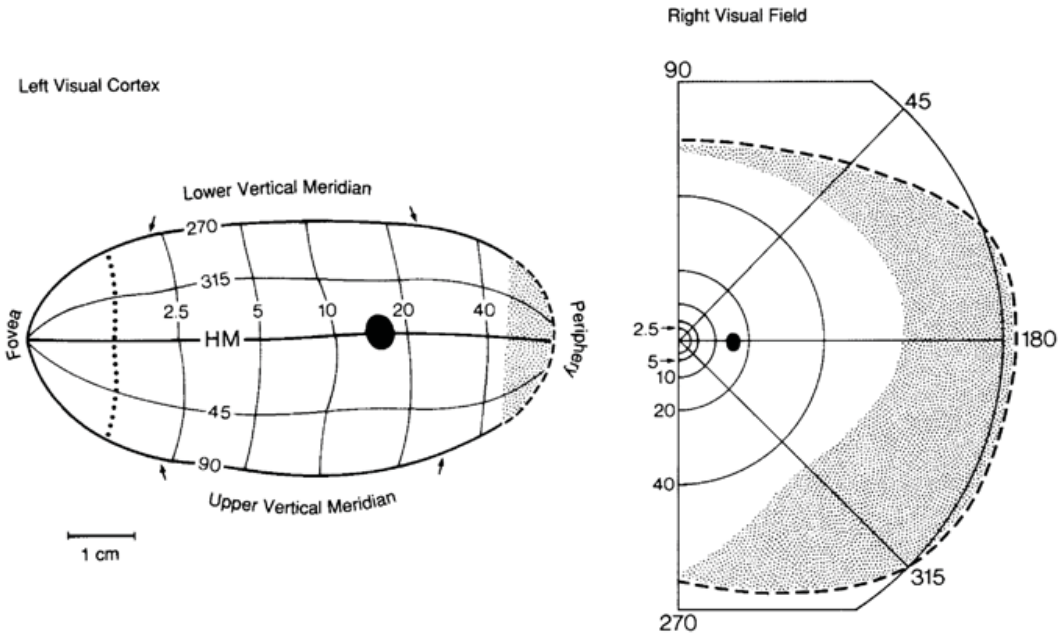


Figure 1.8 Schematic map illustrating the projection of the right visual hemifield (right) onto the left visual cortex (left). The numbers represent eccentricity in degrees. The horizontal lines on the visual cortex (left), represent eccentricity along the vertical VF meridian which corresponds to the straight lines arranged in radial formation on the right VF (right). The vertical lines on the visual cortex (left) represent eccentricity along the horizontal VF meridian which corresponds to the semi-circle lines on the right VF (right) (Reproduced, with permission, from Horton, J. C. & Hoyt, W. F. The representation of the visual field in human striate cortex. A revision of the classic Holmes map. *Arch Ophthalmol*, 109, 816-24. Copyright © (1991) American Medical Association. All rights reserved).

1.2.2.4 FOVEAL AND PERIPHERAL VISION

The heterogeneous nature of the human neural cell mosaic determines how much information is extracted from different parts of the VF. As previously described, the high density of photoreceptors and hence small spacing, coupled with high sampling of the retinal cells in the fovea, results in acute central acuity. In comparison, reduced cell density together with under-sampling and comparatively smaller visual cortex surface area dedicated to the entire peripheral retina results in poorer acuity in the peripheral VF. However, information from the peripheral retina is also assigned a substantial area of the visual cortex. Although studies have shown that ocular growth is likely to be mediated locally as described in Section 1.2.3, the area of the visual

cortex assigned to the peripheral retina is similar to that assigned to the central 10° of vision further emphasizing the importance of peripheral vision.

1.2.3 EVIDENCE FOR THE SIGNIFICANCE OF THE PERIPHERAL RETINA

1.2.3.1 ANIMAL STUDIES

The potential significant influence of the peripheral retina on the development of central refraction can be postulated based on the anatomy of the retina as described in Section 1.2.2. A similar area of visual cortex assigned to foveal vision is also given to peripheral vision. Additionally, the number of photoreceptor cells in the mid and outer peripheral retina significantly outnumbers the number of photoreceptor cells in the fovea. Further evidence of the significance of the peripheral retina also arises from recent animal studies.

Numerous animal studies have provided evidence to show that ocular growth and refractive error development are controlled locally. Optic nerve section and pharmacologic blockade appear to not interfere with lens compensation (Norton et al., 1994, Troilo et al., 1987, Wildsoet and Pettigrew, 1988, Wildsoet and Wallman, 1995). Additionally, hemi-retinal form deprivation causes corresponding regional retinal changes (Diether and Schaeffel, 1997, Hodos and Kuenzel, 1984, Smith et al., 2009a, Wallman et al., 1987).

Smith et al (2005 & 2007) published two landmark studies demonstrating that peripheral vision can have an apparent large influence on central refractive error development and an intact fovea does not seem essential for the normal emmetropisation process. Twelve infant rhesus monkeys were reared with diffusers with 4 or 8 mm apertures allowing 24° or 37° of unrestricted central vision, respectively. Smith et al (2005) found that peripheral form deprivation resulted in axial myopia even in the presence of apparently unrestricted foveal vision.

Elimination of a functioning fovea through photoablation appeared to not interfere with recovery from induced refractive errors. Furthermore, foveal ablation did not interfere with the normal emmetropisation process or with the development of form deprivation myopia (Smith et al., 2007). A functioning fovea appears to not be necessary in the normal emmetropisation process or vision dependent refractive changes, at least in the monkey model. Depriving peripheral vision and allowing unrestricted central vision typically resulted in axial myopia in both monkeys and chicks (Smith et al., 2005, Smith et al., 2007, Stone et al., 2006) indicating peripheral vision signals seem to dominate over foveal signals, directing overall ocular growth. However, conflicting results were demonstrated in another study involving chicks (Schippert and Schaeffel, 2006) where the same behaviour was not observed. Smith et al (2009b) proposed that methodological differences in rearing strategies may be the cause of this discrepancy. Apertures were held at 2mm in chicks (Schippert and Schaeffel, 2006) and this small vertex distance would allow approximately 95° unrestricted central VF.

Liu and Wildsoet (2011) recently published an interesting study investigating the effects of two-zone concentric bifocal spectacle lenses with varying central correction zone diameters in chicks and demonstrated that peripheral defocus could have an influence on the development of central refractive error. Spectacle lenses with a plano centre and a +5D peripheral correction tended to produce central hyperopia while lenses with +5D centre and plano periphery appeared to have minimal effect on central refraction except where central zones were greater than 4.5mm. Lenses with a plano centre and a -5D periphery tended to create myopic central refraction while a -5D centre and plano periphery had little influence on central refraction until the central correction zone diameter was 6.5mm. The response with positive lenses was exaggerated compared to minus lenses. Lenses with plano centre and +5D periphery appeared to inhibit axial length elongation.

1.2.3.2 PATHOLOGIES OF THE RETINA AND RESULTING REFRACTIVE ERRORS

The influence of the peripheral retina on central refractive error development is further reinforced by studies investigating ocular pathologies and resulting refractive error development in humans. Similar patterns of ocular response in animal models (described in Section 1.2.3.1) to deprivation of vision in the peripheral retina have been described in humans.

Eye diseases affecting peripheral, or peripheral and foveal vision, such as vitreous hemorrhages, congenital cataracts and retinitis pigmentosa have been found to typically lead to myopia (Hoyt et al., 1981, Miller-Meeks et al., 1990, Nathan et al., 1985, O'Leary and Millodot, 1979, Sieving and Fishman, 1978, von Noorden and Lewis, 1987). Moreover, diseases affecting only foveal vision including maculopathy and rod monochromacies have been found to generally result in mild hyperopia (Johnson et al., 1982, Nastri et al., 1984, Nathan et al., 1985).

1.2.4 PERIPHERAL REFRACTION IN HUMANS

With evidence from human (Section 1.2.3.2) and animal studies (Section 1.2.3.1) demonstrating the potentially significant influence of the peripheral retina on the development of central refractive error, researchers have begun to measure and describe peripheral refraction in both children and adult humans.

Some of the early peripheral refraction studies were conducted by Ferree et al (1931, 1932 & 1933) in the early 1930s. They measured peripheral refraction up to 60° in the nasal and temporal VF using a refractometer. Refraction measurements were plotted on charts whereby the x-axis represented VF eccentricity and the y-axis represented the amount of refractive error (Figure 1.9). Refraction in the vertical (sagittal) and horizontal (tangential) planes at points along the horizontal visual field meridian were plotted as dotted and solid lines, respectively. Refraction in the vertical plane gave

apparent information of ocular shape. The amount of astigmatism which generally increased with eccentricity was given by the value of the Interval of Sturm read from the vertical axis between corresponding points on the vertical and horizontal refractive planes. According to this model, the breadth of the Interval of Sturm also gave an indication of the strength of the refractive system with a wider interval or larger astigmatism in the peripheral visual field corresponding to a stronger refractive system. A weaker refractive system would result in a shorter Interval of Sturm or less astigmatism at the corresponding point. The strength of the refractive system coupled with central refraction was assumed to give information on the length of the eyeball. For example, an emmetrope with peripheral compound hyperopic astigmatism would appear to have a weak refracting system and a correspondingly long or oval eye ball. An emmetrope with peripheral compound myopic astigmatism would appear to have a strong refractive system and hence a short eyeball. Ferree et al (1931, 1932 & 1933) classified peripheral refractive measurements into 3 types (Figure 1.9):

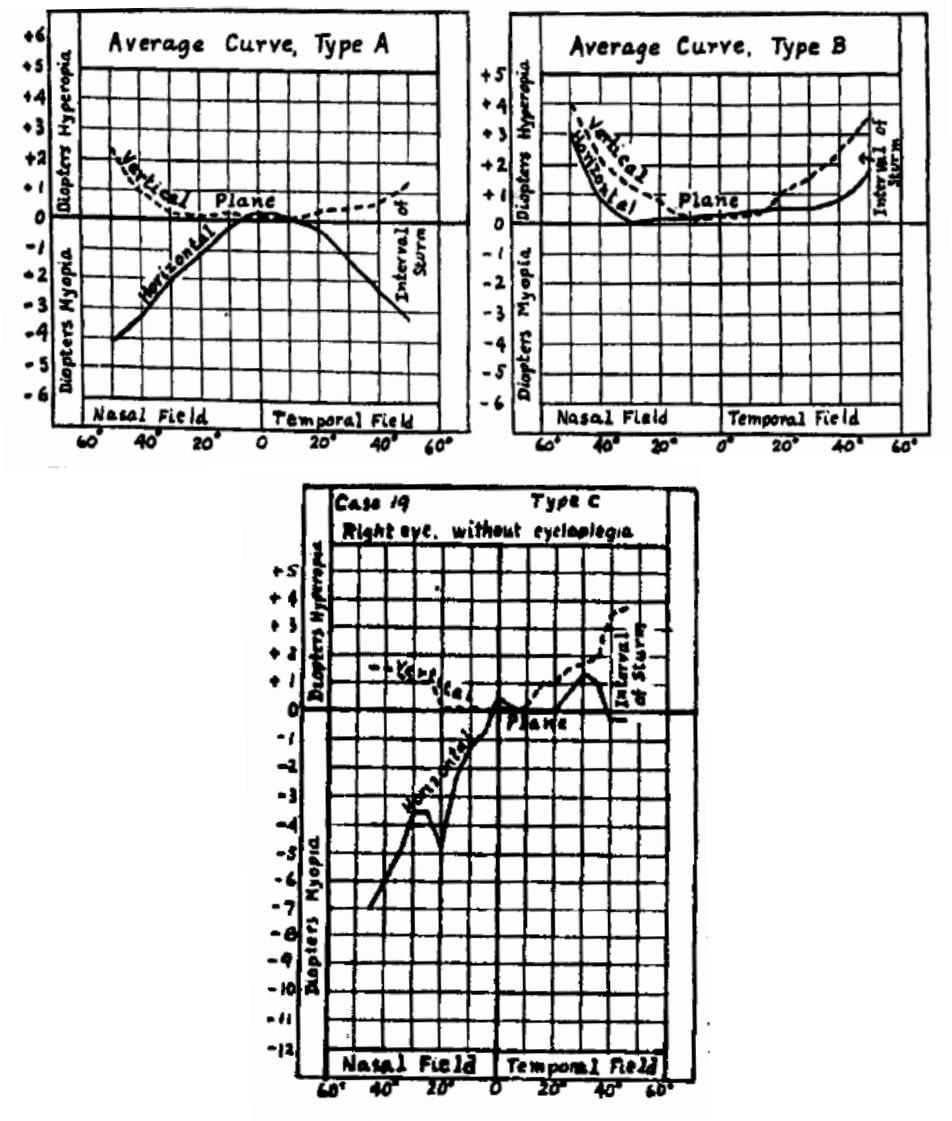


Figure 1.9 Diagram of the three types of peripheral refractive error measurements as classified by Ferree et al (1931, 1932 & 1933) (Reproduced from Ferree, C. E., Rand, G. & Hardy, C. Refractive asymmetry in the temporal and nasal halves of the visual field. *Am J Ophthalmol*, 15, 513-22. Copyright (1932), with permission from Elsevier).

Type A - the horizontal plane becomes more myopic towards the periphery and more hyperopic in the vertical plane typically resulting in mixed astigmatism in the periphery.

Type B - the horizontal plane becomes less myopic towards the periphery and more hyperopic in the vertical plane resulting in compound hyperopic astigmatism.

Type C - the peripheral refraction profile was asymmetrical in the nasal and temporal fields. It was proposed that the asymmetry may possibly be due to misalignment of the optics of the eye, asymmetry in the shape of the nasal and temporal halves of the eyeball or a combination of both.

There was very little written about peripheral refraction subsequent to these studies until 40 years later when an interesting study was published in 1971 (Hoogerheide et al., 1971, Rempt et al., 1971). Using retinoscopy along the horizontal meridian at 20° intervals up to 60° in both the temporal and nasal VF, Hoogeheide et al (1971) and Rempt et al (1971) were able to take peripheral refraction measurements and record findings in a diagram which they termed the skiagram. The skiagram was based on the same principles as the charts drawn by Ferree et al (1931, 1932 & 1933). The x-axis represented VF eccentricity and the vertical axis represented the amount of refractive error. They classified results into 5 categories (Figure 1.10):

Type I - equivalent to Type B from Ferree et al's (1931, 1932 & 1933) studies.

Type II - refraction in the vertical plane becomes more hyperopic with increasing eccentricity while the horizontal remains unchanged.

Type III - equivalent to Type C from Ferree et al's (1931, 1932 & 1933) studies.

Type IV - equivalent to Type A from Ferree et al's (1931, 1932 & 1933) studies. This was considered to be the normal skiagram.

Type V - refraction in the horizontal plane become more myopic while the vertical plane remains the same.

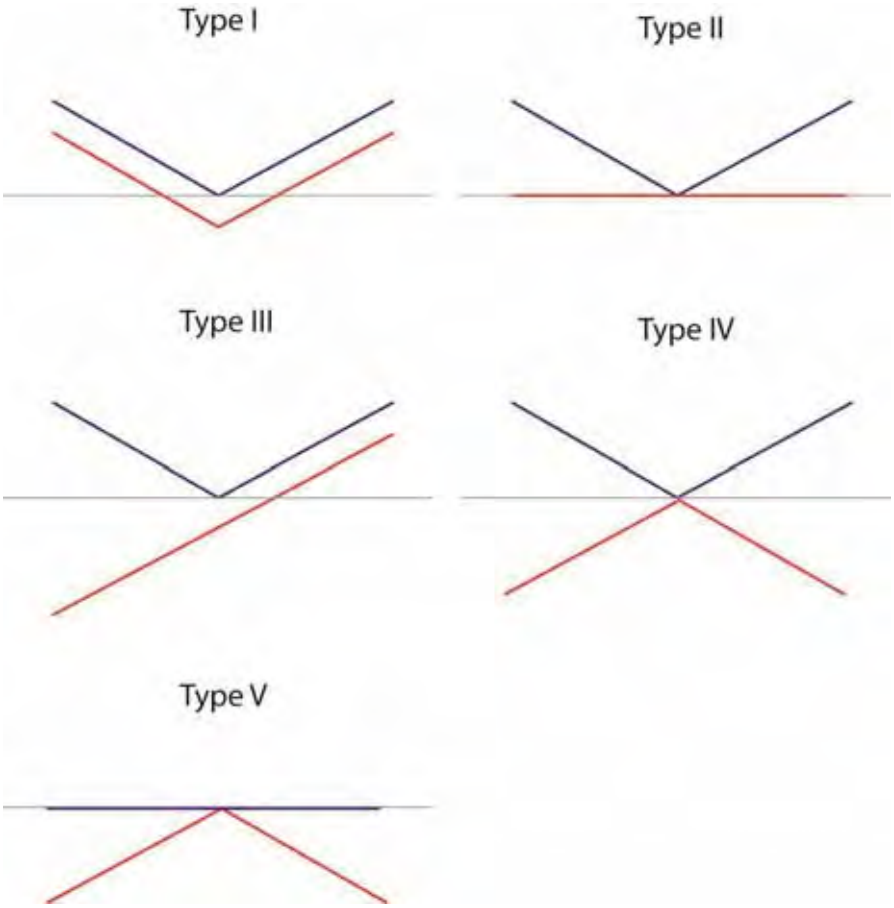


Figure 1.10 The 5 types of peripheral refraction as classified by Hoogeheide et al (1971) and Rempt et al (1971). The blue lines represent the vertical (sagittal) plane while the red lines represent the horizontal (tangential) plane (Adapted from Hoogerheide et al, 1971).

On measuring peripheral refraction in 442 pilots, they found that most had similar skiagrams for both eyes. Confirming Ferree et al (1931, 1932 & 1933), they also found that in many, the Interval of Sturm increased with eccentricity and was similar for the nasal and temporal VFs. Rempt et al (1971) also noted a few cases of asymmetricial peripheral refraction profiles. It was noticed that emmetropic and hyperopic eyes tended to have Type IV skiagrams while myopic eyes tended to have Type I. Type V was only seen in hyperopic eyes while Type III was also exclusively seen in emmetropic eyes. It was proposed that the asymmetry in the peripheral refraction in the nasal and temporal VFs was an indication of asymmetry in ocular shape.

They followed up 214 of the 442 pilots and once again measured and classified peripheral refraction measurements into one of the 5 skiagram categories. They

found that many of the emmetropic and hyperopic pilots who had a myopic shift in central refraction had type I skiagrams (45% and 77%, respectively). Those who remained hyperopic or emmetropic with no significant central myopic shift typically had type IV skiagrams (66%). It was proposed that the skiagram most likely does not change during the course of one's life and it may reveal an indication as to whether a pilot was at risk of becoming myopic in the future. Thus they were the first to propose an association of myopia development with peripheral refraction. However, the authors failed to disclose the time interval during which measurements were taken. Furthermore, the association of adult-onset myopia development with peripheral refractive errors may not necessarily be the same as for youth-onset myopia.

More recently, Mutti el al (2007) published a study measuring peripheral refractive error up to 5 years before, during and up to 5 years after the onset of myopia in 6 to 14 year old children who were participating in the CLEERE study. Children who became myopic had longer axial lengths from 3 years before the onset of myopia compared to children who remained emmetropic. Furthermore, children who became myopic developed relatively hyperopic peripheral refraction from 2 years before the onset of myopia. It was proposed that a child's peripheral refractive status could be used to predict myopia onset. However, peripheral refraction was only measured at 30° in the temporal retina.

Schmid (2011) measured peripheral eye length at the posterior pole and found that retinal steepness in the temporal retina has a weak but significant correlation with central myopia development. Eyes with a steeper temporal retina demonstrated greater central myopic shifts over an approximate 30 month period.

With the possible association of myopia development and peripheral refraction from the above human and animal studies, numerous researchers have since investigated peripheral refraction in humans. Various methods have also been employed to measure peripheral refraction, and these will be described in Section 2.1.2.

1.2.4.1 PERIPHERAL REFRACTION AND OCULAR SHAPE

The eye is a complex structure and describing its shape becomes difficult as the eye does not follow any definitions of mathematically derived three-dimensional shape, and also shows great individual variability. Therefore, in an attempt to describe ocular shape, the length, width and height dimensions of the eye have been measured so that ocular shape can be categorised as being apparently spherical, prolate or oblate based on a simple ellipse (Figure 1.11). When the eye has the same axial length, width and height dimensions, the eye can be estimated to be spherical in shape. If the eye is longer in length than height and width, the eye can be described as being prolate in shape and if the eye is longer in width and height compared to length, then it can be estimated to be oblate in shape.

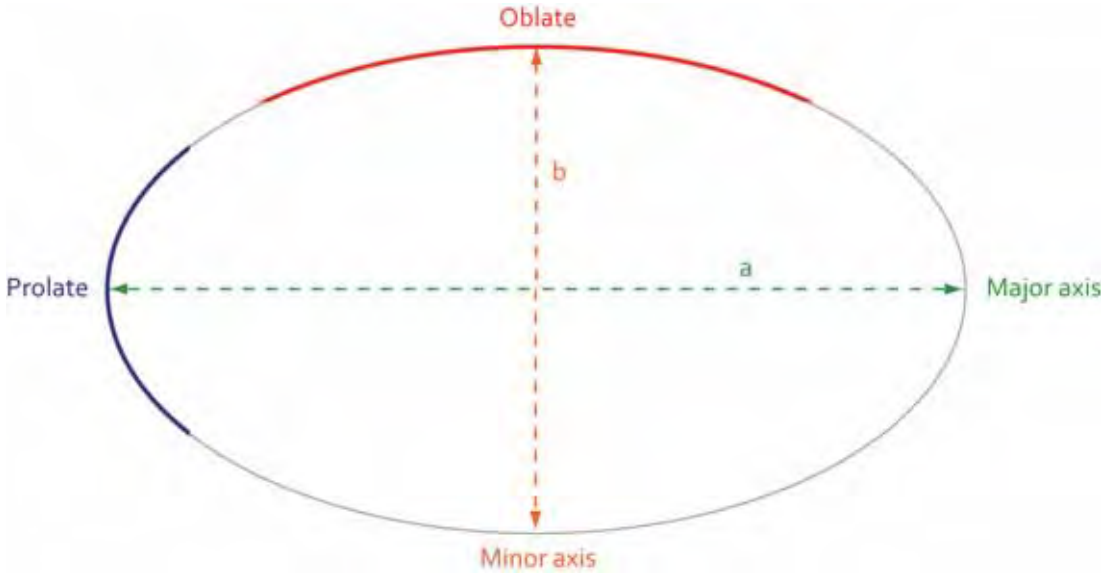


Figure 1.11 Diagram of an ellipse describing the major and minor axes as well as the prolate and oblate apices.

One of the main techniques utilised to determine ocular shape in vivo is magnetic resonance imaging (MRI). Cheng (1991) characterised ocular shape of 21 individuals from images along the axial, horizontal (width) and vertical (height) planes. No significant difference in ocular shape was found between emmetropes, hyperopes or

myopes whereby most had spheroelliptical ocular shapes with the longest axis along the axial plane. The distinguishing factor was that myopic eyes were largest in all three dimensions. Atchison et al (2004) found similar results with myopic eyes being bigger in all three dimensions, largest axially, then vertically then horizontally. Although there was variability in measurements, axial elongation or prolate ocular shape best described the myopic eye. Another study (Miller et al., 2004) involving 78 subjects found that myopic eyes were longest in both the axial and horizontal plane compared to emmetropes and hyperopes although difference in horizontal dimensions were not as dramatic compared to axial length difference between refractive groups. The difference between axial length and horizontal diameter was the greatest in myopes followed by emmetropes and hyperopes indicating that myopes have a more prolate ocular shape. With advances in technology and technique, Singh et al (2006) and more recently Lim et al (2011) were able to generate three-dimensional shape of the entire human eye through two-dimensional MRI scans. Although the study consisted of a small sample size, Singh et al (2006) demonstrated great variability of ocular shape in individuals with the same central refractive error. Estimating ocular shape using two spheres where one modelled the entire corneal region and the other the entire posterior pole, Lim et al (2011) demonstrated that greater myopic refraction was associated with longer axial lengths and, to a lesser extent, wider widths suggesting an asymmetric axial global elongation leading to prolate ocular shapes in myopes.

Other less commonly used methods include x-ray and computed tomography (CT). Deller (1947) demonstrated through x-rays that myopic eyes had axial lengths exceeding both the vertical and horizontal diameters. Wang et al (1994) took CT scans of 255 eyes and calculated the ratio of the antero-posterior axis to the horizontal transverse axis. A ratio of one reflected a spherical ocular shape which was best described by emmetropic eyes. A ratio of less than one indicated an oblate eye shape while a ratio of greater than one suggested a prolate eye shape which was best reflected by hyperopes and myopes, respectively. They demonstrated that myopes possessed prolate ocular shapes, emmetropes had either spherical or oblate ocular shapes while hyperopes typically had oblate ocular shapes.

Ocular shape is highly variable (Atchison et al., 2004, Cheng et al., 1992, Singh et al., 2006) and does not follow a mathematical formula. Although categorising ocular shape into these three definitions using only three dimensions is an oversimplification, it provides a simple method of describing and classifying eye shapes. Although there is no consensus on the shape of the eye for different refractive groups, it appears that myopes tend to typically have prolate ocular shapes while emmetropes and hyperopes typically have oblate eye shapes, which are consistent with results from peripheral refraction studies which will be described in Section 1.2.4.2.

Techniques have been modified in an attempt to derive overall ocular shape from the contour of the retinal surface at the posterior pole because obtaining measurements in the axial, horizontal and vertical meridians is difficult. Atchison et al (2005a) found considerable variability in the shape of the retinal surface in their 87 subjects. MRI images were taken and software was used to fit ellipsoids onto the retinal surface. They found that nearly all of the 21 emmetropic eyes were oblate in shape in both axial and sagittal planes. Myopic eyes were less oblate in shape and only 12% had retinas which were actually prolate. It has been suggested that posterior retinal contour can be inferred from peripheral refraction by assuming that the image shell is spherical. Ray tracing (Atchison and Smith, 2000) has approximated that M lies quite close to the retina (within 0.75D) out to 60° in the VF through optical equations verifying that peripheral refraction is able to reflect posterior ocular shape with reasonable accuracy. Schmid (2003b) found that there was a strong suggestion to indicate that peripheral refraction (Logan et al., 1995) correlated with retinal steepness using an optical low coherence reflectometer although measurements were taken only 15° from the visual axis. However, eye modelling studies have shown that inferring ocular shape from peripheral refraction may be an oversimplification and hence does not necessarily describe ocular shape (Dunne, 1995, Logan et al., 1995). Furthermore, peripheral refraction is typically measured out to only 35° from the visual axis along the horizontal meridian and thus can only reflect a part of the shape of the entire eye.

If the retinal contour is spherical, then the image shell will lie parallel to the retina resulting in peripheral refraction that is identical to central refraction. If the retinal contour is prolate in shape, when the centre of the image shell is coincident with the fovea, the peripheral image shell will lie behind the retina as the vertex curvature of the prolate eye will be steeper than the spherical image shell. Peripheral refraction will be relatively hyperopic compared to central refraction. On the other hand, if the eye is oblate in shape, then the image shell will lie in front of the retina as the vertex curvature of the retina will be flatter than the spherical image shell causing peripheral refraction to be relatively myopic compared to the centre (Figure 1.12).

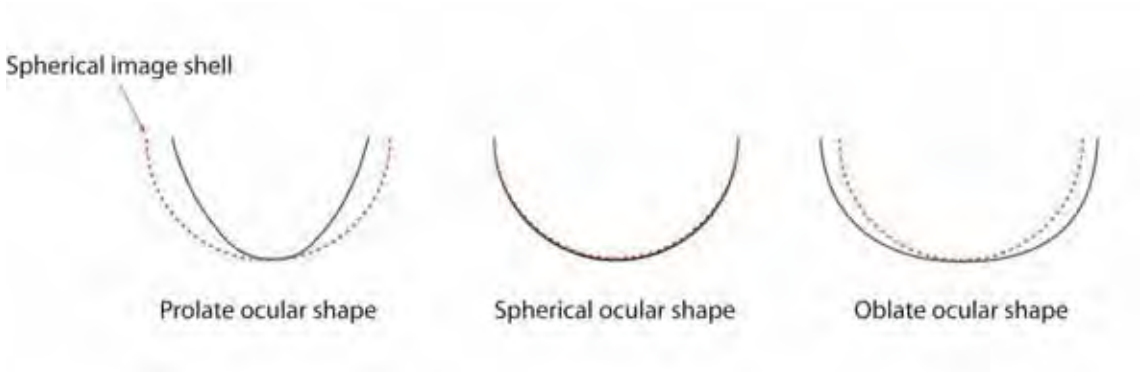


Figure 1.12 Diagram of the relationship between the image shell and posterior retina from which ocular shape is inferred (adapted from Stone and Flitcroft, 2004).

Studies describing characteristic peripheral refraction profiles in different refractive groups (Section 1.2.4.1) have often inferred ocular shape from their refraction measurements. As myopes typically show relative peripheral hyperopia, they are often described as having a prolate ocular shape. Emmetropes and hyperopes who tend to have relative myopia in the periphery are believed to have a more oblate ocular shape which is more pronounced in hyperopes as they tend to have greater relative myopia in the periphery. As previously mentioned, this is an oversimplification as refraction measurements are generally taken only along the horizontal meridian out to 35° in the temporal and nasal VF. Although retinal contour at the meridian of interest may be described as being prolate, it does not necessarily

mean that the overall ocular shape is prolate. However, many studies have made this association.

As described in Section 1.1.2, myopia typically develops from elongation of the eye which can occur through three general forms of elongation; equatorial (peripheral) stretching, elongation of the central posterior pole, or through global expansion as illustrated in Figure 1.2 a, b and c, respectively. If the eye elongates through equatorial or peripheral stretching the peripheral retina will flatten while equatorial diameter does not change. Elongation can result in relative peripheral hyperopia. If the eye elongated through the elongation of the central posterior pole, the equatorial diameter of the eye would not change causing the periphery of the eye to remain constant and only the central retina would steepen. This would cause the overall curvature of the eye to steepen which would also present relative peripheral hyperopia. If the eye globally expands equally in all axes such that the vertex curvature of the eye did not change, then myopes will likely to present relative emmetropia in the periphery of the eye. Therefore there are limitations in categorising myopes as having prolate ocular shapes as the type of elongation of the eye will determine ocular shape as well as the status of peripheral refraction.

A recent study (Ehsaei et al., 2011) measured peripheral refraction in emmetropes and myopes along the horizontal, vertical and two oblique meridians (45-225° and 135-315°) in 10° intervals out to ±30°. They found relative peripheral hyperopia along all meridians in 31 myopes and relatively emmetropic peripheral refraction along all meridians in 20 emmetropes. They inferred an ellipsoid ocular shape for myopes and a more globular ocular shape for emmetropes from peripheral refraction measurements. Although these measurements were restricted to the posterior pole, the results indicate that inferring ocular shape from horizontal retinal contours as described by many studies may not be such an inaccurate assumption.

Inferring ocular shape from peripheral refraction offers a non-invasive, inexpensive and readily available alternative to other methods of direct measurement of retinal contour. MRI, radiography and CT directly measure ocular shape independent of ocular parameters. However, peripheral refraction offers a non-invasive and simple

alternative technique which can convey relatively accurate information on posterior retinal contour in individuals. This has made peripheral refraction a popular technique to adopt.

Studies describing characteristic peripheral refraction profiles in different refractive groups (Section 1.2.4.2) have often inferred ocular shape from their refraction measurements although this is a oversimplification. Peripheral refraction is measured along a single meridian out to only 35° in the nasal and temporal VF and hence peripheral refraction can only infer retinal contour along a section of the entire eye. However, to maintain consistency with published studies, from this point onwards in the thesis, peripheral refraction will be stated to supposedly reflect ocular shape, albeit with knowledge of the limitations of using such an inference.

1.2.4.2 CHARACTERISTIC PERIPHERAL REFRACTION PROFILES

Characteristic peripheral refraction profiles have been frequently described in the different refractive groups. Measurements are in general taken across the horizontal meridian. Emmetropes (Atchison and Markwell, 2008) and hyperopes have been found to typically have relatively myopic peripheral refraction with greater myopic shift measured in hyperopes reflecting a more oblate eye shape (Chen et al., 2010, Mutti et al., 2000b, Seidemann et al., 2002). On the other hand myopes, particularly those greater than -2.50DS (Atchison et al., 2006, Logan et al., 2004), have been found to have a relatively hyperopic peripheral refraction (Chen et al., 2010, Logan et al., 2004, Mutti et al., 2000b, Seidemann et al., 2002) reflecting a more prolate eye shape. The differences in peripheral refraction profiles between emmetropes and myopes are illustrated in Figure 1.13. Relative peripheral refraction (RPR) profiles in different refractive groups are shown in Figure 1.14.

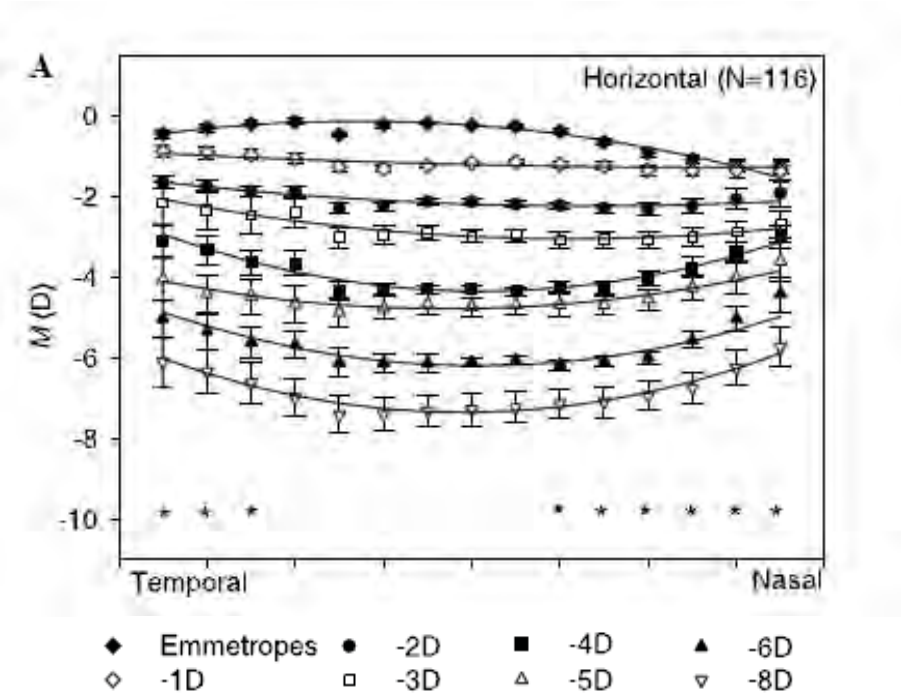


Figure 1.13 Graph of spherical equivalent (M) along the horizontal VF in emmetropic and myopic subjects. Differences between peripheral and central M were significantly correlated with central M at VF positions marked with asterisks (Reproduced from Atchison, D. A., Pritchard, N. & Schmid, K. L. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res*, 46, 1450-8. Copyright (2006), with permission from Elsevier).

Asymmetry has also been found in spherical or M refraction across the horizontal VF (Chen et al., 2010) and has been attributed to regional differences in sclera growth. Charman and Atchison (2009) suggested that a combination of angle alpha and lack of rotational symmetry in the retinal surface contributes to the asymmetry in M across the horizontal meridian.

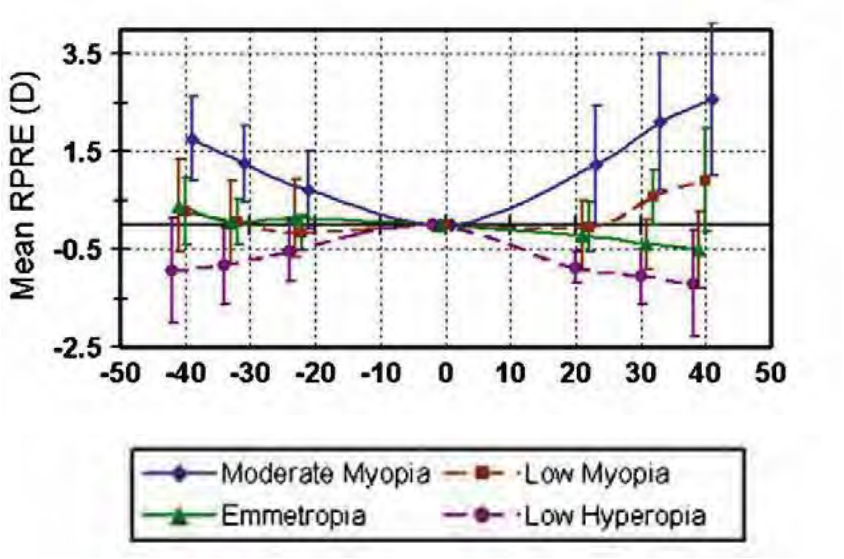


Figure 1.14 Relative peripheral M profile along the horizontal meridian in adult subjects (Reproduced from Chen, X., Sankaridurg, P., Donovan, L., Lin, Z., Li, L., Martinez, A., Holden, B. A. & Ge, J. Characteristics of peripheral refractive errors of myopic and non-myopic Chinese eyes. *Vision Res,* 50, 31-5. Copyright (2010), with permission from Elsevier).

There have only been a handful of studies which have investigated peripheral refraction along the vertical meridian. Interestingly, Atchison et al (2006) found peripheral myopic shifts along the vertical VF, in contrast to the horizontal meridian where relative hyperopia has been reported, in both emmetropes and myopes which were independent of central refractive error (Figure 1.15). Relative M profiles along the vertical VF in hyperopes, emmetropes and myopes are demonstrated in Figure 1.16.

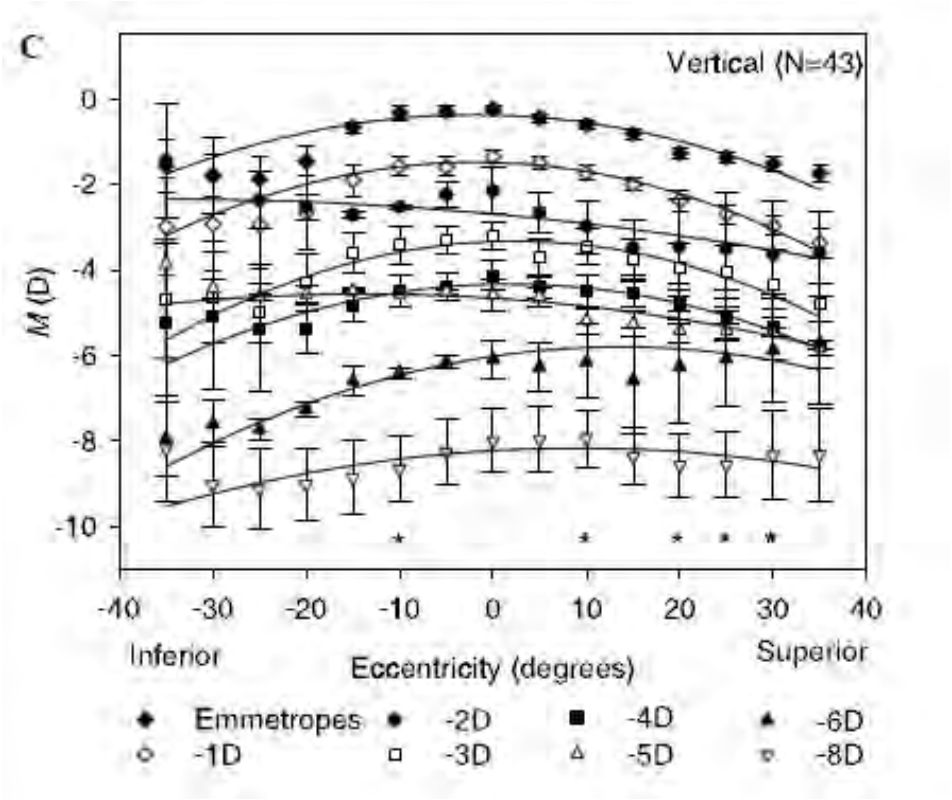


Figure 1.15 Graph of M along the vertical VF in both emmetropes and myopes (Reproduced from Atchison, D. A., Pritchard, N. & Schmid, K. L. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res*, 46, 1450-8. Copyright (2006), with permission from Elsevier).

Seidemann et al (2002) also found a peripheral myopic shift in the vertical VF but to a greater degree in the lower VF. They proposed that it may be a similar adaptation as found in other species, such as birds and reptiles (Hodos and Erichsen, 1990, Schaeffel et al., 1994), to keep the ground in focus with relaxed accommodation. Chen et al (2010) also measured myopic shifts in the superior and inferior VF with no appreciable differences in vertical refraction profiles in different refractive groups (Figure 1.16). More recently, Ehsaei et al (2011) similarly measured relative peripheral myopia in emmetropes but found relative peripheral hyperopia along the vertical meridian in myopes.

The growth of the eye is asymmetrical with typical myopic eyes being longest along the z-axis, followed by the y-axis and then the x-axis compared with emmetropic eyes (Atchison et al., 2004). The asymmetric growth of the myopic eye will result in the eye

being more oblate along the vertical direction compared to the horizontal direction which agrees with the results from Atchison et al (2006), Seidemann et al (2002) and Chen et al (2010) who all found myopic peripheral shifts in the lower and upper retina.

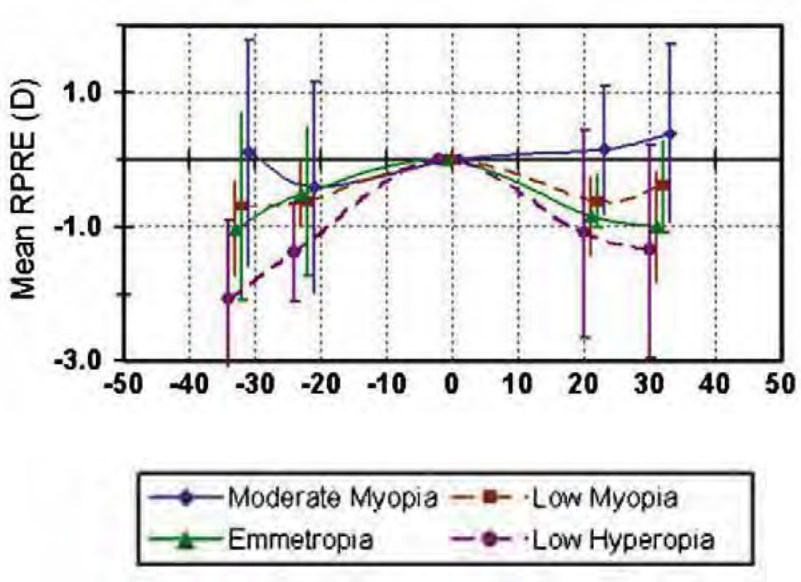


Figure 1.16 Relative peripheral M profile along the vertical VF in adult subjects (Reproduced from Chen, X., Sankaridurg, P., Donovan, L., Lin, Z., Li, L., Martinez, A., Holden, B. A. & Ge, J. Characteristics of peripheral refractive errors of myopic and non-myopic Chinese eyes. *Vision Res,* 50, 31-5. Copyright (2010), with permission from Elsevier).

Oblique astigmatism is also commonly described in different refraction groups. J_{180} is the 90° to 180° astigmatism component and J_{45} is the 45° to 135° astigmatism component (Thibos et al., 1997). J_{180} typically increases negatively with eccentricity and asymmetry is commonly seen. Greater negative J_{180} has been measured in the nasal VF (Atchison et al., 2006, Calver et al., 2007, Charman and Jennings, 2006, Chen et al., 2010, Mathur et al., 2009, Seidemann et al., 2002) (Figure 1.17). Decrease in temporal-nasal asymmetry has also been associated with increase in central myopia (Atchison et al., 2006, Atchison et al., 2005b, Millodot, 1981, Seidemann et al., 2002).

J_{45} typically demonstrates a positive linear relationship with eccentricity although the dioptric range is small (Atchison et al., 2006, Atchison et al., 2005b, Calver et al., 2007,

Chen et al., 2010) (Figure 1.17). J_{180} and J_{45} profiles appear to be similar between different refractive groups (Atchison et al., 2006, Calver et al., 2007).

The asymmetry in astigmatism (J_{180} and J_{45}) across the VF is believed to be caused by numerous factors including tilted or translated crystalline lens, rotated cornea, misalignment from the optic axis as well as lack of symmetry of the anterior optical surfaces based on modelling schematic eyes (Atchison et al., 2006, Barnes et al., 1987, Dunne et al., 1993). Moreover, a significant correlation between angle alpha and the turning point of J_{180} was evident (Atchison et al., 2006). Angle alpha is the angle between the optic axis and visual axis and the least amount of J_{180} appeared to lie or be very close to the visual axis such that the J_{180} profile seemed to be most symmetrical about the visual axis. Atchison et al measured the turning point to lie at 6.0 ± 5.0° on the temporal VF (Atchison et al., 2006) while Lotmar and Lotmar (1974) analysed Rempt et al's (1971) data and found the mean turning point to be at approximately 4° temporal. The turning point of J_{180} became more temporal (VF) with larger angle alpha values (Atchison et al., 2006). However, some have found no relationship between angle alpha and the J_{180} turning point (Dunne et al., 1993).

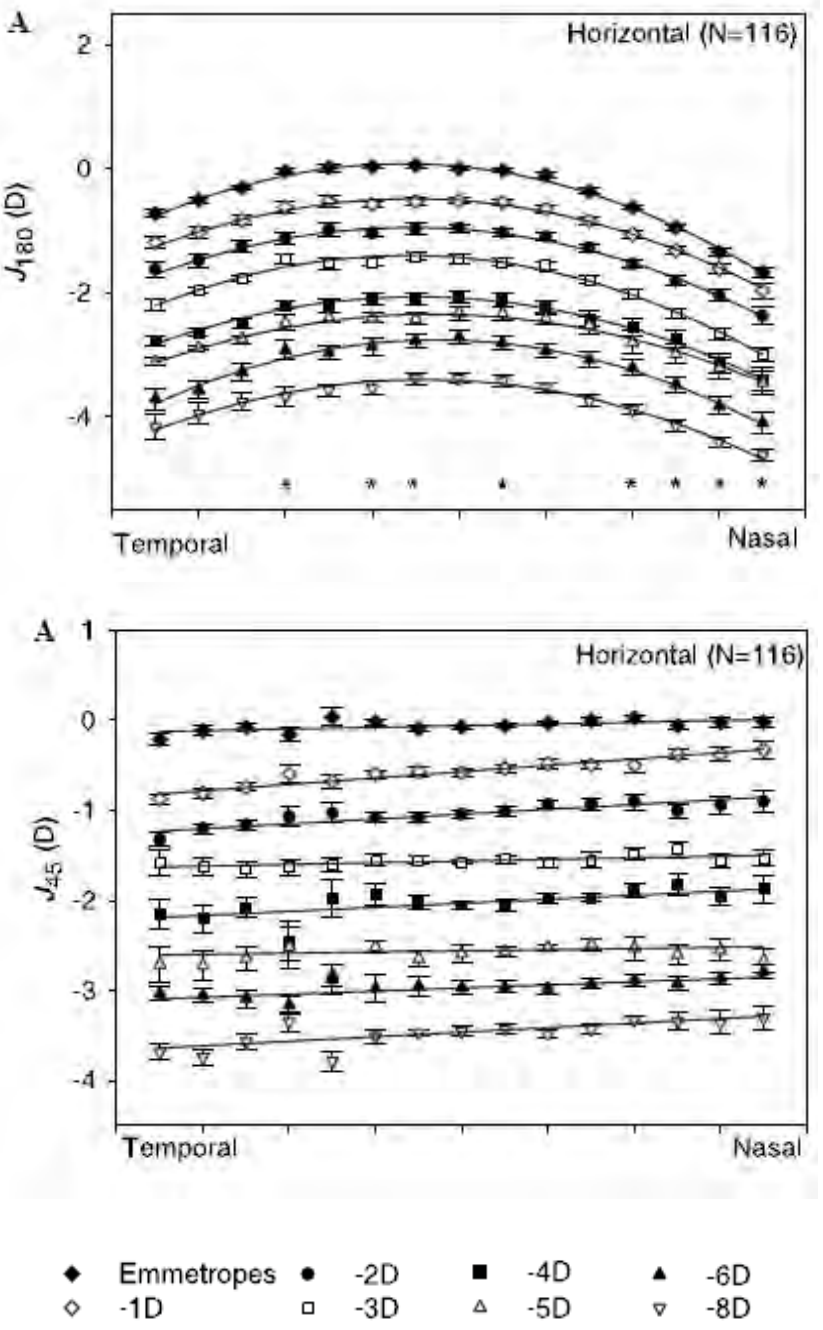


Figure 1.17 J_{180} (top) and J_{45} (bottom) peripheral refraction profiles in emmetropic and myopic subjects along the vertical VF (Reproduced from Atchison, D. A., Pritchard, N. & Schmid, K. L. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res,* 46, 1450-8. Copyright (2006), with permission from Elsevier).

J_{180} along the vertical VF has been measured to be positive with the superior VF demonstrating greater amounts of J_{180} (Atchison et al., 2006; Elhsaei et al., 2011). No relationship between J_{180} profile and central refraction was found (Atchison et al.,

2006) (Figure 1.18). Similar to the profile along the horizontal meridian, J_{45} had a positive increase with eccentricity along the vertical VF although the rate of change was three times greater along the vertical VF (Atchison et al., 2006; Ehsaei et al., 2011) (Figure 1.18).

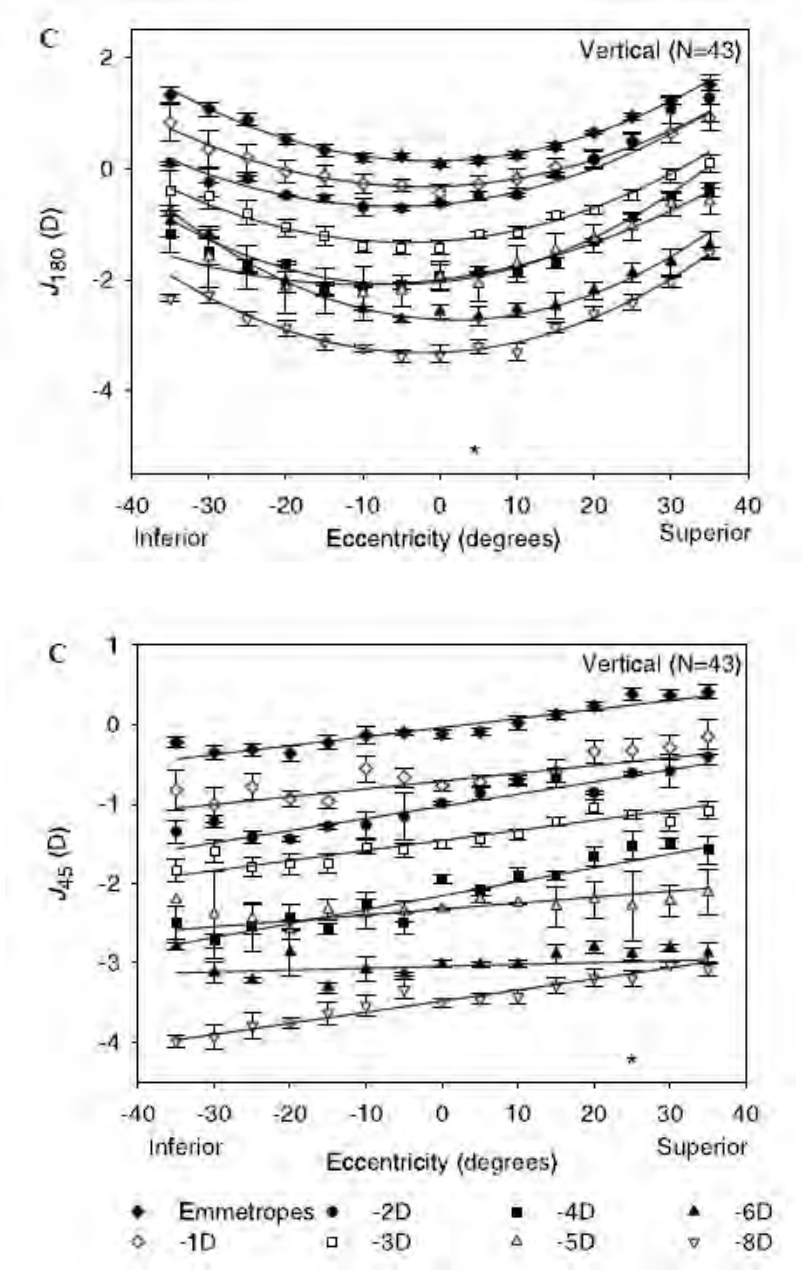


Figure 1.18 J_{180} (top) and J_{45} (bottom) peripheral refraction profiles in emmetropic and myopic subjects along the vertical VF (Reproduced from Atchison, D. A., Pritchard, N. & Schmid, K. L. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res,* 46, 1450-8. Copyright (2006), with permission from Elsevier).

With evidence of the possible effect of accommodation on development of myopia, as discussed in Section 1.1.5.3.2, there have been a few studies investigating whether accommodation has any effect on peripheral refraction. Accommodation was found to cause a myopic shift in peripheral refraction, although measurements were taken only at 30° in the nasal retina by Walker and Mutti (2002).

They found that this myopic shift regressed back to baseline by the completion of the second hour of accommodation. Mechanically induced change in ocular shape during accommodation has been proposed as a possible cause of the induced peripheral myopic shift with accommodation (Whatham et al., 2009). Calver et al (2007) found that accommodation appeared to have no significant effect on astigmatism in emmetropes and myopes while Whatham et al (2009) found a negative increase in J_{180} with accommodation (increase in against-the-rule astigmatism) while no effect was found on the J_{45} profile. Although minor changes have been reported with accommodation, further investigation is required to determine if novel myopia control devices (discussed in Section 1.2.4.4) targeting the peripheral retina induce appropriate peripheral defocus manipulations taking into consideration possible peripheral refractive changes occurring with near work. Currently the Study of Theories about Myopia Progression (STAMP) study (Berntsen et al., 2010), a 2 year randomised clinical trial, has commenced to investigate the effects of PALs compared to SV spectacle lenses on accommodative function, central refraction as well as peripheral refraction in both the horizontal and vertical VFs.

1.2.4.3 PERIPHERAL REFRACTION AND EMMETROPISATION

As mentioned in Section 1.2.4, peripheral refraction has been associated with the onset of myopia. The earliest study proposing this connection was Hoogerheide et al (1971). They found that of the pilots who later developed myopia, many had relative hyperopia measured in the peripheral retina before the onset of myopia. Mutti et al (2007) recently reconfirmed this hypothesis by measuring relatively hyperopic peripheral refraction from 2 years before the onset of myopia in a group of 6 to 14 year old children who were participating in the CLEERE study. It was hypothesised

that a child's peripheral refractive status could be used to predict myopia onset. It was proposed that the eye responds to the peripheral hyperopia demonstrated before the onset of central myopia by growing in axial length to bring the peripheral retina in focus with the peripheral image despite the development of central myopia (Charman, 2005, Charman, 2006, Collins et al., 1995, Seidemann et al., 2002, Smith, 2011, Wallman and Winawer, 2004). The eye also receives conflicting signals along the vertical and horizontal meridians. As described in Section 1.2.4.2, myopes typically experience relative myopia in the periphery along the vertical meridian while the opposite (relative hyperopia) is generally evident along the horizontal meridian. Wallman and Winawer (2004) proposed that the eye will grow in axial length until the myopic central retina balances the hyperopic periphery. It may be that this concept applies along the horizontal and vertical meridian. The eye may elongate asymmetrically along the horizontal and vertical meridians until balance is reached which may explain why relative myopia is found along the vertical meridian in myopic eyes. Emphasis has been put on peripheral refraction along the horizontal meridian and many novel anti-myopia optical devices (described in Section 1.2.4.4), try to correct the relative hyperopia in the periphery while ignoring the relative myopia typically evident along the vertical meridian. Section 1.2.2.1 and 1.2.2.2 describe the topography of cone and ganglion cells in the retina, respectively. The density of both cone and ganglion decrease more rapidly along the vertical meridian than the horizontal meridian and this may reflect the potentially dominating effect of the visual signals along the horizontal compared to the vertical VF. There are more cone and ganglion cells along the horizontal compared to the vertical retinal meridian.

However, a recent publication by Mutti et al (2011) reported no association between relative peripheral hyperopia and axial elongation or the rate of myopia progression in children participating in the CLEERE study who became myopic. Furthermore, the strongest odds ratio between hyperopic relative peripheral refractive error in the third grade and the risk of onset of myopia by the eighth grade was only 1.56 in children of Asian ethnicity. However, this study only measured peripheral refraction at 30° in the nasal VF. Sng et al (2011) found that the development of myopia was associated with a change in peripheral refraction from relative myopia to relative hyperopia indicating

that peripheral refraction may be more a reflection of ocular shape rather than being a myopiogenic factor.

Animal studies have provided compelling evidence supporting the possibility of predicting myopia from an individual's peripheral refractive status by demonstrating the strong influence of the peripheral retina in the emmetropisation process and showing that an intact fovea appears to not be necessary in the normal emmetropisation process or the development of vision dependent refractive errors (Smith et al., 2005, Smith et al., 2007). Recently, Smith et al (2009b) imposed hyperopic peripheral defocus with unrestricted central vision in infant rhesus monkeys with intact and photoablated foveas. Imposing this hyperopic defocus in the periphery was found to promote the development of central axial myopia in the presence of both functioning and non-functional foveas. Similarly, Liu and Wildsoet (2011) demonstrated in the chick eye model that a plano centre and +5D periphery concentric bifocal spectacle lens tended to produce central hyperopia coupled with apparent inhibition of axial length elongation.

Large amounts of astigmatism have been demonstrated in the periphery (Atchison et al., 2006, Millodot, 1981, Seidemann et al., 2002) and the question has been raised as to which meridian the human eye could potentially emmetropise towards. Calver et al (2007) and Seidmann et al (2002) suggested that the human eye emmetropises towards the least myopic meridian. Conversely, animal studies have demonstrated the opposite. When a large amount of astigmatism was imposed onto the retina of infant monkeys, the eyes tended to emmetropise towards one of the two focal planes and not the circle of least confusion. Most of the treated animals tended to become more hyperopic (Kee et al., 2004). Similar results have been demonstrated in chicks reared with ±10DC spectacle lenses (Schmid and Wildsoet, 1997). Chicks appeared to emmetropise towards the more myopic meridian to become hyperopic.

1.2.4.4 PERIPHERAL REFRACTION AND MYOPIA CONTROL

There is debate on whether the relatively hyperopic defocus is simply a reflection of the more prolate ocular shape commonly seen in myopes (Atchison et al., 2006, Schmid, 2003b, Seidemann et al., 2002, Sng et al., 2011) or whether it is a myopiogenic factor (Collins et al., 1995, Smith, 2011, Wallman and Winawer, 2004). As human studies have demonstrated the presence of relative peripheral hyperopia before the onset of myopia, it appears that it could be a potential myopiogenic factor. Therefore, it has been proposed that correcting this relative hyperopia or inducing myopia onto the peripheral retina of myopic individuals could possible slow down or stop the progression of myopia (Charman and Radhakrishnan, 2010, Smith, 2011, Wallman and Winawer, 2004). If indeed peripheral hyperopia is a myopiogenic factor, it remains unknown why the eye stops elongating axially even with the continuing presence of peripheral hyperopia because most myopic eyes eventually stop progressing (Goss et al., 1985, Grosvenor and Goss, 1999). Furthermore, the amount of defocus change required on the peripheral retina to have an effect on myopia development and progression in the human eye is unknown.

Conventional corrections of myopia with spectacle lenses have been reported to increase the amount of relative hyperopia in the periphery (Lin et al., 2010, Tabernero et al., 2009). On the other hand, Shen et al (2010) found a decrease in relative hyperopia with correction of myopia with SCLs and RGP lenses although only 11 subjects with central refraction ranging from -1.00 to -6.50D were measured. As peripheral defocus cannot be manipulated with conventional forms of myopia correction, novel spectacle lens and CL designs have been developed to induce a myopic shift onto the peripheral retina. Currently, only a handful of data has been published on some of these innovative optical devices.

The anti-myopia spectacle lens was developed by Vision CRC (Brien Holden Vision Institute; Sydney, Australia) and manufactured by Carl Zeiss Vision (Adelaide, Australia) (Sankaridurg et al., 2010). These novel lenses have a plus power in the periphery to change the peripheral field curvature to become more myopic which could potentially slow down or stop the progression of myopia. Out of the 4 different

lens designs developed and investigated, only one was found to differ in myopia progression from SV spectacles. Children with a parental history of myopia had a reduced myopia progression of 0.29 ± 0.11D. This novel lens was asymmetric in design to reduce astigmatism in the horizontal meridian. A central aperture allowed correction of central vision which extended approximately 10mm from the centre along the horizontal meridian and inferiorly, and a plus power of 1.95D was achieved in the periphery. When assessing peripheral refraction, correction of myopia with either conventional SV lenses or the novel multifocal lenses created a hyperopic shift in M at all positions along the horizontal meridian. Moreover, no significant difference in peripheral refraction profile was evident between conventional SV lenses and the novel multifocal lenses. It is unknown why this particular lens design had an effect on myopia progression in a subset of children with a history of parental myopia.

There are also two commercially available multifocal SCLs aimed to induce myopia onto the peripheral retina of myopic individuals as described in Section 1.1.6.2.2. These have been reported to reduce myopia progression in myopic children (Anstice and Phillips, 2011, Holden et al., 2010) although the states of peripheral defocus with these novel multifocal SCLs are yet to be published.

OK lenses (as described in Section 1.1.5.4.3) are another form of correction which has been found to change the state of peripheral defocus through modification of the anterior corneal curvature. Similar to multifocal SCLs, OK lenses have been shown to reduce myopia progression in myopic children. Although the exact mechanism behind the reduced myopia progression and axial elongation in myopic children is unknown, it has been hypothesised that steepening in the para-central cornea with OK lens wear may induce changes in peripheral defocus which in turn may cause reduced myopia progression (Walline et al., 2009).

Only two studies have investigated the effects of OK lenses on peripheral refraction (Charman et al., 2006, Queirós et al., 2010) in adult myopes. Hyperopic shifts in M occur between ±10° (Charman et al., 2006) to ± 20° (Queirós et al., 2010) along the horizontal VF with OK while leaving the refraction in the peripheral VF relatively unchanged. Negative increase in J_{180} or against the rule astigmatism has also been

measured in the periphery while J_{45} profile remained unchanged during OK lens wear (Figure 1.19).

The myopic defocus in the peripheral retina coupled with corrected central vision is believed to be the possible mechanism behind reduced myopia progression reported in children (Holden et al., 2010, Anstice and Phillips, 2011, Walline et al., 2009). Investigation into potential rebound effects occurring after cessation of these novel CLs and spectacles is required.

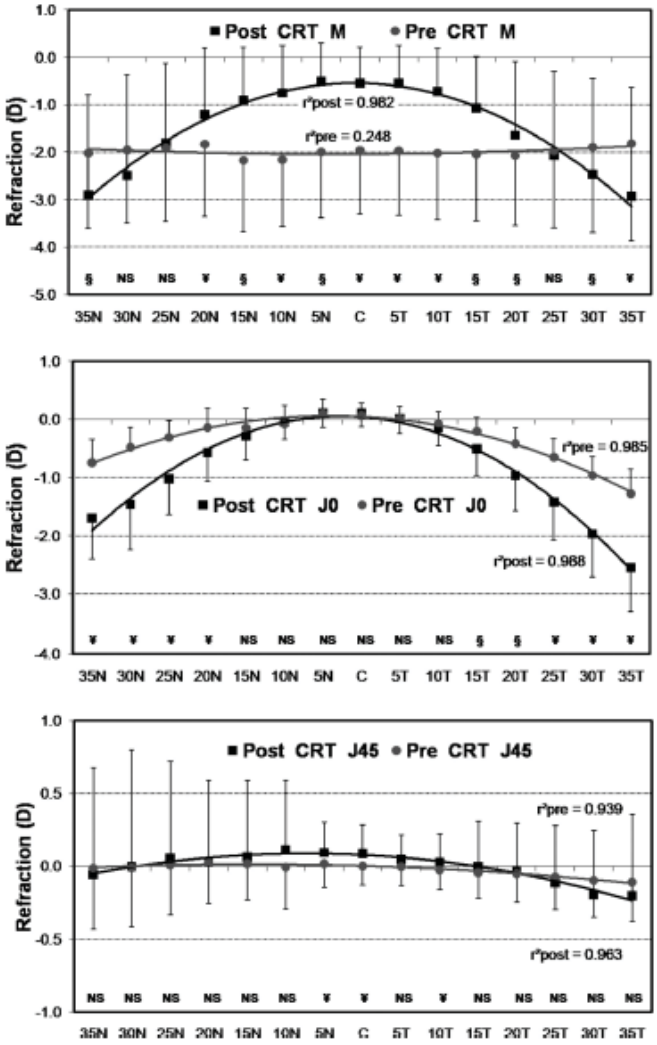


Figure 1.19 Peripheral refraction profiles of M (top), J_{180} (middle) and J_{45} (bottom) before and after OK lens wear (Reproduced from Quierós A., Gonzalez-Meijome, J. M., Jorge, J., Villa-Collar, C. & Gutierrez, A. R. 2010. Peripheral refraction in myopic patients after orthokeratology. *Optom Vis Sci,* **87, 323-9. Copyright (2010), with permission from Lippincott Williams & Wilkins).**

1.3 RATIONALE AND STRUCTURE OF THESIS

With increasing evidence of the involvement of the peripheral retina in the development of central refractive error, innovative CLs and spectacle lenses have been developed to induce a myopic field curvature in myopic individuals as described in Section 1.2.4.4. It is currently hypothesised that correcting the relative hyperopic defocus typically measured in myopes, or inducing myopic defocus onto the peripheral retina of myopic individuals, could possibly slow down or stop the progression of myopia. Peripheral refraction or ocular shape is highly variable and hence the amount of change required in each myope to be potentially anti-myopiogenic will also be highly variable. Ideally, peripheral refraction should be measured to calculate the exact amount of myopic shift required on the peripheral retina for each individual. The recently developed novel SCLs and spectacle lenses which apparently impose myopic defocus onto the peripheral retina are manufactured in limited power parameters and hence restrict the level of myopic peripheral shift that can be achieved.

OK inadvertently changes the state of peripheral defocus in the manner believed to potentially slow down myopia progression and there is limited research into the mechanisms behind this optical change. It is believed that the change in peripheral defocus resultant from OK occurs due to changes in corneal topography. Therefore the aim of the research presented in this thesis is to investigate the effects of different OK lens designs on peripheral refraction change. This will provide information on potentially developing new OK lens designs that are able to impose specified peripheral defocus changes.

Chapter 2 describes different methods and instrumentation used in the clinical studies described in this thesis. Chapter 3 then describes the first study of this thesis investigating differences in peripheral refraction profiles between different ethnicities. As Asia presents the highest prevalence of myopia, peripheral refraction profiles in East Asian and Caucasian emmetropes and myopes were compared to determine if differences in ocular shape inferred from peripheral refraction could

possibly explain differences in myopia prevalence between different ethnicities. This led to the study described in Chapter 4 which attempted to verify if peripheral refraction does indeed describe ocular shape. Chapter 5 then investigated changes in peripheral refraction subsequent to OK lens wear in both myopic children and adults. Time course of corneal topography and refraction effects were explored. To gain an understanding behind the mechanisms involved in peripheral refraction change, Chapter 6 explored relationships between corneal topography change and corresponding peripheral refraction change after OK. This lead to investigation of the effects of different OK lens parameters on corneal topography and corresponding changes in peripheral refraction in order to determine the feasibility of OK to be used as a means of inducing specified peripheral refractive defocus changes. Chapter 7 then explored the possibility of peripheral refraction manipulation with SCLs. This thesis concludes with Chapter 8 which presents an overall summary of results and conclusions of the various studies described in this thesis and discusses the realistic potential of OK lenses to be used to create customised changes in peripheral defocus.

CHAPTER 2

MATERIALS AND INSTRUMENTATION

This chapter explores the different methods and instrumentation used in the clinical studies described in the following chapters. The first section of this chapter describes different instruments and methods available for measurement of ocular parameters of interest including practical and theoretical limitations. The second section of this chapter continues with the description of methods and instrumentation used in the clinical studies described in this thesis. The third section of this chapter describes clinical evaluation of these instruments used in the clinical studies and the chapter concludes with explanation of statistical data analysis used to evaluate different ocular parameters.

2.1 INSTRUMENTATION AND METHODS

2.1.1 CENTRAL REFRACTION

2.1.1.1 SUBJECTIVE REFRACTION

Subjective non-cycloplegic sphero-cylindrical refraction is measured using standard optometric techniques. Monocular subjective sphere endpoint is determined by the method of maximum plus power for best VA (Grosvenor, 2007) while astigmatism power and axis is determined by the Jackson Cross Cylinder (Rosenfield, 2009).

Subjective refraction is often considered the gold standard for on-axis refraction with reliability within 0.25 to 0.50D (Goss and Grosvenor, 1996).

2.1.1.2 OBJECTIVE REFRACTION

Autorefraction is commonly used in optometric and ophthalmic practices to measure central refraction. There are currently three open-field autorefractors that measure central refraction; the Canon Autoref R-1 (Tokyo, Japan), Shin-Nippon SRW-5000, also branded as Grand Seiko WV-500 (Tokyo, Japan), and the Shin-Nippon NVision-K 5001, also branded as Grand Seiko WR-5100K (Tokyo, Japan). These open-field autorefractors avoid proximal accommodation which is a problem inherent in closed-field autorefractors with inadequate fogging mechanisms (Hung et al., 1996, Rosenfield et al., 1990). The open view nature of these open-field autorefractors offers the freedom of target choice and the benefit of natural viewing conditions.

2.1.1.2.1 SHIN-NIPPON NVISION-K 5001 AUTOREFRACTOR

The Shin-Nippon NVision-K 5001 autorefractor is a binocular open-field infra-red autorefractor measuring objective refraction. It utilises an infrared ring target (wavelength near 850nm, 2.3mm diameter) which is reflected off the retina. A lens

moves along a motorised track to focus the imaged ring and the ring is subsequently digitally analysed in size and in multiple meridians to calculate refraction. This instrument takes static refractive error measurements between ±22.00D sphere and ±10.00D cylinder in 0.12D increments and 1° steps for the cylindrical axis. Measured refraction is an average across the 2.3mm infrared ring.

2.1.2 PERIPHERAL REFRACTION

There are various techniques used to measure peripheral refraction as outlined below.

2.1.2.1 OPTOMETER

Optometers are a group of instruments which are able to measure the refractive error of the eye. They incorporate various principles, generally more than one, into a single optometer including parallax, Scheiner, split-image/vernier alignment, retinoscopic, best-focus, knife-edge, ray-deflection and image size approaches. Optometers determine refraction in either a subjective or objective manner and can be manual or automated. Manual or visual optometers use visible light while automated optometers typically use infrared light (Atchison, 2009).

The split-image or vernier alignment principle is generally combined with the Scheiner principle. They are incorporated into the Zeiss coincidence optometer (Hartinger optometer) and Topcon refractometer model III which are the only optometers that have been used to measure peripheral refraction (Millodot, 1981, Millodot, 1984, Millodot and Lamont, 1974). Only these two principles will be briefly discussed.

2.1.2.1.1 SPLIT-IMAGE/VERNIER ALIGNMENT PRINCIPLE

A target with a straight edge is split into two and imaged onto the retina through different parts of the pupil. Refractive error misaligns the target which is seen by

either the participant (subjective measure) or as a reflection off the fundus by the clinician. If the participant is emmetropic, the two halves of the target will be seen in alignment (or in coincidence). To measure astigmatism, the instrument is rotated to match the astigmatic axis of the eye in order bring the target into alignment (Atchison, 2009).

2.1.2.1.2 SCHEINER PRINCIPLE

A Scheiner disk is a mask incorporating two small holes which is placed near the subject's eye. Light rays entering through the mask will focus in the eye. If the eye is emmetropic, a single point image will be seen. If the eye is either myopic or hyperopic, diplopia will be experienced: uncrossed-diplopia for myopic eyes and crossed-diplopia for hyperopic eyes. The target position required to eliminate the diplopia determines the refractive error of the eye. For astigmatism, the Scheiner disk is rotated such that the orientation of the pin holes coincides with the principal meridians of the astigmatic eye (Atchison, 2009).

2.1.2.1.3 OPTOMETERS IN PERIPHERAL REFRACTION

Early studies on peripheral refraction were conducted in the early 1930s by Ferree et al (1931, 1932 & 1933) using the Zeiss parallax optometer. More recent studies which have utilised the Zeiss coincidence optometer have found difficulty and inconsistent measurements beyond 40° (Dunne and Barnes, 1990, Dunne et al., 1993) even though Ferree et al (1931, 1932 & 1933) reported that they were able to take measurements out to 60°.

The principles featured in the Zeiss coincidence optometer and Topcon refractometer model III require a good fundus image quality. The elliptical pupil resulting from eccentric gaze will induce aberrations that can affect quality of the fundus image and hence the accuracy of peripheral refraction measurements (Atchison, 2009). The

cumbersome nature of this instrument (Rempt et al., 1971) is another reason that the optometer is not often used.

2.1.2.2 AUTOREFRACTION

Automated refraction offers speed, accuracy and repeatability. The open view autorefractors as described in Section 2.1.1.2. have the additional advantage of eccentric target viewing and therefore have often been used to measure peripheral refraction. The Shin-Nippon NVision-K 5001 autorefractor is an optometer which is commonly used to measure peripheral refraction, and will be described in more detail in Section 2.2.3.1.

2.1.2.3 ABERROMETRY

The eye is not an optically perfect system and imperfections in the optics of the eye cause entering light rays to deviate to create irregularities in the image which are referred to as optical aberrations. The effect of these optical imperfections on a phase of light as it passes through the eye is known as wave aberration and is generally defined mathematically by a series of polynomials known as Zernike polynomials. They are categorised into different types and levels. Aberrometers are instruments which are able to provide measurements of the wave aberrations of the eye (Lombardo and Lombardo, 2010).

Modifications have allowed aberrometers to take off-axis aberration measurements as described by Atchison et al (2007). Atchison et al (2003) were able to convert wave aberrations into peripheral refractive errors and demonstrated agreement between the Hartmann-Shack aberrometer and the Shin-Nippon SRW-5000 autorefractor (former model) (Atchison, 2003). Other studies (Berntsen et al., 2008, Donovan et al., 2007) have found that the Complete Ophthalmic Analysis System (COAS; ANI Wavefront Sciences, Albuquerque, NM, USA) aberrometer, which is a Hartmann-Shack aberrometer, gives comparable peripheral refraction measurements to the

Shin-Nippon NVision-K 5001 autorefractor. A common observation was that aberrometers (Atchison, 2003, Donovan et al., 2007, Lundstrom et al., 2005) gave more myopic values compared to the autorefractor. This is thought to be due to differences in calibration or operation principles between aberrometers and autorefractors (Atchison, 2003, Berntsen et al., 2008).

Although aberrometers are able to provide accurate and simultaneous measurements of peripheral refraction and aberrations, the high cost of these instruments limits their use.

2.1.2.4 DOUBLE-PASS TECHNIQUE

The double-pass method or ophthalmoscopic technique has been extensively used to assess central retinal image quality. The double-pass technique analyses images of a point source, typically a reduced intensity Helium-Neon laser light beam, that has been projected then reflected off the retina and double-passed through the ocular media. To calculate refractive error, a lens scans through the double-pass images and determines the positions of the extremes of the Interval of Sturm (Artal, 2000, Fedtke et al., 2009). Modification of this technique has allowed assessment of peripheral retinal image quality and measurement of peripheral refraction as astigmatism is one of the main monochromatic aberrations in the periphery of the eye (Artal et al., 1995a).

Jennings and Charman first reported peripheral optical quality using the double-pass technique (Jennings and Charman, 1978, Jennings and Charman, 1981b) and attempted to correct peripheral refraction to measure critical fusion frequency (Jennings and Charman, 1981a). More recently, the double-pass technique has been employed to measure peripheral refraction in different refractive groups (Gustafsson et al., 2001, Seidemann et al., 2002).

However, there are difficulties in assessing retinal image quality in the peripheral retina due to the loss of paraxial aberrations (Artal et al., 1995b, Fedtke et al., 2009,

Navarro et al., 1993). Another disadvantage of this technique is that it is not commercially available and variations exist between different research groups due to the custom-made nature of the instrument. Therefore, this technique is not readily utilised to measure peripheral refraction.

2.1.2.5 PHOTOREFRACTION

Photorefractors are another type of optometer which are able to calculate the refractive error of the eye from the distribution of light in the pupil. A light source illuminates the eye and the reflected image of the illumination at the pupil plane is photographed then analysed. As measurements can be taken from both eyes simultaneously from afar, this instrument suits infants and uncooperative subjects. The PowerRefractor is a newly developed photorefractor which was found to be comparable but to measure less myopia compared to the Nidek AR800 closed-field autorefractor (Choi et al., 2000).

Gustafsson and Unsbo (2003) used a large concentric ring fixation pattern with horizontal and vertical support lines to guide and stabilise gaze direction in seven participants with central VF loss and subsequent eccentric fixation. Five concentric rings were placed in 5° intervals up to 25° and peripheral photorefraction measurements were taken with the PowerRefractor around the centre of each subject's eccentric fixation to determine if correction of refractive error at this position could improve visual function in these subjects with no central vision. Seidemann et al (2002) also used the PowerRefractor to measure peripheral refraction, up to ±25° from fixation, in different refractive groups and found results to be similar to refraction derived from the double-pass technique. However, a more recent study by Lundström et al (2005) found the PowerRefractor tended to underestimate high myopia (<-6.00D). Furthermore, correction of peripheral refractive error obtained by the Hart-Shackman aberrometer was found to give better visual function in six out of seven participants compared with correction obtained by the PowerRefractor. This difference was believed to be due to the fact that the PowerRefractor was not designed for peripheral measurements (Lundstrom et al., 2007). With eccentric gaze,

the pupil becomes elliptical and this change in shape may affect results as refraction is calculated from the light distribution throughout the pupil. Elliptical pupils from eccentric gaze have also been found to be too narrow and therefore unable to be analysed in some cases (Lundstrom et al., 2007). Due to these limitations, the PowerRefractor has not been frequently used to measure peripheral refraction.

2.1.2.6 SUBJECTIVE PERIPHERAL REFRACTION

Subjective peripheral refraction is determined by introducing trial lenses into the peripheral viewing path. The trial lens which gives maximum VA or the highest contrast sensitivity is deemed the refractive error at that particular eccentricity. The earliest study adopting this technique was published in 1971 which described subjective refraction in one subject at 60° in the temporal VF (Ronchi, 1971). Subjective peripheral refraction has been found to be comparable to retinoscopy and to stimulate less accommodation compared to the refractometer (Millodot and Lamont, 1974). Wang et al (1996) also found that subjective refraction compared well with eccentric retinoscopy. However, these studies were conducted on only 3 and 4 subjects, respectively. A more recent study conducted on 50 subjects concluded that subjective peripheral refraction had large variance and was a time-consuming technique. Difficulty with stabilising attention and determining the criterion of seeing was also encountered (Lundstrom et al., 2005). Furthermore, the testing methods (using contrast detection or target resolution) have not been consistent and no standard method has been developed. Repeatability has also never been assessed, and there are difficulties in accurately determining cylinder axis (Fedtke et al., 2009, Lundstrom et al., 2005). With these disadvantages, subjective refraction has only been adopted by a small number of researchers and is currently rarely used.

2.1.2.7 ECCENTRIC RETINOSCOPY

Streak retinoscopy is routinely used by clinicians to measure central refraction. It is considered an objective measurement although it involves subjective decisions by the clinician. In streak retinoscopy, the movement of the participant's retinal reflex is assessed and neutralised with a trial lens to determine the eye's refractive error. An advantage of this technique is that it requires no active participation by the subject and therefore can be used on pediatric or uncooperative participants. Retinoscopy has been used to measure peripheral refraction by assessing the retinal reflex from an angle eccentric to the visual axis.

Rempt et al (1971) first introduced eccentric retinoscopy and developed the skiagram to record and categorise different peripheral refractive errors. Leibowitz el al (1972) and Johnson and Leibowitz (1974) were able to measure out to 80° in 3 and 4 participants, respectively, although some have found unreliable measurements beyond 50° (Millodot and Lamont, 1974). However, eccentric retinoscopy is a cumbersome technique. The pupil becomes elliptical in shape with greater eccentric gaze and coupled with an increase in aberrations produces poor retinal image quality. The retinoscopy reflex thus splits or acts differently in different parts of the pupil making it very difficult for the clinician to make accurate judgements (Jackson et al., 2004, Lundstrom et al., 2005, Rempt et al., 1971).

2.1.3 CORNEAL TOPOGRAPHY

Measurement of anterior corneal profile allows quantitative measurement of the strongest refractive surface of the eye. This is particularly important when investigating the peripheral refractive state of the eye. Furthermore, measurement of corneal shape plays a role in CL fitting and monitoring CL induced corneal changes such as with OK.

Early studies have reported the normal cornea to have an average apical radius ranging between 7.68mm to 7.85mm (Douthwaite et al., 1999, Eghbali et al., 1995,

Guillon et al., 1986, Kiely et al., 1982b). More recently, Read et al (2006) found through conic fitting that the average apical radius in 100 young adult subjects was 7.77 ± 0.2mm with a mean asphericity Q of -0.19 ± 0.1 when measuring across a 6mm corneal diameter zone. For a 10mm corneal diameter zone, apical radius changed to 7.72 ± 0.2mm and Q to -0.36 ± 0.1. Typically the peripheral cornea is flatter and less astigmatic than the centre. Due to the peripheral flattening of the anterior corneal curvature, the human cornea is typically described as being prolate in shape.

Younger adults predominantly have with-the-rule astigmatism whereby the vertical corneal meridian is steeper than the horizontal (Goto et al., 2001). Some have found no age-related changes in the anterior corneal curvature (Atchison et al., 2008) while others have reported flattening of the vertical corneal meridian and steepening of the horizontal meridian (an increase in against-the-rule astigmatism) evident in both males and females over the age of 50, although more prominent in males (Goto et al., 2001).

Studies have found a weak correlation between refractive error and corneal shape. Myopes appeared to have steeper corneas (Budak et al., 1999, Carney et al., 1997, Grosvenor and Goss, 1998, Read et al., 2006) while hyperopes have flatter corneas (Llorente et al., 2004, Sheridan and Douthwaite, 1989). However, others have reported no relationship between corneal curvature and refractive error (McBrien and Millodot, 1987).

Furthermore, the cornea undergoes slight diurnal variation with the greatest change observed upon waking. Regional differences in corneal swelling upon awakening cause both steepening of posterior corneal curvature and flattening of anterior corneal curvature (Handa et al., 2002, Kiely et al., 1982a, Read and Collins, 2009).

2.1.3.1 EXTRAOCULAR MUSCLES AND CORNEAL TOPOGRAPHY

Extraocular muscles (EOMs) generate a substantial amount of force (Collins et al., 1981) which is highlighted by changes in corneal topography evident after EOM

surgery. Hainsworth et al (1999) found that change in tension of a particular muscle after EOM surgery did not produce a change in the adjacent corneal quadrant but instead a significant change was noticed over the entire cornea. Topographic changes subsequent to strabismus surgery have been noticed by others (Kwitko et al., 1992, Nardi et al., 1997, Rajavi et al., 2008) and secondary changes in forces applied from EOMs to the cornea via the sclera have been proposed as a possible cause (Bagheri et al., 2003).

It is therefore not surprising that Read et al (2010a) found changes in topography after 15 minute convergence tasks. Slight steepening of the nasal cornea was observed which was postulated to be related to changes in horizontal rectus muscle force changes concurrent with convergence. Hence it is possible that peripheral refraction measurements taken with prolonged eccentric fixation might change corneal topography and thus give erroneous refraction measurements. Studies (Mathur et al., 2009, Radhakrishnan and Charman, 2008) have investigated the effect of eye rotation on peripheral refraction measurements and no effect on peripheral refraction was found after 2.5 and 3 minutes of oblique viewing.

2.1.3.2 CORNEAL SHAPE DESCRIPTORS

The simplest description of the shape of the cornea is a section of a sphere. However, this is a gross estimation as it has been well established that the cornea significantly changes in shape towards the periphery (Read et al., 2006).

A more accurate portrayal of corneal shape is a section of an ellipse and can be represented by the equation proposed by Baker (1943) then later described by Bennett (1966):

$$X^2 + Y^2 + (1+Q)Z^2 - 2ZR = 0$$

where X and Y are the major axes of the ellipse, Z is the axis of revolution of a conicoid, R is the radius of curvature at the corneal apex and Q is asphericity. Q describes how far a curve departs from a sphere, as shown in Figure 2.1. Prolate or

flattening surfaces are assigned negative Q values while oblate or steepening surfaces are assigned positive Q values.

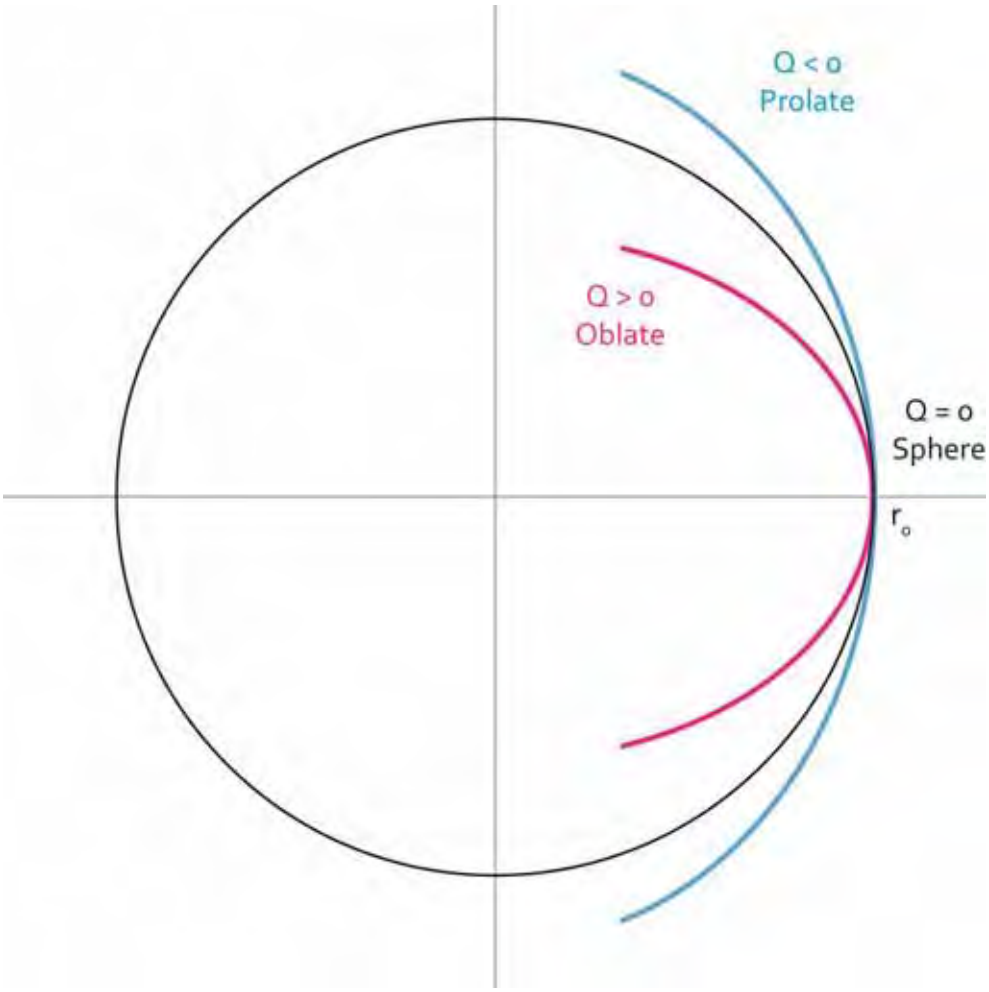


Figure 2.1 Prolate and oblate curves departing from a sphere or asphericity (Q).

Other descriptors have also been developed to describe the cornea. Corneal shape can be described in terms of P or the "shape factor". P is calculated from the equation below:

$$p = 1 + Q$$

The cornea can also be described in terms of eccentricity of an ellipse (e) which is calculated from the semi-diameter corresponding to the optic axis (a) and the semi-diameter at right angles to the optic axis (b) with the equation:

$$e^2 = 1 - b^2/a^2$$

When the cornea is prolate in shape, e^2 is a positive number. A problem arises when trying to describe an oblate cornea, which may result from refractive surgery or OK, as e^2 is a negative number and an e-value cannot be calculated.

The relationship between the different corneal shape indices are shown in Figure 2.2.

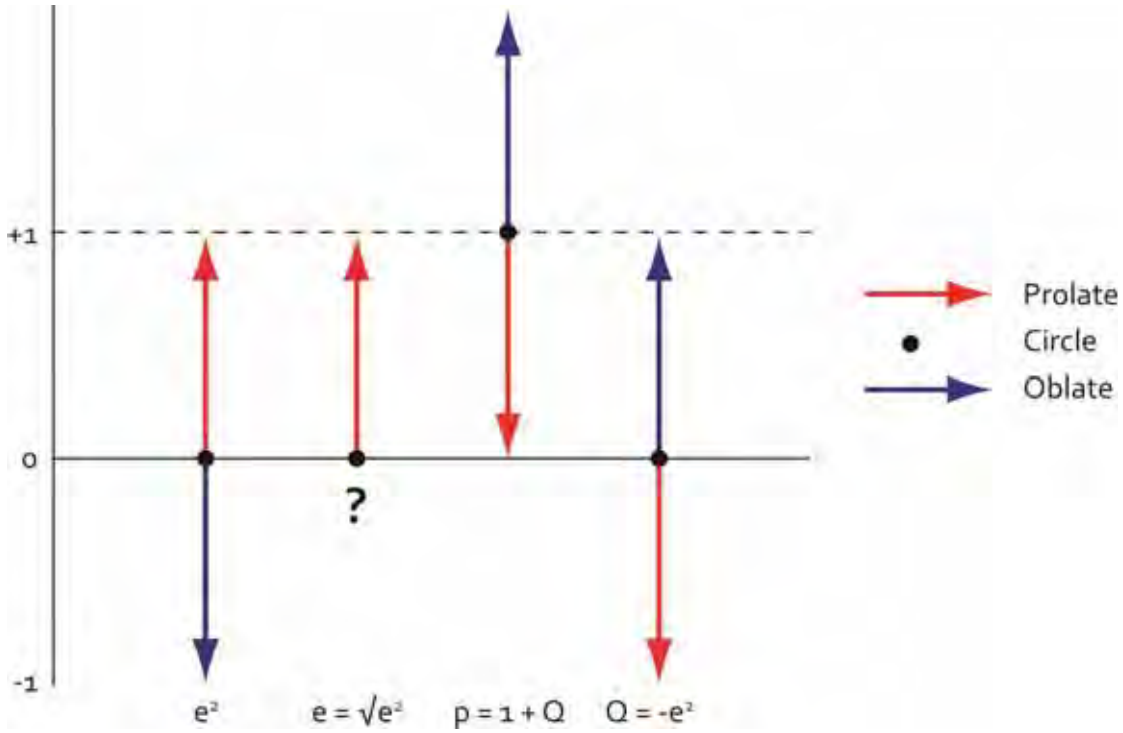


Figure 2.2 Relationship between the three different corneal shape indices e, p, and Q. e cannot describe oblate shapes (adapted from Swarbrick, 2004).

2.1.3.3 KERATOMETRY

Keratometry utilises the ability of the cornea to behave like a convex mirror and uses reflections off the anterior surface of the cornea (Purkinje I) along 2 orthogonal

meridians to calculate corneal radius of curvature (Belin and Khachikian, 2009, Rabbetts, 2007a). It measures the maximum and minimum power at four positions along these two meridians from a small area of the cornea (between 1 to 1.7mm from the centre of the cornea). Hence it provides limited information about corneal shape (Klyce and Wilson, 1989). More potential errors are introduced with keratometry because reflections which are used to determine the curvature of the eye are dependent on the quality of the tear film. Furthermore, the keratometer assumes that the cornea is a segment of a sphere along each of the orthogonal meridians of interest (Rabbetts, 2007a). Despite these limitations, the keratometer is a fundamental instrument in clinical practice to aid in CL fitting.

2.1.3.4 KERATOSCOPY

The keratoscope profiles the corneal contour over an area of the cornea greater than that analysed by the keratometer. The hand-held Placido disc is a flat disc consisting of black and white concentric rings and is considered to be invented by Plácido in 1880 as described by Levene (1965). This is the simplest form of a keratoscope. The concentric circles are illuminated and reflected off the anterior cornea and examined through an aperture placed in the centre of the Placido disc. Any distortions or irregularities will produce corresponding distorted and asymmetric reflections (Rabbetts, 2007a). Quantitative analysis is achieved by photographing the reflections and is termed photokeratoscopy. The slope of the cornea can be determined with the knowledge of the geometry of the rings and resultant spacing of the reflected rings. Ludlam and Wittenberg (1966) demonstrated that an ellipsoid target surface projected a more suitable and flatter image of the concentric rings and this modification has since been adopted into all Placido disc-based corneal topography systems. In general, the closer the reflected mires, the steeper that particular part of the cornea is and vice versa. Although only large amounts of astigmatism can be visualised with this technique, it supersedes the keratometer by providing information on a substantially larger portion of cornea (Belin and Khachikian, 2009).

2.1.3.5 COMPUTER-ASSISTED VIDEOKERATOSCOPY

Improvements in computer processing and technology and advances in digital imaging have led to the development of digitised corneal topographers. Computer-assisted videokeratoscopes consist of a Placido disc target with a digital video camera and computer system. The Placido disc image is captured and analysed along multiple meridians to calculate corneal slope with knowledge of the geometry of the Placido disc rings.

Off-axis points on the cornea have two focal points (tangential and sagittal points) measured by the videokeratoscope, due to the ellipsoid nature of the cornea. Tangential (or instantaneous) curvature describes the tangential focal point which lies in the tangential plane which contains target mires. Sagittal (or axial) curvature describes the sagittal focal point which lies on a plane that is perpendicular to the tangential plane (Dave, 2004) (Figure 2.3). Tangential and sagittal radii can be used to calculate tangential and sagittal power maps (using $F = 337.5 / r$; where F is power (D) and r is radius of curvature (mm)). Tangential power maps reflect true corneal shape and sagittal power maps reflect the optical effects of corneal topography.

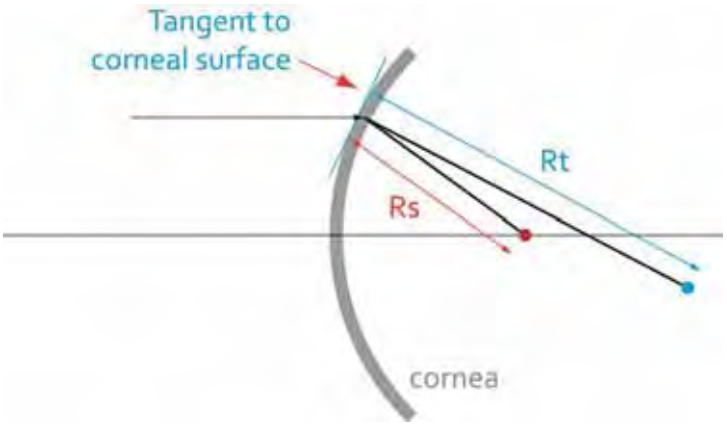


Figure 2.3 Sagittal (Rs) and tangential (Rt) radius of curvature for an aspheric surface (adapted from Dave, 2004).

Computer-assisted videokeratoscopes also display corneal sagittal height or elevation maps from a fixed flat plane which is typically zeroed on the corneal apex. Subtracting

a reference surface from the height data (typically a best fit sphere of BFS) allows subtle changes in corneal elevation to be uncovered (Dave, 2004).

OK CL fitting requires the use of subtraction or difference maps which display the change between two chosen maps as shown in Figure 2.4. Subtle changes in corneal topography with OK lens wear are easily monitored with this function which is essential for appropriate management of these lenses.

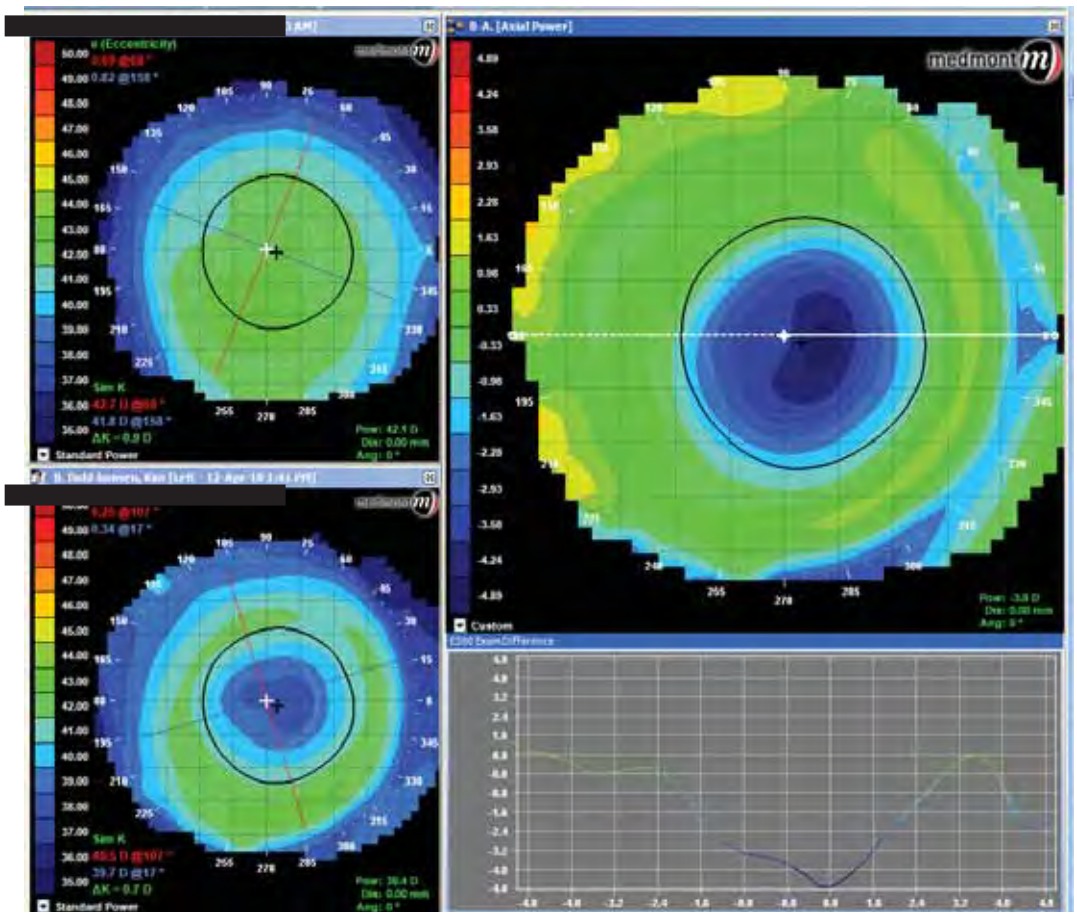


Figure 2.4 Difference map displaying corneal change after OK lens wear. The top left map is the axial power map before OK lens wear and the bottom left map is the axial power map after OK lens wear. The top right map is the difference map of the two selected maps and the difference in axial powers between the two maps along a selected meridian (horizontal meridian in this example) is plotted on a profile graph shown in the bottom right.

The Medmont E300 (Medmont Pty Ltd, Melbourne, Australia) is a Placido disc videokeratoscope commonly used in clinical practice. Tang et al (2000) reported that the Medmont had high accuracy in measuring spherical and aspheric surfaces and the Medmont had greatest precision compared to two other Placido disc videokeratoscopes, the Keratron videokeratoscope (Alliance Medical Marketing, Jacksonville, FL) and Topographic Modeling System (TMS) (Computed Anatomy Inc., New York, NY). The greatest standard error measurement of ±9.8μm was found for a 5.0 bicurve test surface. The Medmont videokeratoscope has also been found to have good in vivo repeatability and reproducibility with only 2 repeated readings required to limit the standard error of the repeated measurements to 2μm for corneal elevation data (Cho et al., 2002).

The Medmont E300 videokeratoscope displays corneal topography measurements in the form of colour-coded contour maps (Figure 2.4) in addition to mathematical descriptors. Cool colours (blue) correspond to flatter regions or areas of less corneal power while warmer colours (red) correspond to steeper regions or areas of greater corneal power.

2.1.3.6 NON-PLACIDO DISC-BASED MEASUREMENT OF CORNEAL TOPOGRAPHY

Placido disc based corneal topography measurements have intrinsic limitations including reduced data point acquisition over the central 2mm of the cornea which reduces accuracy (Belin and Ratliff, 1996), and potential for errors in alignment, focus and centration (Seitz et al., 1997). This led to the development of elevation-based topography. Multiple optic sections are taken across the entire cornea with a scanning-slit technique which reconstructs not only the anterior corneal surface, but also the posterior corneal surface and measures the corneal thickness profile (Belin and Khachikian, 2009).

Elevation-based topography does not present actual raw elevation data, but displays the deviation of the measured surface from a reference shape, typically a best fit

sphere (BFS). This allows subtle changes in the topography of the cornea to be easily detected. There is no standard corneal chord to fit the BFS on an elevation-based topography map but 8 to 9mm zones appear to provide adequate data points. Larger zones typically produce flatter BFSs while smaller zones provide steeper BFSs (Macfadden et al., 2007). This means that elevation maps will vary depending on size of the zone for fitting the BFS (Cairns and McGhee, 2005). Furthermore, zones can be chosen automatically by the instrument software or manually chosen by the user. Another consideration is where to locate the BFS relative to the corneal surface. If the BFS is not placed on the same position then true changes in elevation or shape will not be revealed. Due to the non-standardised nature of elevation-based topography, there are reservations on using this novel technique for research applications.

The Orbscan II (Bausch & Lomb, NY, USA) is a non-contact device which uses both a Placido disc and scanning slit to determine corneal curvature. The Orbscan II provides total optical power to describe anterior and posterior corneal shape. A combination of Placido disc-derived anterior corneal refractive power and scanning slit-derived posterior corneal refractive power is used to construct total optical power maps (Cairns and McGhee, 2005). Unfortunately, manufacturers provide very little information on exactly how these maps are constructed. Although the Orbscan II has been found to accurately measure anterior surface elevation on test surfaces (Cairns et al., 2002), Cho et al (2002) found poor repeatability and reproducibility of topography maps with the Orbscan compared to other topographers. A total of 552 repeated readings were required to achieve a precision of 2µm.

The Pentacam (Oculus Inc, Dutenhofen, Germany) is an apparatus which is capable of modelling the anterior chamber by using a rotating Scheimpflug camera and a blue LED slit light source (475nm). Together these rotate 180 degrees around the optic axis of the eye acquiring 25 images containing 500 measurement points on the anterior and posterior corneal surfaces to construct true elevation maps and calculate corneal thickness. The Pentacam scans the entire cornea and anterior chamber in approximately 2 seconds. The Pentacam has been found to have good repeatability and close agreement with the Medmont E300 videokeratoscope for anterior corneal

axial curvature (Read et al., 2009) and provides repeatable measurements of both axial and tangential anterior and posterior corneal curves (Chen and Lam, 2009).

There are a few studies which have looked at the effects of OK on the cornea with the Orbscan and Pentacam. Soni et al (2003) found flattening of the anterior corneal curvature with the Orbscan. Tsukiyama et al (2008) found no change in either the posterior corneal curvature or anterior chamber depth with OK lens wear using the Pentacam. This supports the hypothesis that OK lenses achieve their refractive effects by altering the anterior corneal curvature rather than through overall corneal bending (Alharbi and Swarbrick, 2003, Swarbrick et al., 1998). This study using elevation-based topography to detect changes in corneal curvature after OK lens wear does not mention the size of the zone selected for BFS. Due to the novel nature of elevation-based topography, further investigation and standardisation is required to determine the most accurate method for constructing elevation-based topographic data after altering corneal shape by procedures such as OK.

2.1.4 CORNEAL THICKNESS

Measurement of corneal thickness, also termed pachometry, provides significant information on the physiological integrity of the cornea. It is well known that thickness changes occur with various ocular pathological conditions and corneal edema results from a number of physiological stresses including CL wear, trauma and hypoxia. Therefore corneal thickness is often used as an indicator of corneal metabolic status and function (Ehlers and Hjortdal, 2004). It is also used as an integral part of keratorefractive procedures which manipulate corneal thickness to correct refractive error. Additionally, corneal thickness allows appropriate modification of intraocular pressure (IOP) measurements for glaucoma assessment and management (Ehlers and Hjortdal, 2004).

One of the earliest values of corneal thickness was obtained in 1723 by a French surgeon named Petit who measured thickness to be approximately 0.4mm. In 1880, Blix, a physiologist, measured corneal thickness using specular reflections off the

anterior and posterior corneal surfaces in the living eye and found values between 0.482 and 0.576mm. He was the first to perform a direct optical measurement of corneal thickness in a living eye (Chan-Ling and Pye, 1994, Ehlers and Hansen, 1971, Von Bahr, 1948). Since then, various modern methods have been developed and are able to determine corneal thickness to an accuracy of 5-6µm.

The central corneal thickness is reported to be on average 531µm (Herse and Yao, 1993) and corneal thickness increases towards the periphery in all 4 quadrants of the cornea (Hirji and Larke, 1978, Kiely et al., 1982a, Tomlinson, 1972). After the third decade of life, thinning in the periphery is typically observed (Alsbirk, 1978, Lam and Douthwaite, 1998, Martola and Baum, 1968, Olsen and Ehlers, 1984). Corneal thickness undergoes natural diurnal variations and is typically thickest upon awakening after overnight eyelid closure which creates a hypoxic environment resulting in corneal swelling and hence increased thickness. Corneal thickness returns to baseline measurements (pre-sleep) within the first 2 hrs of awakening (du Toit et al., 2003, Feng et al., 2001, Harper et al., 1996, Kiely et al., 1982a, Mertz, 1980, Read and Collins, 2009). Central corneal thickness also appears to be independent of age (Ehlers and Hansen, 1971, Martola and Baum, 1968, Siu and Herse, 1993) and gender (Herse and Yao, 1993, Lam and Douthwaite, 1998, Tomlinson, 1972).

Corneal thickness can be measured independently through a variety of techniques including optical and ultrasound pachometry. Alternatively, there are modern instruments which allow simultaneous measurement of corneal thickness and topography such as the Pentacam and Orbscan.

2.1.4.1 OPTICAL PACHOMETRY

The modern optical pachometer is constructed by mounting a Haag-Streit pachometer onto a slit lamp biomicroscope which is interfaced with a computer. The Holden-Payor pachometer (Holden et al., 1979, Holden et al., 1982) is a result of numerous modifications since its conception by Blix in 1880.

The Holden-Payor pachometer utilises the principle of observing both the anterior and posterior cornea with an optic section from the slit lamp biomicroscope as described by Jaeger (Chan-Ling and Pye, 1994, Olsen et al., 1980a, Olsen et al., 1980b). A split image device using rotating plates is placed into one eyepiece of the slit lamp. The two glass plates are positioned on top of each other where the top plate is able to rotate and the lower plate is fixed. The rotating upper plate is able to shift the illumination path, and consequently move the upper image of the optic section laterally in relation to the fixed lower plate and image. The vertical optic section has an apparent width of 0.2mm and is arranged so that the angle between the illumination and observation system is 65° and is not symmetrical about the optic axis (Figure 2.5). This allows a wider corneal section to be observed providing better resolution (Chan-Ling and Pye, 1994) in addition to thickness measurement of various corneal layers. Brennan et al (1989) developed an equation which enabled the measurement of true corneal thickness for any corneal location and for any combination of observation and illumination angles which may or may not be symmetrical about the normal of the cornea:

$$x = \frac{\mathbf{Rc\ sin\beta}}{\sqrt{\mathbf{1 + Qsin^2\beta}}}$$

Where x = lateral position on anterior cornea (mm)

Rc = apical radius of anterior cornea (mm)

Q = asphericity of anterior cornea

β = angular rotation of fixation (degrees)

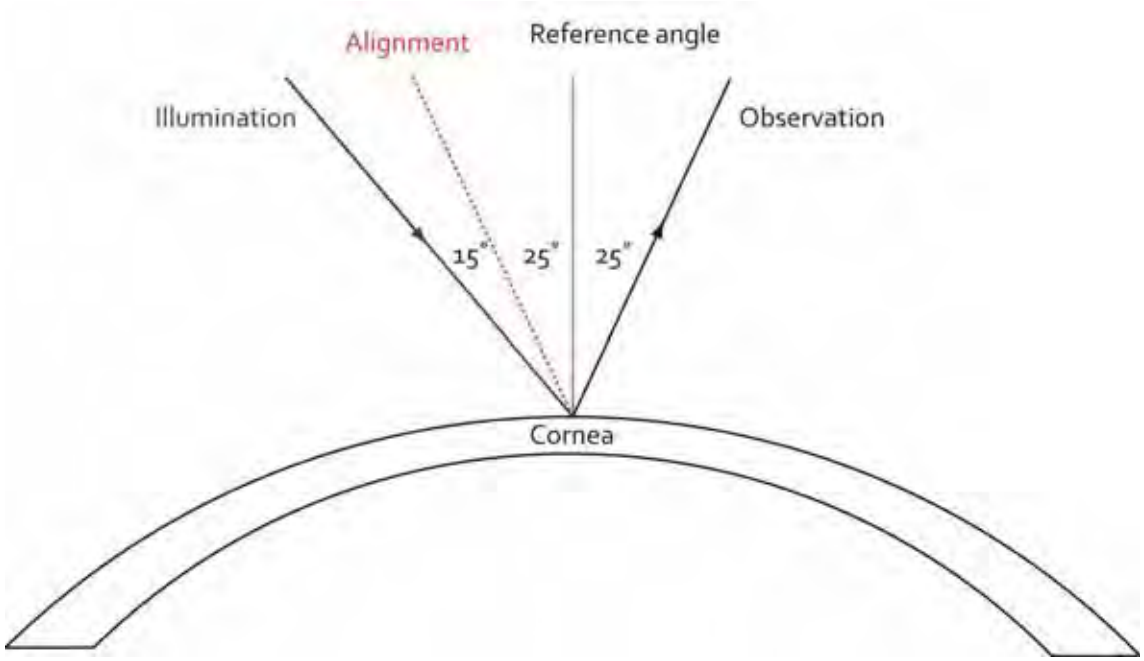


Figure 2.5 Configuration of the Holden-Payor optical pachometer.

Recent published data suggest that good repeatability can be obtained by a trained observer (Swarbrick et al., 1998). Alharbi and Swarbrick (2003) found a maximum standard deviation (SD) of 2µm at the centre and 4.3µm at the para-central cornea for consecutive thickness measurements and an average difference of 3.2 ± 2.2µm (mean ± SD) over two different measurement sessions.

2.1.4.2 ULTRASOUND PACHOMETRY

Ultrasound pachometry measurements are based on the velocity of sound. The time elapsed between the echoes of high frequency sound waves from the anterior and posterior corneal surface is used to calculate the thickness of corneal tissue. Ultrasound pachometers are portable and reports have revealed high repeatability (Gordon et al., 1990, Miglior et al., 2004, Salz et al., 1983, Tam and Rootman, 2003).

The velocity of sound in human corneal tissue is approximately 1590 m/sec (Salz et al., 1983) but it has been found to vary between individuals and with tissue hydration (Chan-Ling and Pye, 1994, Liu et al., 2008). Furthermore local anaesthetic is required

as the probe contacts the cornea. There are also potential errors in alignment and corneal location with repeated measurements (Chan-Ling and Pye, 1994). As repeated measurements in corneal thickness are required at numerous positions along the cornea in the envisaged research, the ultrasound pachometer is unsuitable for the studies described in this thesis.

2.1.5 AXIAL LENGTH

Myopia is typically associated with increases in axial length and therefore increase in axial length is used as a robust measure of myopia progression (Grosvenor and Scott, 1991, Luo et al., 2006, McBrien and Adams, 1997, Xie et al., 2009).

2.1.5.1 IOLMASTER

The IOLMaster (Zeiss, Germany) is one of the most commonly used instruments to measure ocular biometry and utilises partial coherence interferometry (PCI) to measure axial length. PCI involves emitting sequential wavelets of infrared light (780nm) which are reflected off the retinal pigment epithelium. Axial length is calculated by the time delay between reflections off the anterior surface of the cornea and retinal pigment epithelium. Measurements are fast and non-invasive. Additionally, the IOLMaster has been shown to take comparable and repeatable measurements compared to A-scan ultrasonography in both adults (Lam et al., 2001, Santodomingo-Rubido et al., 2002, Sheng et al., 2004) and children (Carkeet et al., 2004). Chan et al (2006) found the IOLMaster to be repeatable in measuring axial length in subjects after wearing OK lenses. Axial length and anterior chamber depth were not affected by the altered anterior corneal surface with both the IOLMaster and A-scan ultrasonic biometers, which was unexpected as reduced axial length was anticipated because corneal thinning has been shown to occur with OK lens wear (Swarbrick, 2006). This may be due to changes in corneal refractive index after OK which may influence axial biometry (Chan et al., 2006).

2.2 MEASUREMENTS AND METHODS

This section describes the specific methods and instrumentation used in the research described in this thesis.

2.2.1 VISUAL ACUITY

Monocular high contrast VA was measured at 6m using a mirror and a computerised logMAR chart (Test Chart Pro, Thomson Software Solutions, London, England). Letter presentation on the charts was randomised with each measure to minimise learning effects. VA was measured in standard room illumination of 530.2 ± 3.1 lux (mean ± SD; 3 measurements).

2.2.2 CENTRAL REFRACTION

Both subjective and objective techniques were used to measure central refraction in the studies described in this thesis. Subjective refraction was measured as described in section 2.1.1.1. Objective central refraction was measured using the Shin-Nippon NVision-K 5001 autorefractor as described in Section 2.1.1.2.1.

2.2.2.1 SHIN-NIPPON NVISION-K 5001 MEASUREMENT TECHNIQUE

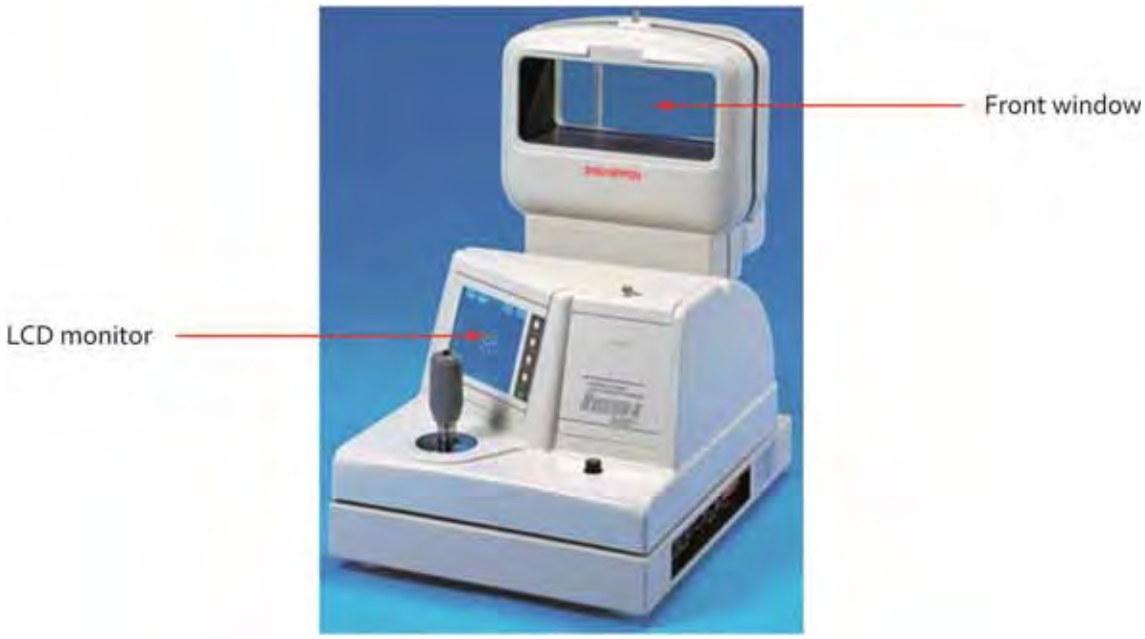


Figure 2.6 The Shin-Nippon NVision-K 5001 autorefractor.

The Shin-Nippon NVision-K 5001 autorefractor (Figure 2.6) has a chin rest and a forehead rest allowing steady view of targets through the front view window. The eye and entrance pupil appear on the LCD monitor and alignment is performed for accurate measurements; the alignment mark is brought into the centre of the reticle mark while the entrance pupil and iris are in focus. Measurements are taken as shown in Figure 2.7.

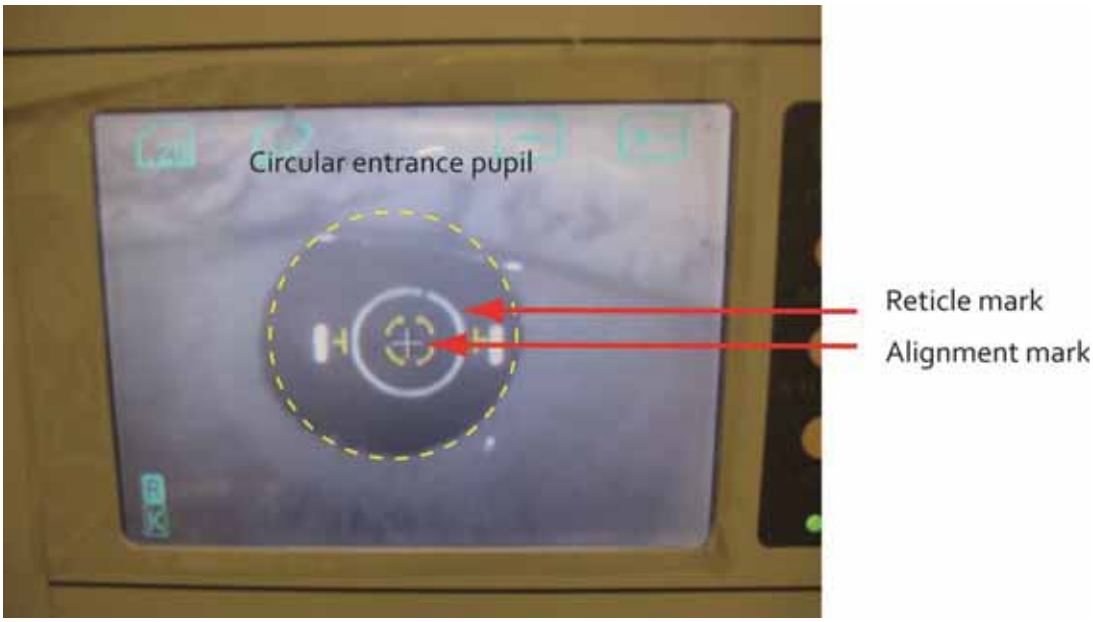


Figure 2.7 The alignment and reticle marks in the entrance pupil during primary gaze.

2.2.2.1.1 FIXATION TARGET

Stable accommodation is required as changes in accommodation can affect refraction measurements. There are numerous cues inherent in the eye that are used to achieve and maintain accurate accommodation including spherical and chromatic aberrations and convergence of the eye. Cues from the target also serve to maintain stable accommodation.

Targets observed by subjects who are emmetropic or with low refractive errors will possess less retinal blur compared to individuals with moderate refractive error. Characteristics of the target as described below were anticipated to maintain steady accommodation in subjects with low refractive errors. For moderate myopes or hyperopes, characteristics of the target will not significantly influence the state of accommodation as the level of blur will cause enough image degradation to not stimulate accommodation. The target will be an ineffective stimulus and cause random fluctuations near the level of tonic accommodation therefore keeping accommodative status relatively stable (Ciuffreda, 1991).

A laser spot of a wavelength of 532nm and power <1mW (Class II Laser product) was projected on a white wall 4.3m away and served as a target. Reasons for this selection are described below.

2.2.2.1.1.1 Polychromatic vs monochromatic targets

Ocular media cause dispersion of white-polychromatic light resulting in chromatic aberrations. Shorter wavelengths come to focus more anterior in the eye than longer wavelengths. The difference in focus between the two extremes of the visible spectrum is approximately 2D. There is evidence to suggest that longitudinal chromatic aberrations (LCA) aid in accurate control of focus and are important cues in dynamic accommodation (Aggarwala et al., 1995b, Kruger et al., 1993). Previous research has shown that compared to white-polychromatic light, targets which are illuminated by narrow-band, achromatising or monochromatic light hinder the eye's ability to accommodate accurately (Aggarwala et al., 1995b, Kruger et al., 1993). Monochromatic targets with mid spectral illumination demonstrated the best dynamic accommodative control compared to targets illuminated from any other wavelengths within the visible spectrum (Aggarwala et al., 1995b). The narrower the target's band spectrum, the more debilitating it was to accuracy of accommodation (Aggarwala et al., 1995a). However, LCA may not play such a significant role in static accommodation (Bobier et al., 1992). At low temporal frequencies and therefore almost stationary targets, the level of accommodative control was the same between white and monochromatic targets (Kruger and Pola, 1986). For the studies reported in this thesis, monochromatic light was selected as it would sufficiently control steady-state accommodation during autorefraction measurements.

2.2.2.1.1.2 Target wavelength and contrast

Early studies have suggested that targets of varying colours caused differing accommodative responses. There was an increased response to red targets compared to either yellow or green targets in agreement with the LCA of the eye (Charman and

Tucker, 1978). However, subsequent studies have found that targets of different colour must vary in luminance to produce differing responses. Accommodation was not influenced by different wavelengths focused on the retina (Bobier et al., 1992) although slightly more accurate and hence steady accommodation was noticed with mid-spectral illumination (Aggarwala et al., 1995b). Therefore, a target of midrange wavelength (532nm) target was chosen for our studies.

Targets and backgrounds that were different in colour but isoluminant caused similar accommodative responses (Ciuffreda et al., 1990, Switkes et al., 1990, Wolfe and Owens, 1981). It appeared that the ocular system was unable to use chromatic contrast to initialise and maintain steady focus and a minimal level of luminance contrast was required to elicit substantial and reliable accommodation (Switkes et al., 1990). High contrast levels were found to be essential in focusing stability (Bour, 1981, Raymond et al., 1984) and no significant effect or systemic variation in steady-state accommodation was found with changing target luminance until low levels between -10 to -30dB were reached (Ciuffreda and Rumpf, 1985). Contrast values smaller than this were insufficient to drive and maintain accommodation and resulted in steady accommodation near tonic or dark focus levels (Ciuffreda and Rumpf, 1985). Therefore a target with high luminance contrast was chosen for this research.

2.2.2.1.1.3 Target size

Target size alone can be an accommodative cue. However there are inconsistent findings in the literature on the effect of target size on accommodation. Increasing the target size gives the perception that the target is closer and was found to induce accommodation (Kruger and Pola, 1987). However, a Snellen letter of 6/9 size at 6m stimulated the least accommodative response and letters which were either smaller or bigger in size increased this response (Tan and O'Leary, 1985). Conversely, a subsequent study investigating the effects of different target sizes at the same working distance found that although there were considerable inter-subject variations in accommodation levels, the response across different letter target sizes for an individual was less than 0.5D. Thus accommodation was relatively stable at both

distance and near irrespective of target size (Lovasik et al., 1987). A more recent study however found that larger letters induced larger lags of accommodation compared to smaller letters (Landrum, 2009).

Due to the inconsistent results of the effect of target size on accommodation, a point target was selected. Point targets have been demonstrated to be non-accommodative. Accommodation was found to constantly fluctuate near tonic accommodation levels regardless of the optical distance of the target to the eye (Owens and Leibowitz, 1975).

2.2.3 PERIPHERAL REFRACTION

The Shin-Nippon NVision-K 5001 autorefractor was used to measure objective peripheral refraction in the studies described in this thesis. Eye rotation was used for eccentric measurements.

2.2.3.1 SHIN-NIPPON NVISION-K 5001 MEASUREMENT TECHNIQUE

There are three different techniques commonly utilised to measure peripheral refraction with open field autorefractors. Measurements can be taken with either eye, head or instrument rotation. Eye rotation is the most commonly used technique and this method was used for measuring peripheral refraction using the Shin-Nippon NVision-K 5001 autorefractor in the clinical studies described in the following chapters. The effect of pupil size and accommodation are also discussed below.

2.2.3.1.1 EYE ROTATION

When taking peripheral refraction measurements with eye rotation, the subject's head is in primary gaze position and is stabilised by the chin and forehead rest of the

Shin-Nippon NVision-K 5001 autorefractor. Subjects are instructed to keep their head still and rotate their eyes to fixate on an eccentric target which is projected at defined peripheral angles. Typically, targets are presented in either 5° or 10° intervals along the horizontal meridian up to ±35°. Measurements cannot be taken beyond 35° due to field of view restrictions from the casing around the window of the autorefractor.

The eye appears on the LCD monitor and the circular entrance pupil seen during primary gaze changes to a vertical oval during eccentric fixation. The autorefractor is aligned for peripheral refraction measurements by focusing the vertical meridian running through the centre of the oval entrance pupil as shown in Figure 2.8.

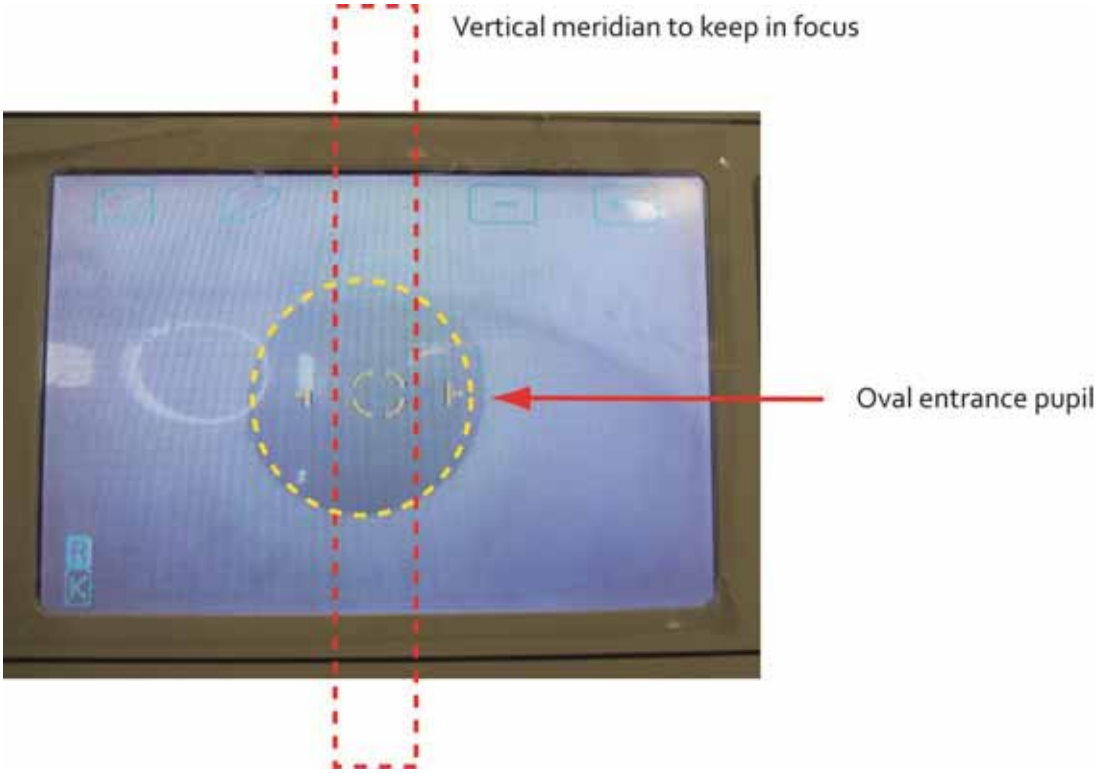


Figure 2.8 Entrance pupil observed on the LCD monitor of the Shin-Nippon NVision-K 5001 autorefractor during eccentric fixation.

Some earlier studies discovered myopic shifts in peripheral refraction with eccentric fixation by as much as 2.5D (Ferree et al., 1932, Ferree et al., 1931, Seidemann et al., 2002). EOMs changing the shape of the eye during prolonged eccentric fixation has

been proposed as a possible cause. Ferree et al (1931 & 1932) noticed this phenomenon, but failed to disclose the peripheral angle at which measurements were taken and the time that eccentric fixation was maintained. On the contrary, in a study consisting of ten subjects, Radhakrishnan and Charman (2008) found there were no significant differences in measurements taken with eye or head rotation up to 30° for a 1 minute fixation period or at 25° for a 2.5 minute fixation period. Mathur et al (2009) found axial and peripheral refraction measurements were not significantly affected by short periods (3 minutes) of oblique viewing out to 30° in the horizontal meridian with cycloplegia. Measurements taken in the clinical studies described in the following chapters did not require peripheral fixation for periods longer than 2.5 minutes.

2.2.3.1.2 HEAD ROTATION

Peripheral refraction measurements with head rotation require subjects to keep their eyes in primary gaze and rotate their heads at required peripheral angles. Similar to eye rotation, the entrance pupil appears as a vertical oval and measurements are taken in a similar manner as outlined in section 2.2.3.1.1. This technique generally requires modification of the chin rest to allow subjects to comfortably rotate their heads in the appropriate direction.

2.2.3.1.3 INSTRUMENT ROTATION

Peripheral refraction measurements can be taken with the subjects' head and eyes positioned at primary gaze while rotating the instrument at required peripheral angles. Similarly, the entrance pupil appears as a vertical oval and measurements are taken in a similar nature to that described in section 2.2.3.1.1. Although the subject does not actively participate in measurements with this technique, it can be a tedious and time consuming task moving the instrument around the subject.

2.2.3.1.4 ACCOMMODATION

Autorefraction measurements can be taken with or without cycloplegia. To examine the effect of accommodation on the validity of refraction measurements, the Shin-Nippon NVision-K 5001 autorefractor was modified to incorporate fogging lenses which were capable of relaxing accommodation enough such that refraction with fogging lenses were comparable to that obtained under cycloplegia (Queirós et al., 2009). Pharmalogical (2 drops of 1% cyclopentolate) and optical methods (+2.00D fogging lens) of relaxing accommodation rendered no statistically significant difference in refraction measurements for emmetropes and hyperopes at all eccentric locations along the horizontal meridian. Fogging lenses were found to have a greater effect of relaxing accommodation compared to cycloplegia in myopes. A difference between the two methods of -0.31 ± 0.40D was found at 20° nasal retina, -0.44 ± 0.51 at 10° nasal retina, -0.37 ± 0.56D at centre, -0.47 ± 0.54D at 10° temporal retina and -0.44 ± 0.39D at 20° temporal retina. Relaxation of accommodation through either method produced hyperopic shifts in M at centre, 10° and 20° in nasal retina and 10° in the temporal retina for hyperopes and only at centre and 10° in the nasal retina for emmetropes. There was no statistically significant difference in measurements taken with or without relaxation of accommodation at all eccentricities for myopes (Queirós et al., 2009). Smith et al (1988) have also shown that up to 2D of accommodation has very little effect on peripheral astigmatism for eccentric fixation angles up to 30° in 11 emmetropic subjects aged between 12 to 33 years.

No cycloplegic was used in the studies reported in this thesis unless stated, as our clinical protocols would induce less than 2D of accommodation at all eccentricities.

2.2.3.1.5 PUPIL SIZE

Pupil size can have an effect on peripheral refraction measurements. A larger pupil size has been reported to cause a myopic shift which was greater along the visual axis than in the periphery (Atchison, 2003). Radhakrishnan and Charman (2007) observed

significant constriction of the pupil with oblique viewing and suggested that this could cause a hyperopic increase in refraction.

In the research reported in this thesis, habitual pupil sizes were used unless stated and clinical setting maintained such that pupil sizes would remain relatively similar during different sessions. As a result changes in pupil size will have little influence on measured ocular parameters. Additionally, aberrations will increase with pupil size (Liang and Williams, 1997, Wang et al., 2003b) and therefore non-dilated pupils were chosen to reflect the habitual refractive status of the eye (Charman, 2005).

2.2.3.1.6 FIXATION TARGET

A laser spot as described in Section 2.2.2.1.1 was used as the fixation target for peripheral refraction measurements. A custom-made rotating device was manufactured to hold the device which emitted the laser spot as shown in Figure 2.9. This device was placed on the centre of the top casing of the autorefractor and allowed the fixation target to rotate precisely in 5° intervals along the horizontal plane of the line of sight in primary gaze. The studies described in this thesis typically used 10° intervals.

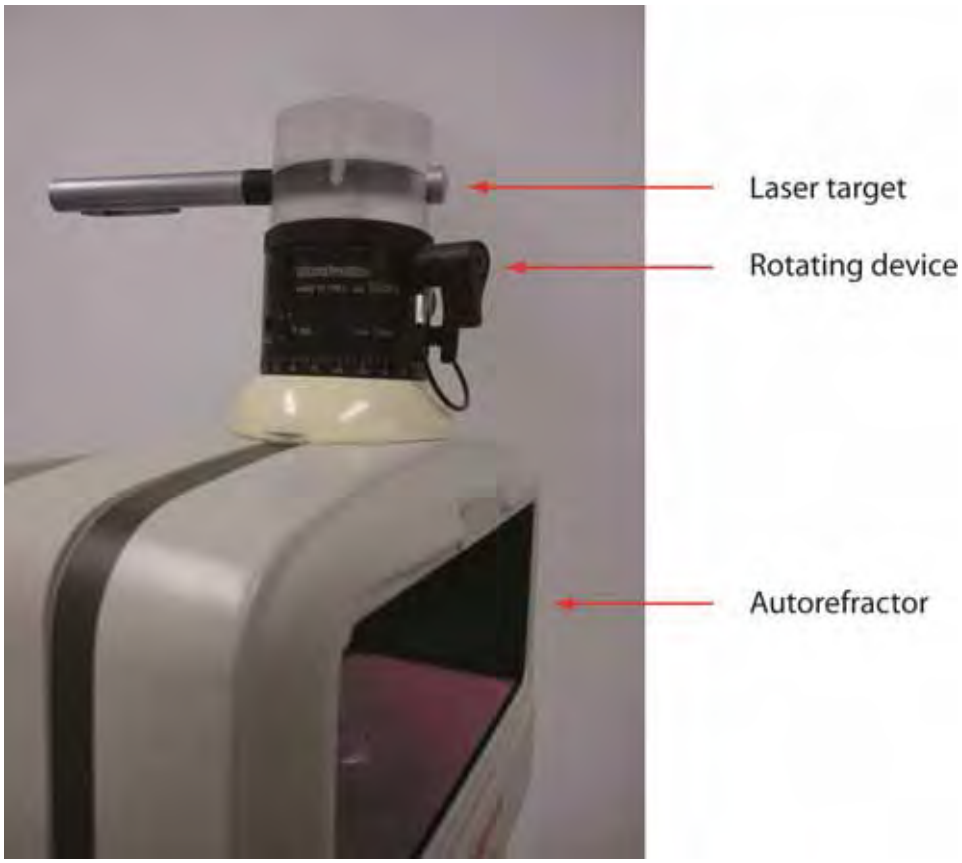


Figure 2.9 Custom-made laser-target fixation device.

The target was displayed in a consultation room, the dimensions of which are displayed in Figure 2.10. The fixation target was in a plane 10cm in front of the subject's eyes as it was placed on top of the autorefractor. This caused a discrepancy in the angle subtended by the target and that at the plane of the cornea. Trigonometric calculations were applied and the difference in the target angle between the two distances are shown in Table 2.1. There was less than a 1° difference between the angle projected by the target and that at the subject's corneal plane at all eccentricities and thus was deemed not to be of significance.

Projected angle	Angle of target at corneal plane	Projected angle	Angle of target at corneal plane
0	0	20	19.53
5	4.89	25	24.39
10	9.77	30	29.25
15	14.65	35	34.09

Table 2.1 Angle (degrees) of target as projected and at the plane of the subject's cornea.

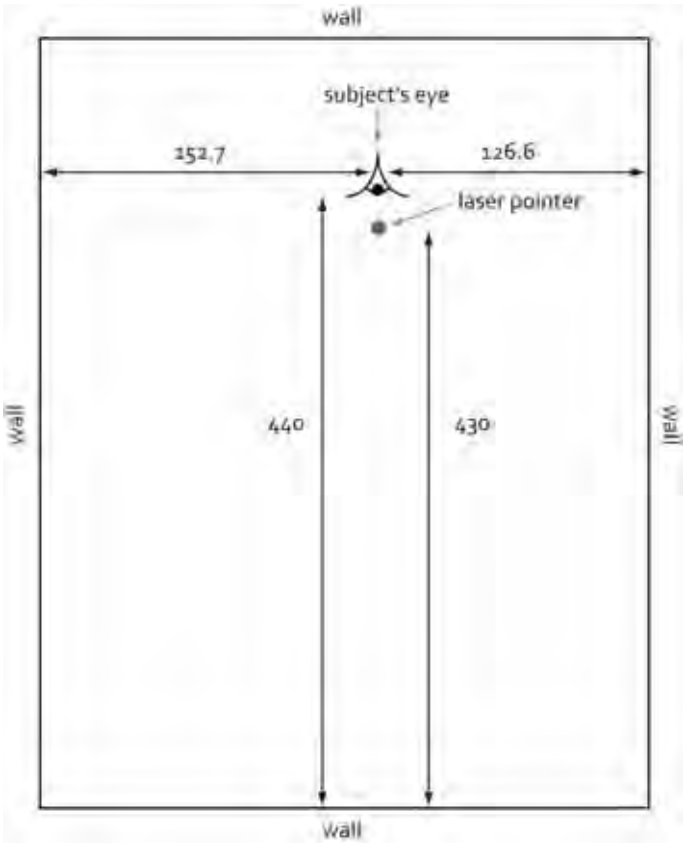


Figure 2.10 Dimensions of the consultation room (cm).

There are differences in target distance between central and peripheral fixation caused by the shape of the consultation room. Central fixation has a working distance of 440cm while the shortest peripheral working distance occurs during 35° temporal gaze of the left eye. This distance was calculated out to be 220.72cm through simple trigonometric calculations. This means that accommodation will vary approximately between 0.23D to 0.46D when shifting from central to peripheral fixation, a change which is clinically insignificant.

2.2.4 CORNEAL TOPOGRAPHY

2.2.4.1 MEDMONT E300 CORNEAL TOPOGRAPHER

The Medmont E300 videokeratoscope was used throughout this thesis (Medmont Pty Ltd, Melbourne, Australia). Four maps were typically captured and extrapolated data averaged using Medmont Studio 4 software.

Eccentricity or e and apical radius of corneal curvature (mm) are used to describe corneal shape throughout this thesis.

2.2.4.2 ANATOMICAL CLASSIFICATION

OK causes changes in power and shape in various parts of the cornea. To better recognise where such changes are occurring, the cornea was described by four anatomical zones (Figure 2.11), as developed by Waring (1989), throughout this thesis.

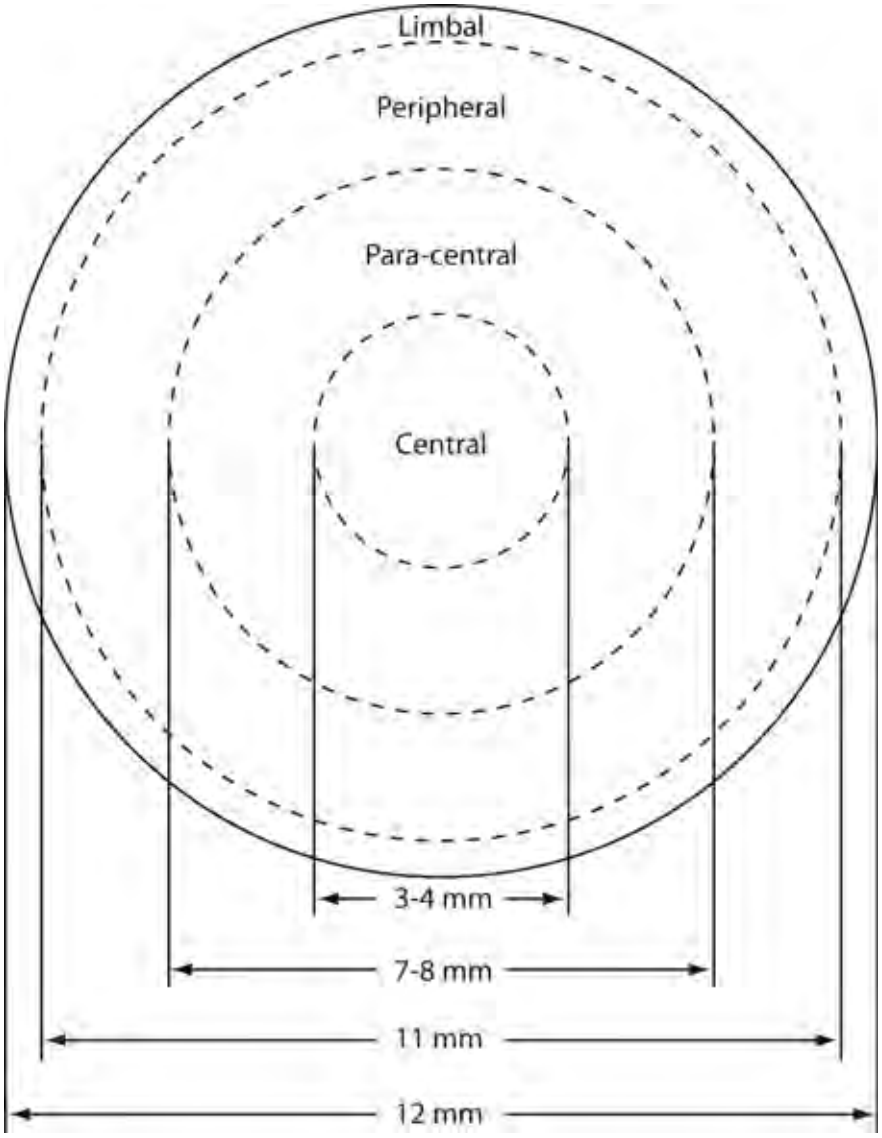


Figure 2.11 Corneal anatomical zones as described by Waring (1989).

2.2.4.3 CORRESPONDING CORNEAL LOCATIONS

Peripheral refraction measurements are typically taken at 5° or 10° intervals along the horizontal meridian and involve the cornea. Simple ray tracing determined corresponding corneal locations where peripheral refraction measurements were taken (Table 2.2). Ray tracing diagrams for the calculation of corneal locations are presented in Appendix A. The following assumptions of the average eye were made (Rabbetts and Mallen, 2007):

- Angle alpha is 5°
- Pupil is decentered by 0.250mm nasally from the optic axis of the cornea
- Corneal magnification factor of 1.1x for the pupil
- Anterior chamber depth of 3mm (cornea to entrance pupil)

VF angle	-35	-30	-25	-20	-15	-10	-5	0
Corneal location	-1.46	-1.12	-0.82	-0.53	-0.25	-0.01	0.00	0.54
VF angle	5	10	15	20	25	30	35	
Corneal location	0.80	1.08	1.37	1.67	1.89	2.38	2.75	

Table 2.2 Peripheral refraction measurement angles (degrees) and corresponding corneal locations (mm). Negative values for VF angle denote the temporal VF, positive values denote the nasal VF and C denotes the visual axis. Negative values for corneal location denote the temporal cornea while positive values denote the nasal cornea.

The parameters used for the calculation of corneal locations are an average value and thus may vary considerably between individuals and may be dependent on refractive error.

2.2.5 CORNEAL THICKNESS

The Holden-Payor optical pachometer was used for measurement of corneal thickness as described in Section 2.1.4.1.

2.2.5.1 MEASUREMENT TECHNIQUE

There are two different criteria which can be used for final measurement setting as shown in Figures 2.12a and b. In the touch method, the upper image of the posterior endothelium just touches the lower image of the anterior epithelium of the cornea (Figure 2.12a). In the overlap method, the upper image of the posterior endothelium overlaps the lower image of the anterior epithelium of the cornea (Figure 2.12b) (Chan-Ling and Pye, 1994, Mandell et al., 1988). Although Molinari and Bonds (Molinari and Bonds, 1983) found a difference in measurements between these two techniques, this is not relevant when calculating thickness changes as long as the same technique is consistently used (Chan-Ling and Pye, 1994). The touch method was used by the author.

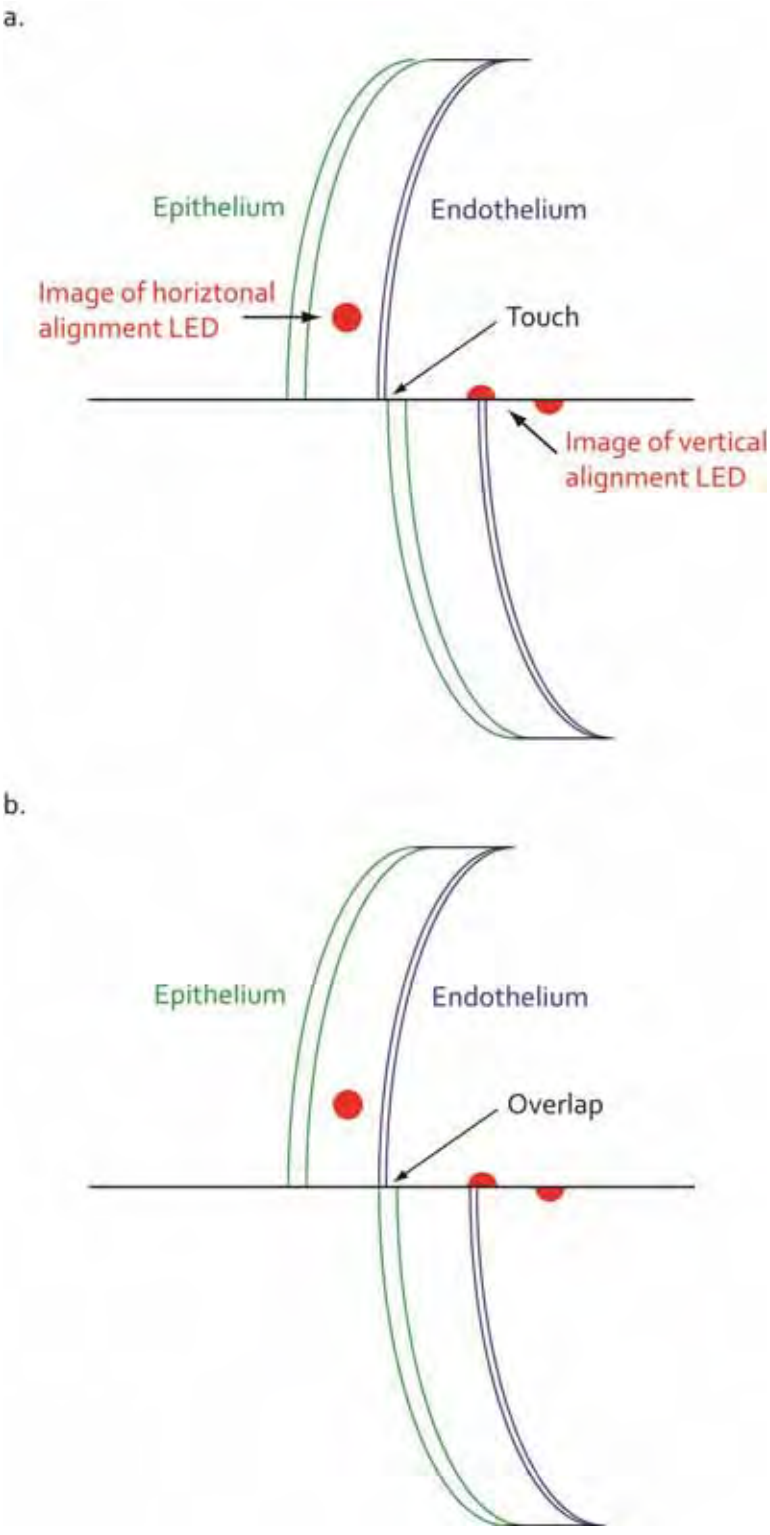


Figure 2.12 Measurement criteria for a) touch and b) overlap. In the touch method (top), the upper image of the posterior endothelium just touches the lower image of the anterior epithelium whereas in the overlap method (bottom), the upper image of the posterior endothelium overlaps the lower image of the anterior epithelium.

2.2.5.1.1 HORIZONTAL CORNEAL LOCATIONS

The Holden-Payor optical pachometer has 19 fixed LED fixation lights arranged along a horizontal arc to allow for peripheral corneal thickness measurements. Brennan's equation (1989) with Rc = 7.8mm and Q = -0.25 was used to calculate the position of corneal thickness measurements. The angles of the fixation LEDs on the pachometer were determined by Yoon (2009). Table 2.3 lists the angles of the LED lights used and corresponding calculated temporal corneal measurement locations from the corneal apex while Table 2.4 shows calculated corneal measurement locations on the nasal cornea.

LED	L9	L7	L6	L4	L2	C
Actual angle of LED	34.3	27.1	23.4	15.7	7.8	0.3
Distance	4.58	3.65	3.16	2.13	1.06	0.04

Table 2.3 Calculated measurement location on the temporal cornea (mm). Positive angle values (degrees) denotes angles that are anticlockwise from the reference angle while negative angle values denotes angles that are clockwise from the reference angle (Figure 2.5).

LED	R2	R4	R6	R7	R9
Actual angle of LED	-7.8	-15.5	-23.8	-27.3	-35.2
Distance	1.06	2.10	3.21	3.68	4.70

Table 2.4 Calculated measurement location on the nasal cornea (mm). Positive angle values (degrees) denotes angles that are anticlockwise from the reference angle while negative angle values denotes angles that are clockwise from the reference angle (Figure 2.5).

2.3 CLINICAL EVALUATION

Clinical evaluation of an instrument requires assessment of both the accuracy and repeatability of the measurements derived from the instrument. This section describes clinical evaluations of methods and instruments used in the studies described in this thesis to confirm their suitability.

2.3.1 CONVERSION OF REFRACTION TO POWER VECTORS

Refraction was recorded in minus cylindrical form and converted to power vectors using the equations derived by Thibos et al (1997):

$$M = S + C/2$$

$$J_{180} = -(C/2)\cos 2\Theta$$

$$J_{45} = -(C/2)\sin 2\Theta$$

where M is the mean spherical equivalent, J_{180} is the 90° to 180° astigmatism component and J_{45} is the 45° to 135° astigmatism component. This is a conversion of sphero-cylindrical refraction measured in polar form to a spherical lens and two cross-cylinders orientated at axis 0° and 45°. Refraction is represented as a vector of a power profile which can be statistically analysed.

Relative data were calculated by subtracting central refraction from the peripheral refraction. Relative data were used for comparison of refraction profile shapes.

2.3.2 CLINICAL EVALUATION OF THE SHIN-NIPPON NVISION-K 5001 AUTOREFRACTOR FOR CENTRAL REFRACTION MEASUREMENTS

2.3.2.1 MATERIALS AND METHODS

2.3.2.1.1 STUDY DESIGN

Subjective central refraction without cycloplegia was measured in the right eye of all subjects as described in Section 2.1.1.1. Objective central refraction without cycloplegia was subsequently measured on all subjects as described in Section 2.2.2.1. Five consecutive objective measurements were taken from the right eye and averaged. Subjects were instructed to return approximately 1 week later at around the same time of the day and five consecutive objective measurements were once again taken from the right eye and averaged. All measurements were carried out by the author.

2.3.2.1.2 STUDY SETTING

The target as described Section 2.2.2.1.1 was projected onto a white wall 4.3m away along the subject's visual axis.

2.3.2.1.3 SUBJECTS

Ten young adult subjects (age range 20 - 34 years; 3M, 7F) were recruited for this study. Subjects were screened prior to enrolment and found to be in good ocular health and free from ocular disease. To be eligible for the study, subjects were required to be non-RGP wearers, and SCL wearers were instructed to cease lens wear for at least 24 hours before measurements were to be taken. Central refraction was required to be between +4.00DS and -4.00DS with ≤-1.50DC.

2.3.2.1.4 DATA ANALYSIS

Validity was assessed by comparing subjective and mean objective refraction. The bias between measurements was calculated.

Repeatability was evaluated as suggested by Bland and Altman (1999). Intra-session repeatability was determined by observing the SD of the results in one session. Inter-session repeatability was analysed by comparing measurements taken on two separate sessions. 95% limits of agreement were calculated from the following equation:

95% limits of agreement = Mean difference ± 1.96 x SD

A narrow limits of agreement range reflects a more repeatable instrument. Furthermore, the Repeatability Coefficient was calculated using the following equation (Bland and Altman, 1999):

Repeatability Coefficient = 1.96 x (SD of differences)

The Repeatability Coefficient determines the minimum difference able to be detected by the instrument.

2.3.2.2 RESULTS

2.3.2.2.1 VALIDITY

Mean subjective and objective refractions are listed in Table 2.5.

	M	J_{180}	J_{45}
Subjective distance refraction	-1.23 ± 1.13D	-0.09 ± 0.17D	-0.01 ± 0.07D
Objective distance refraction	-1.08 ± 1.03D	-0.08 ± 0.20D	0.07 ± 0.18D

Table 2.5 Subjective and objective refraction values (D; mean ± SD).

All refraction components were slightly more hyperopic when measured objectively by the autorefractor (Figure 2.13 and Table 2.6). Student's t-test determined that the difference in M between subjective and objective methods was significantly different from zero (t=-2.757, p=0.022). The difference between subjective and objective methods for J_{180} and J_{45} was not significantly different from zero (t_{J180}=-0.506, p=0.625; t_{J45}=-1.606, p=0.143). Overall, the difference found between subjective and objective techniques was clinically insignificant (<0.25D).

	Difference*	SD	95% Limits of agreement**	Within ±0.25D	Within ±0.50D
M	-0.15	0.17	-0.48 to 0.19D	60%	100%
J_{180}	-0.01	0.08	-0.16 to 0.14D	100%	100%
J_{45}	-0.08	0.16	-0.40 to 0.23D	80%	100%

Table 2.6 Difference (D; mean) between objective and subjective refraction values.

**Difference = Mean subjective refraction – mean objective refraction.*

***95% limits of agreement = mean difference ± 1.96 x SD of the differences.*

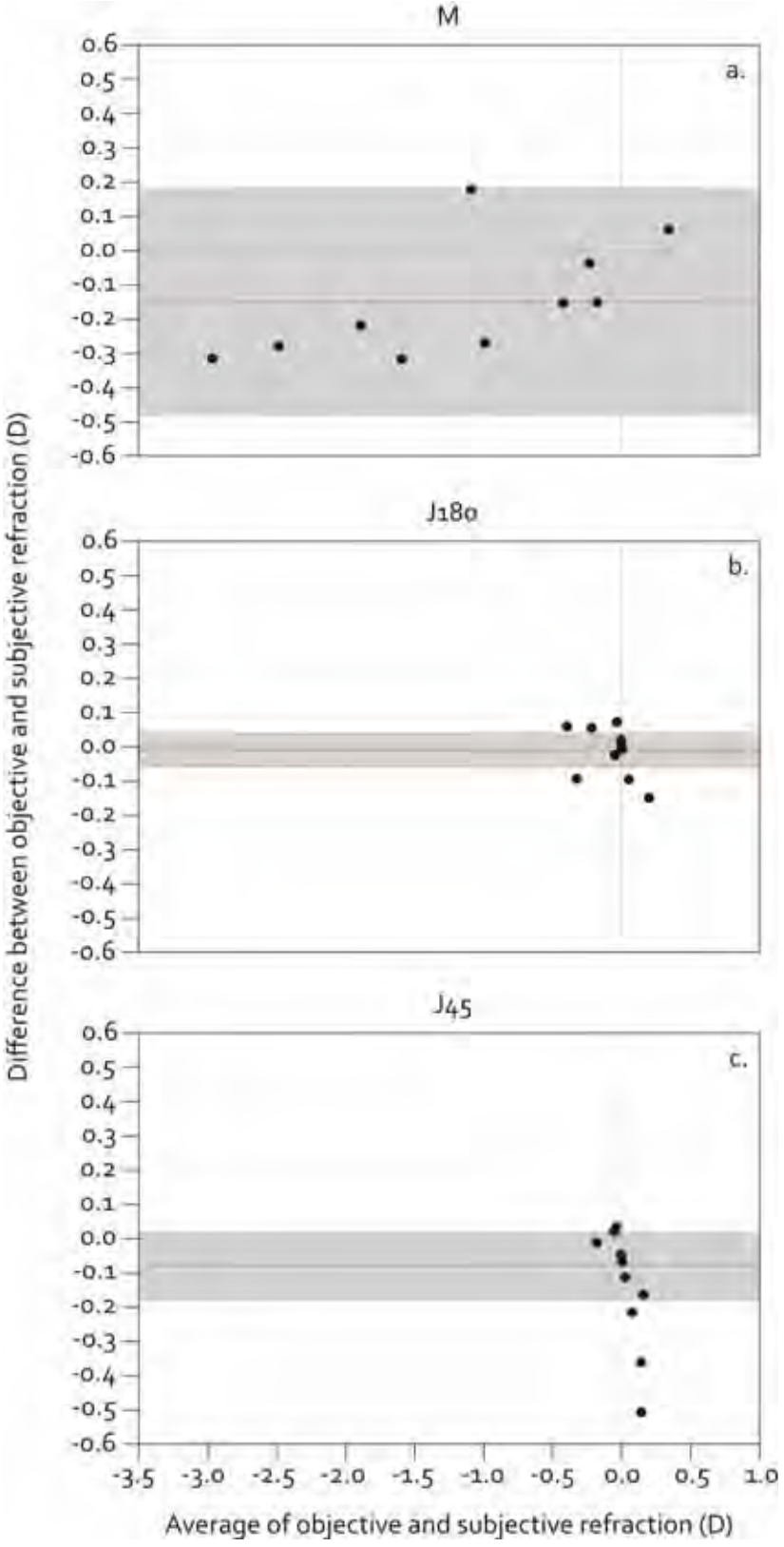


Figure 2.13 Average of subjective and objective a) M, b) J_{180} and c) J_{45} against their difference (D). *Mean difference (bias) is indicated by the solid red line and the upper and lower dotted lines indicate 95% limits of agreement.*

2.3.2.2.2 REPEATABILITY

The average intra-session repeatability for objective refraction measurements was 0.08D, 0.06D and 0.07D for M, J_{180} and J_{45}, respectively. Furthermore, inter-session repeatability was found to be small with all measurements taken on the second visit being within 0.75D for M and 0.50D for both astigmatism components (Table 2.7). Repeatability Coefficients were 0.53D, 0.26D and 0.31D for M, J_{180} and J_{45}, respectively.

	M	J_{180}	J_{45}
Difference	0.08 ± 0.26D	0.07 ± 0.13D	0.05 ± 0.15D
Within ±0.25D	60%	80%	80%
Within ±0.50D	90%	100%	100%
Within ±0.75D	100%	100%	100%

Table 2.7 Difference (D; mean ± SD) in objective refraction taken on different sessions.

2.3.2.3 DISCUSSION

The Shin-Nippon NVision-K 5001 autorefractor was found to measure refraction accurately with all objective refraction measurements being slightly hyperopic by a clinically insignificant amount (<0.25D) compared to subjective measurements. These results are similar to reports by Davies et al (2003) who also found slightly more hyperopic measurements with the Shin-Nippon NVision-K 5001 autorefractor compared to subjective refraction by 0.14 ± 0.35D, 0.10 ± 0.16D and 0.04 ± 0.11D for M, J_{180} and J_{45}, respectively. The discrepancy found between objective and subjective

refraction in this study could also be due to variability errors in conventional subjective refraction (French and Jennings, 1974).

The autorefractor was found to have good intra and inter-session repeatability with consecutive measurements varying less than 0.25D and approximately all measurements being within 0.75D of a second measurement for M, J_{180} and J_{45}. These results reflect those published by Davies et al (2003) who found intra-session repeatability to be 0.11D, 0.13D and 0.09D for M, J_{180} and J_{45}, respectively and nearly all second session measurements being within ±1.00D of the first. Repeatability Coefficients for inter-session repeatability were also found to be small.

The accuracy and repeatability of the Shin-Nippon NVision-K 5001 autorefractor is further emphasised by evaluations of the preceding model, the Shin-Nippon SRW500 autorefractor, which has very similar technical specifications. Clinical evaluations have found that the Shin-Nippon SRW-5000 gives accurate and repeatable central refraction measurements in both children (Chat and Edwards, 2001) and adults (Mallen et al., 2001).

The Shin-Nippon NVision-K 5001 autorefractor is able to obtain accurate and repeatable objective central refraction measurements in our clinical setting and hence is able to accurately monitor changes in central refraction. Therefore, this autorefractor was selected to be used to measure central objective refraction in the clinical studies described in the following chapters.

2.3.3 THE EFFECT OF CYCLOPLEGIA ON CENTRAL REFRACTION

2.3.3.1 MATERIALS AND METHODS

2.3.3.1.1 STUDY DESIGN

Five consecutive non-cycloplegic objective measurements were taken from the right eye and averaged. One drop of 1% Cyclopentolate was instilled into both eyes. Five

consecutive objective central refraction measurements were then taken again and averaged 40 minutes after Cyclopentolate instillation. All measurements were carried out by the author.

2.3.3.1.2 STUDY SETTING

The target as described in Section 2.2.2.1.1 was projected onto a white wall 4.3m away along the subject's visual axis.

2.3.3.1.3 SUBJECTS

Twenty-six adult subjects (age range 20 – 26 years; 13M, 13F) were recruited for this study. Subjects were screened prior to enrolment and found to be in good ocular health and free from ocular disease. To be eligible for the study, subjects were required to be non-RGP wearers, and SCL wearers were instructed to cease lens wear for at least 24 hours before measurements were to be taken. Central refraction was required to be between +4.00DS and -4.00DS with ≤-1.50DC.

Subjects were screened for suitability for cycloplegia through observation of anterior chamber angle with a slit-lamp biomicroscope. Cyclopentolate can precipitate acute glaucoma attacks (Frazier and Jaanus, 2008, Jones and Hodes, 1991) and therefore individuals with Van Herrick ratios of less than 0.3 were excluded from the study.

2.3.3.1.4 DATA ANALYSIS

Paired Student t-tests were conducted to elucidate any differences in refraction between baseline and after cycloplegia.

2.3.3.2 RESULTS

Central refraction results before and after cycloplegia are shown in Table 2.8.

	M	J_{180}	J_{45}
Baseline	-0.94 ± 1.38	-0.02 ± 0.21	0.06 ± 0.13
Cycloplegia	-0.66 ± 1.53	0.02 ± 0.21	0.06 ± 0.13

Table 2.8 Objective central refraction (D; mean ± SD) before and after cycloplegia.

There was no significant difference in J_{180} or J_{45} measured at baseline or after Cyclopentolate instillation ($t_{(25)J180}$=-1.839, p=0.078; $t_{(25)J45}$=-0.067, p=0.947). However a difference in M between baseline and after cycloplegia was detected ($t_{(25)M}$=-4.723, p<0.001). A hyperopic shift in M of +0.27 ± 0.29D was found with cycloplegia.

2.3.3.3 DISCUSSION

Cycloplegia is commonly used in clinical practice for the diagnosis and management of numerous ocular and refractive conditions due to its effects on accommodation and pupil size. One drop of 1% Cyclopentolate will cause a maximum mydriasis (average 6.5 to 7.5mm) after 20 to 30 minutes and paralysis of accommodation occurring within 30 to 60 minutes after instillation. Average residual accommodation of 1.25D has been measured subjectively (Frazier and Jaanus, 2008).

An expected hyperopic shift in M of +0.27 ± 0.29D was found after cycloplegia. Similar results were found using the former model, the Shin-Nippon SRW-5000, in children with cycloplegic objective refraction yielding a more hyperopic refraction of approximately 0.50D which was more apparent in emmetropes and hyperopes compared to myopes. No changes in astigmatism were evident in this pilot study.

Although a statistically significant difference in M was found between with and without cycloplegia, the difference was borderline clinically significant. Therefore, to investigate the habitual state of the eye, measurements were taken without cycloplegia, unless stated otherwise. To monitor for changes in refraction, measurement techniques were kept consistent across studies.

2.3.4 CLINICAL EVALUATION OF THE SHIN-NIPPON NVISION-K 5001 AUTOREFRACTOR FOR PERIPHERAL REFRACTION MEASUREMENTS

The Shin Nippon NVision-K 5001 autorefractor is able to measure central refraction accurately and has high inter-session and intra-session repeatability in our clinical setting (Section 2.3.2). Further investigation was conducted to determine if repeatable peripheral refraction measurements could also be obtained from the same autorefractor.

2.3.4.1 MATERIALS AND METHODS

2.3.4.1.1 STUDY DESIGN

Objective peripheral refraction measurements without cycloplegia were taken at centre, 10° and 30° in the temporal and nasal VF along the horizontal meridian as described in section 2.2.3.1. Five consecutive measurements were taken from the right eye and averaged. Subjects were instructed to return approximately 1 week later at around the same time of the day and five consecutive measurements were once again taken from the right eye. All measurements were carried out by the author.

2.3.4.1.2 STUDY SETTING

The fixation target as described in Section 2.2.3.1.6 was used to project the laser spot along the subjects' visual axis and rotated at 10° and 30° in the temporal and nasal VF along the horizontal meridian.

2.3.4.1.3 SUBJECTS

Seventeen young adult subjects (age range 20 – 37 years; 9M, 8F) were recruited for this study. Subjects were screened prior to enrolment and found to be in good ocular health and free from ocular disease. To be eligible for the study, subjects were required to be non-RGP wearers, and SCL wearers were instructed to cease lens wear for at least 24 hours before measurements were to be taken. Central refraction was required to be between +4.00DS and -4.00DS with ≤-1.50DC.

2.3.4.1.4 DATA ANALYSIS

Inter-session and intra-session repeatability were evaluated as described in Section 2.3.2.1.2.

2.3.4.2 RESULTS

The average intra-session repeatability was less than 0.25D for M, J_{180} and J_{45} at all locations as outlined in Table 2.9.

VF	M	J_{180}	J_{45}
Nasal 10°	0.07	0.05	0.04
Nasal 30°	0.11	0.13	0.06
Temporal 10°	0.08	0.07	0.06
Temporal 30°	0.11	0.05	0.06

Table 2.9 SD (D) of 5 consecutive measurements in a single session.

Inter-session repeatability was relatively good with most repeated M, J_{180} and J_{45} measurements being within 0.75D of the first measurements as shown in Tables 2.10, 2.11 and 2.12, respectively. The Repeatability Coefficients for M were 0.61D and 0.72D for 10° and 30° in the temporal VF, and 0.47D and 0.92D for 10° and 30° in the nasal VF, respectively.

VF position	T30	T10	N10	N30
Mean difference	0.12 ± 0.46	-0.04 ± 0.23	0.07 ± 0.31	-0.01 ± 0.36
Within ± 0.25D	41.2%	70.6%	76.5%	64.7%
Within ± 0.50D	88.2%	100%	94.1%	88.2%
Within ± 0.75D	100%	100%	100%	94.1%
Within ± 1.00D	100%	100%	100%	100%

Table 2.10 Difference in repeated peripheral objective M measurements (D; mean ± SD) across two separate sessions. T denotes the temporal VF while N denotes the nasal VF.

VF position	T30	T10	N10	N30
Mean difference	0.02 ± 0.18	0.04 ± 0.18	-0.04 ± 0.26	0.14 ± 0.28
Within ± 0.25D	82.4%	76.5%	94.1%	64.7%
Within ± 0.50D	100%	100%	100%	94.1%
Within ± 0.75D	100%	100%	100%	94.1%
Within ± 1.00D	100%	100%	100%	100%

Table 2.11 Difference in repeated peripheral objective J_{180} measurements (D; mean ± SD) across two separate sessions. T denotes temporal VF while N denotes nasal VF.

VF position	T30	T10	N10	N30
Mean difference	0.07 ± 0.19	-0.02 ± 0.12	-0.04 ± 0.14	0.06 ± 0.13
Within ± 0.25D	94.1%	88.2%	100%	76.5%
Within ± 0.50D	100%	100%	100%	100%

Table 2.12 Difference in repeated peripheral objective J_{45} measurements (D; mean ± SD) across two separate sessions. T denotes temporal VF while N denotes nasal VF.

2.3.4.3 DISCUSSION

The few published studies evaluating peripheral refraction measured by open view autorefractors have often compared results to aberrometry-based peripheral refraction measurements. Atchison (2003) compared refraction measured by the Shin-Nippon SRW-5000 autorefractor (former model) with refraction derived from the

Hartmann-Shack wavefront sensor and found that in 5 subjects, the agreement between the Hartmann-Shack and Shin-Nippon autorefractor varied from 0.3D in the centre to 0.7D at 35° in the temporal and nasal VF. The Shin-Nippon autorefractor tended to give more hyperopic refraction values. A more recent study (Berntsen et al., 2008) comparing the Shin-Nippon NVision-K 5001 autorefractor to the COAS aberrometer found that M was more myopic when measured with the COAS aberrometer both centrally and peripherally (centre -0.49 ± 0.25D; 30° nasal retina -0.31 ± 0.56D; 30° temporal retina -0.43 ± 0.86D) compared to the autorefractor. However, the relative differences in central and peripheral refraction between the two instruments were the same. Furthermore, there were no significant differences in measured J_{180} between the two instruments. The autorefractor measured more oblique astigmatism (J_{45}) compared to the COAS in both the temporal and nasal VF. Donovan et al (2007) also found the COAS aberrometer to produce more myopic M values compared to the Shin-Nippon NVision-K 5001 autorefractor centrally, but no differences were found between the two instruments at 30° in the nasal or temporal VF. On-axis astigmatism components were comparable between the two instruments while off-axis astigmatism values were greater when measured with the autorefractor. Furthermore, they found that the Shin-Nippon autorefractor tended to give more myopic M and greater astigmatism values compared to streak retinoscopy both centrally and peripherally.

In the current study, the Shin-Nippon NVision-K 5001 autorefractor was found to have good intra and inter-session repeatability for peripheral refraction. Consecutive measurements varied by less than 0.25D and most M and J_{180} measurements were within 0.75D of the second session measurement. All second session J_{45} measurements were within 0.50D of the first. The Repeatability Coefficient was less than 1D for all peripheral eccentricities. From the results of this pilot study and previous literature, it was concluded that the Shin-Nippon NVision-K 5001 is able to give accurate and repeatable measurements of peripheral refraction and hence was used in the clinical studies described in this thesis.

2.3.5 CLINICAL EVALUATION OF THE HOLDEN-PAYOR OPTICAL PACHOMETER

2.3.5.1 INTRODUCTION

The accuracy and repeatability of corneal thickness measurements taken by the author using the Holden-Payor optical pachometer were evaluated on test lenses of known thickness and subsequently on human eyes.

2.3.5.2 MATERIALS AND METHODS

2.3.5.2.1 STUDY DESIGN

Seven PMMA rigid contact lenses of known thicknesses (previously measured with the Heidenhain thickness gauge) were used to calibrate the Holden-Payor optical pachometer. Five repeated measurements taken from each calibration lens were recorded and averaged. Results were compared to known nominal thickness. All measurements were carried out by the author.

Corneal thickness measurements on human eyes were evaluated at 11 corneal locations as summarised in Tables 2.3 and 2.4. Five repeated measurements were taken after at least 2 hours of awakening and averaged. Subjects were then asked to return for a subsequent set of measurements approximately a week later at the same time of day. Five repeated measurements were once again taken and averaged.

2.3.5.2.2 SUBJECTS

Eight adult subjects (age range 27 - 51 years; 5M, 3F) were recruited for this pilot study. Subjects were screened prior to enrolment and found to be in good ocular health and free from ocular disease. To be eligible for the study, subjects were

required to be non-RGP wearers, and SCL wearers were instructed to cease lens wear for at least 24 hours before measurements were to be taken.

2.3.5.2.3 DATA ANALYSIS

Validity was assessed by comparing known thickness of calibration lenses to measured thickness values. The bias between measurements was calculated as suggested by Bland and Altman (1999). Repeatability was assessed as outlined in Section 2.3.2.1.2.

2.3.5.3 RESULTS

2.3.5.3.1 CALIBRATION LENSES

Lens number	Nominal thickness	Measured average thickness	Difference*	Repeatability Coefficient
1	396.9	399.7 ± 3.4	2.1	4.20
2	457.3	457.3 ± 4.0	0.0	0.03
3	510.1	508.6 ± 1.6	-1.5	3.09
4	547	546.3 ± 3.5	-0.7	1.48
5	586.4	588.8 ± 3.7	2.4	4.82
6	639.7	642.8 ± 2.8	3.1	6.10
7	701.3	706.1 ± 5.8	4.8	4.63

Table 2.13 Nominal and measured lens thickness (µm; mean ± SD), difference between known and measured thicknesses (µm; mean ± SD) and calculated Repeatability Coefficient (µm).

**Mean difference = Mean measured– mean nominal thickness (*µm)

Measured lens thicknesses were found to be within 5µm of the nominal thickness (Table 2.13) with a mean bias of 0.28µm between two repeated measurements as shown in Figure 2.14. The highest Repeatability Coefficient calculated was 6.10µm for calibration lens 6.

Differences between measured and nominal thickness for all lenses were not significantly different from zero as determined by Student's t-test (t_{lens1}=1.372, p=0.242; t_{lens2}=1.400, p=0.234; $t_{lens\ 3}$=-0.08, p=0.994; t_{lens4}=-2.141, p=0.099; t_{lens5}=-0.473; p=0.661; t_{lens6}=1.454, p=0.220; t_{lens7}=2.400, p=0.074).

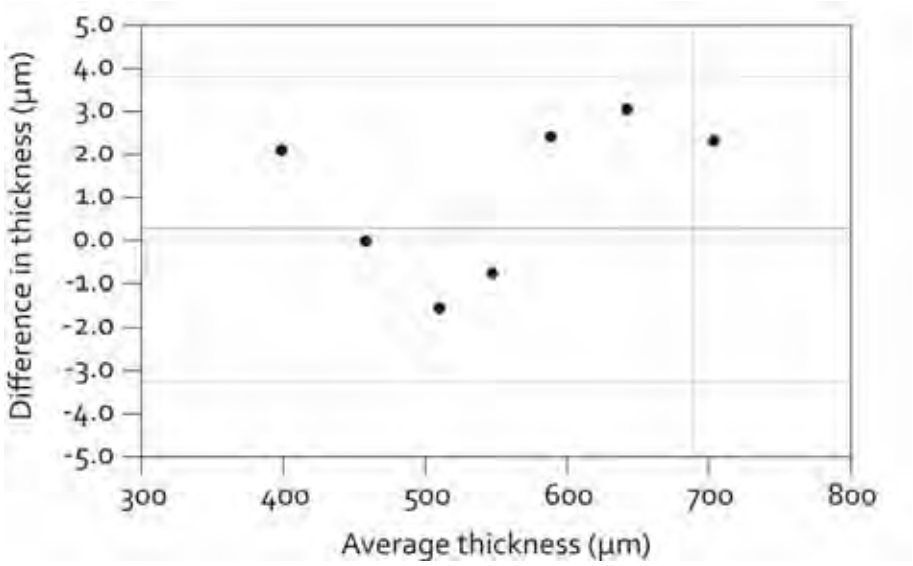


Figure 2.14 Average of measured and nominal thickness of calibration lenses against their difference (µm). Mean difference (bias) is indicated by the solid red line and the upper and lower dotted lines indicate 95% limits of agreement.

2.3.5.3.2 HUMAN EYES

Corneal measurement position	Difference*	95% limits of agreement**	Repeatability Coefficient
L9	-3.93 ± 14.57	-32.49 to 24.63	29.14
L8	4.24 ± 7.98	-11.35 to 19.83	15.90
L6	5.51 ± 8.22	-10.60 to 21.62	16.44
L5	8.03 ± 10.04	-11.64 to 27.70	20.07
L3	6.09 ± 10.49	-14.48 to 26.65	20.99
L2	8.41 ± 9.74	-10.68 to 27.50	19.48
Centre	4.39 ± 7.33	-9.97 to 18.75	14.66
R2	1.25 ± 3.91	-6.41 to 8.91	7.82
R3	-1.51 ± 6.19	-13.64 to 10.62	12.38
R5	0.88 ± 9.54	-17.81 to 19.57	19.07
R6	-1.39 ± 3.98	-9.18 to 6.41	7.95
R8	2.96 ± 14.03	-24.54 to 30.46	28.06
R9	-8.37 ± 11.46	-30.84 to 14.07	22.92

Table 2.14 Difference between corneal thickness measurements (µm; mean ± SD) taken on two different sessions, limits of agreement and calculated Repeatability Coefficient.

**Mean difference = Mean first session value – mean second session value*

***95% limits of agreement = mean difference ± 1.96 x SD of the differences*

The difference between measurements taken at two different sessions was not significantly different from zero ($p>0.05$) except at L2 ($t=2.442$, $p=0.045$). However, the Repeatability Coefficient became larger with greater eccentricity and the highest Repeatability Coefficient on human eyes was at LED L9 (29.14µm).

2.3.5.4 DISCUSSION

Pachometry measurements have developed our understanding of the mechanism behind OK by providing information on the changes in thickness across the cornea after OK lens wear. Epithelial and overall corneal thinning occurs in the centre while stromal thickening is evident in the mid-peripheral cornea (Alharbi and Swarbrick, 2003, Haque et al., 2004). Alharbi and Swarbrick (2003) found central epithelial thinning and mid-peripheral stromal thickening with the Holden-Payor optical pachometer of 19.0 ± 2.6µm and 14.4 ± 5.0µm, respectively, after 90 days of OK lens wear.

High accuracy of thickness measurements with the Holden-Payor optical pachometer was demonstrated with measurements being within 5µm of the actual thickness of the calibration lenses. Although there were no significant differences from zero in the difference in measurements taken at two separate sessions at all locations except at L2, repeatability of thickness measurements taken by the author on the human eye was poor with a Repeatability Coefficient value of 29.14µm found at LED position L9. At LED L2, a statistically significant mean difference of up to 8.41µm between two measurements was detected. As thickness changes with OK lenses will vary across the horizontal corneal meridian by an average of 14.4 to 19.0µm, the author will be unlikely to detect these thickness changes.

Although optical pachometry has been shown to be the least repeatability technique compared to Orbscan and ultrasound pachometry (Marsich and Bullimore, 2000), a trained user will be able to take accurate measurements (Snyder, 1984). Alharbi and Swarbrick (2003) demonstrated a SD of ±2µm for 3 consecutive thickness measurements of the central cornea and a SD of ±4.3 µm for the paracentral cornea.

A maximum difference of 3.2 ± 2.2µm for measurements taken across two different days was found. The author was a novice user which is likely to contribute to the poor repeatability of corneal thickness measurements taken with the Holden-Payor optical pachometer. Therefore, a decision was made not to measure corneal thickness using optical pachometry in the studies described in this thesis.

2.4 DATA ANALYSIS

2.4.1 STATISTICAL ANALYSIS

SPSS (version 18, SPSS Inc, Chicago, IL, USA) was used to statistically analyse collected data.

Paired Student t-tests and analysis of variance (ANOVA) with post hoc t-tests with Bonferroni correction were used to monitor refractive error and anterior corneal topography changes from baseline.

Repeated-measures ANOVA (RM-ANOVA) with planned contrasts were used to describe raw and RPR profiles and multivariate ANOVA (MANOVA) allowed comparison of peripheral refraction profiles between individuals. The same analysis was also applied to corneal topographic data along the horizontal meridian to describe anterior corneal shape and for comparison of corneal topography between individuals. Mauchly's test was used to test for sphericity, and the Greenhouse-Geisser correction was applied if significant differences were found.

Doubly MANOVA was used to monitor changes in peripheral refraction over time. Pairwise comparisons were performed and p values for post hoc tests were adjusted by the SPSS software according to the Bonferonni correction such that a p value of <0.05 denoted statistical significance. Four different statistics are presented by SPSS and Pillai's Trace statistic was chosen to be used as it has been shown to be the most powerful and robust statistic in MANOVA analysis (Olson, 1974). Univariate normality for each dependent variable was checked (as SPSS cannot check multivariate normality) and the assumption of homogeneity of covariance matrices was checked using the Box's test with criteria of less than 0.05 denoting significance.

Linear regression analysis allowed extrapolation of relationships between the amount of para-central corneal refractive power change and corresponding peripheral refraction change.

A critical p value of 0.05 was chosen to denote statistical significance for all analyses.

CHAPTER 3

INVESTIGATION OF PERIPHERAL REFRACTION

The prevalence of myopia has increased dramatically over the past decade and substantially high prevalence rates are repeatedly documented in the East Asian population (Fan et al., 2004, He et al., 2009, Lin et al., 2004, Saw et al., 1996, Zhao et al., 2000) compared with the Caucasian population (Ip et al., 2008, Kleinstein et al., 2003). There appears to be a higher risk of development of myopia in individuals of East Asian ethnicity in both Asia and elsewhere compared to other ethnicities (Ip et al., 2008, Kleinstein et al., 2003). The age of myopia onset is becoming younger (Lin et al., 2004) and faster progression rates have been associated with earlier onset age (Edwards, 1999, Saw et al., 2005b). This not only contributes to increased severity of myopia, but an increased prevalence within the population (Edwards, 1999, Fan et al., 2004, Lin et al., 1999, Saw et al., 2005b).

Recently, there has been a surge of interest in peripheral refraction subsequent to animal (Liu and Wildsoet, 2011, Smith et al., 2005, Smith et al., 2007) and human studies (Hoogerheide et al., 1971, Rempt et al., 1971) that have demonstrated a significant influence of peripheral retinal defocus on the development of central refraction. The idea that peripheral refraction may influence the development of myopia stemmed from early studies by Hoogerheide et al (1971). They noticed that emmetropic trainee pilots who subsequently developed myopia had peripheral refractive errors similar to those seen in already myopic pilots. These pilots were found to have a relatively hyperopic peripheral refraction. It has been proposed that the eye responds to the hyperopic defocus by increasing in axial length in order to bring the peripheral retina in focus with the peripheral image despite a consequent

This chapter has been published: KANG, P., GIFFORD, P., MCNAMARA, P., WU, J., YEO, S., VONG, B. & SWARBRICK, H. Peripheral refraction in different ethnicities. *Invest Ophthalmol Vis Sci* **2010; 51:6059-65**

increase in foveal myopic defocus (Charman, 2005, Charman, 2006, Collins et al., 1995, Seidemann et al., 2002, Smith, 2011, Wallman and Winawer, 2004). Additionally, eye diseases affecting peripheral, or peripheral and foveal vision, such as vitreous haemorrhages, congenital cataracts and retinitis pigmentosa have been found to lead to myopia (Hoyt et al., 1981, Miller-Meeks et al., 1990, Nathan et al., 1985, O'Leary and Millodot, 1979, Sieving and Fishman, 1978, von Noorden and Lewis, 1987) whereas diseases affecting only foveal vision including maculopathy and rod monochromacies have been found to result in mild hyperopia (Johnson et al., 1982, Nastri et al., 1984, Nathan et al., 1985). This further highlights the potential significance of image quality received at the peripheral retina in the development of refractive error.

The study reported in the first part of this chapter set out to describe characteristic peripheral refraction profiles in emmetropic and myopic young adults to confirm previous reports. The second part of this chapter continued to analyse peripheral refraction profiles between different ethnic groups to determine if differences in refraction profiles could explain the higher risk of myopia development and progression in East Asian individuals compared to other ethnicities.

3.1 PERIPHERAL REFRACTION IN DIFFERENT REFRACTIVE GROUPS

3.1.1 INTRODUCTION

Numerous studies have demonstrated typical peripheral refraction patterns along the horizontal meridian in different refractive groups, and the shape of the eye has been commonly inferred from the measured peripheral refraction (Atchison et al., 2005a, Logan et al., 2004, Millodot, 1981, Mutti et al., 2000b, Schmid, 2003b, Seidemann et al., 2002, Stone and Flitcroft, 2004). Emmetropes and hyperopes have been found to typically have relatively myopic peripheral refraction (Atchison and Markwell, 2008) with greater myopic shift measured in hyperopes (Mutti et al., 2000b, Seidemann et al., 2002), and this has been interpreted as reflecting a more oblate ocular shape. Myopes, particularly those greater than -2.50DS, have been found to have a relatively hyperopic peripheral refraction (Atchison et al., 2006) supposedly corresponding to a more prolate ocular shape (Logan et al., 2004, Mutti et al., 2000b, Seidemann et al., 2002).

This study aimed to describe and confirm peripheral refraction profiles in young adult emmetropes, low myopes and moderate myopes. It was hypothesised that characteristic peripheral refraction profiles will be measured in the different refractive groups.

3.1.2 MATERIALS AND METHODS

3.1.2.1 STUDY DESIGN

Peripheral refraction measurements were taken along the horizontal meridian in a group of young adult emmetropic and myopic subjects. Measurements were taken from the subject's right eye at least 2 hours after awakening. This avoided the

problem of diurnal variation in corneal curvature and thickness. Measurements were taken only in the right eye unless it did not meet the inclusion criteria as described in Section 3.1.2.2, in which case the left eye was used.

3.1.2.2 SUBJECTS

Seventy-two subjects (35 Caucasian and 37 East Asian; age range 18 – 38 years; 21 M, 51 F) were recruited for this study. Approval from the institutional Human Research Ethics Advisory Panel (Approval number HREA 084066) was obtained before study commencement. All subjects gave their informed written consent to study participation after being informed about the nature and possible consequences of participating in the study. Subjects were screened prior to enrolment and found to be in good ocular health and free from ocular disease. To be eligible for the study, subjects were required to be non-RGP wearers, and SCL wearers were instructed to cease lens wear for at least 24 hours before measurements were to be taken. Central refraction was required to be between +1.00DS and -5.50DS with ≤-1.50DC. Subjects were not eligible if they were aware of a change in their refractive error within the past year.

Subjects were split into three groups depending on their central refraction. Those with M values between +1.00D and -0.49D were placed in the emmetrope group, between <-0.50D and -2.49D into the low myope group and between <-2.50D and -5.50D into the moderate myope group.

3.1.2.3 MEASUREMENT TECHNIQUES

3.1.2.3.1 CENTRAL AND PERIPHERAL REFRACTION

Objective central refraction was taken with the Shin-Nippon NVision-K 5001 autorefractor as described in Section 2.2.2.1.

Five peripheral refraction measurements were taken in 5° intervals out to 35° in the temporal and nasal VF as described in Section 2.2.3.1.

3.1.2.3.2 CORNEAL TOPOGRAPHY

Corneal topography was captured with the Medmont E300. Four maps were taken and averaged and tangential power (D) along the central 5mm chord was extracted. A 5mm corneal chord was chosen as this was an estimation of the corneal chord through which peripheral refraction measurements were taken. Corneal eccentricity and apical radius (mm) were also extracted and averaged using Medmont Studio 4 software.

3.1.2.4 DATA ANALYSIS

Repeated-measures ANOVA was performed to describe the horizontal peripheral refraction profile in each refractive group. MANOVA analysis at centre and ±30° allowed comparison of peripheral refraction profiles between different refractive groups.

ANOVA was used to compare corneal eccentricity and apical radius between refractive groups.

Previous studies (Radhakrishnan and Charman, 2008, Schmid, 2003b) have found increased variability and difficulty with measurements at temporal 15° which is near the location of the optic disc and have often disregarded data at this eccentricity (Atchison et al., 2006, Radhakrishnan and Charman, 2008). Thus, temporal 15° data were excluded from our analysis.

3.1.3 RESULTS

3.1.3.1 CENTRAL REFRACTION

The average central refraction and number of subjects in each refractive group is outlined in Table 3.1.

	M	J_{180}	J_{45}	n
Emmetrope	+0.19 ± 0.36	-0.06 ± 0.19	0.05 ± 0.15	25; 7 M, 18 F
Low myope	-1.07 ± 0.71	-0.04 ± 0.28	0.04 ± 0.15	21; 8 M, 13 F
Moderate myope	-3.63 ± 0.90	-0.08 ± 0.25	0.06 ± 0.20	26; 6 M 20 F

Table 3.1 Objective central refraction (D; mean ± SD) in each refractive group and number of subjects. F denotes female and M denotes male.

3.1.3.2 PERIPHERAL REFRACTION

Average M, J_{180} and J_{45} along the horizontal meridian between ±35° in the temporal and nasal VF in each refractive group are summarised in Tables 3.2, 3.3 and 3.4, respectively.

A significant difference in raw refraction profile was found between refractive groups ($F=5.239$, $p<0.001$). Analysis of relative refractive data also indicated significant difference in refraction profile shape between refractive groups ($F=3.718$, $p=0.007$) whereby moderate myopes had greater relative hyperopia compared to emmetropes in the nasal VF ($F_{(2,69)}=6.650$, $p=0.002$). No significant difference in M profile was evident between the emmetrope and low myope groups ($F_{(2.505,60.119)EM}=2.409$, $p=0.086$; $F_{(2.922,58.443)LM}=2.155$, $p=0.105$). A difference between central and peripheral M values was found in the moderate myope group ($F_{(2.405,\ 60.117)}=9.543$, $p=0.0210$) with

significant amounts of relative hyperopia at 5°, 25°, 30° and 35° in the nasal VF. Asymmetry was evident at ±10° ($F_{(1,25)}$=5.313, p=0.030) in the moderate myope M profile. The statistics and p values for this analysis are listed in Appendix C1. Relative peripheral M profiles for all refraction groups are shown in Figure 3.1a.

Significant differences between central and peripheral J_{180} values were found ($F_{(2.620, 186.038)}$=104.501, p<0.001) with no difference in J_{180} profiles evident between refractive groups (F=1.544, p=0.058). J_{180} was more negative at all positions compared to the centre and asymmetry was noted at ±25° ($F_{(1,71)}$=7.015, p=0.010) and ±30° ($F_{(1,71)}$=2.043, p=0.028) with J_{180} being significantly more negative in the nasal VF. The statistics and p values for this analysis are listed in Appendix C1. Relative peripheral J_{180} profiles for all refraction groups are shown in Figure 3.1b.

There was no difference in J_{45} refraction profile between different refractive groups (F=0.862, p=0.665). However, there was a statistically significant positive correlation between J_{45} and eccentricity ($F_{(2.158,153.196)}$=45.155, p<0.001). J_{45} was significantly more positive at all positions in the nasal VF compared to the centre and more negative at all positions except 5° in the temporal VF. The statistics and p values for this analysis are listed in Appendix C1. Relative peripheral J_{45} profiles for all refraction groups are shown in Figure 3.1c.

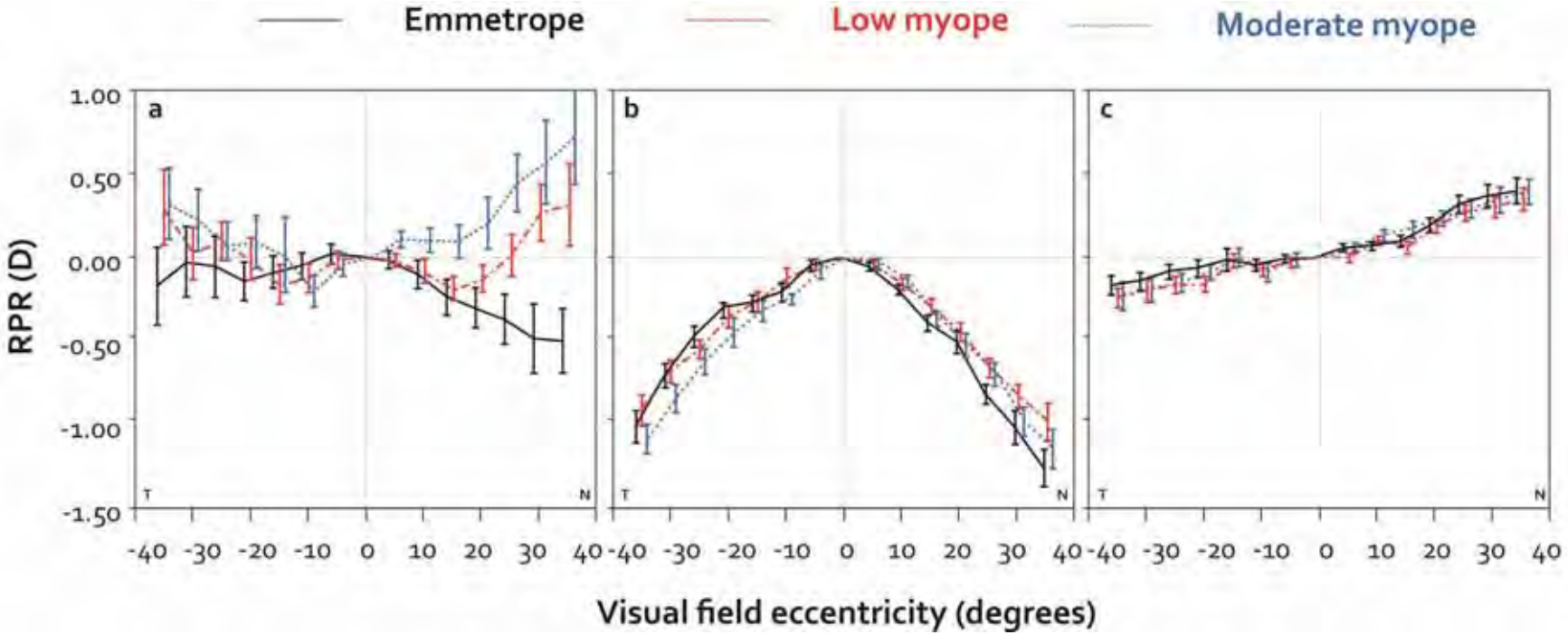


Figure 3.1 RPR profiles (D; mean) for a) M b) J_{180} and c) J_{45}. Error bars represent the standard error of the mean. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

VF	-35°	-30°	-25°	-20°	-15°	-10°	-5°	C	5°	10°	15°	20°	25°	30°	35°
M	0.02 ± 1.22	0.16 ± 1.10	0.13 ± 0.95	0.05 ± 0.66	0.10 ± 0.63	0.14 ± 0.51	0.21 ± 0.47	0.19 ± 0.36	0.17 ± 0.41	0.09 ± 0.52	-0.05 ± 0.64	-0.12 ± 0.68	-0.18 ± 0.82	-0.30 ± 1.06	-0.31 ± 1.09
J_{180}	-1.06 ± 0.47	-0.76 ± 0.41	-0.53 ± 0.33	-0.38 ± 0.33	-0.33 ± 0.32	-0.26 ± 0.35	-0.11 ± 0.26	-0.06 ± 0.19	-0.11 ± 0.21	-0.25 ± 0.30	-0.45 ± 0.31	-0.56 ± 0.46	-0.88 ± 0.41	-1.07 ± 0.60	-1.32 ± 0.61
J_{45}	-0.12 ± 0.28	-0.09 ± 0.28	-0.04 ± 0.22	-0.01 ± 0.35	0.04 ± 0.33	0.01 ± 0.21	0.04 ± 0.17	0.05 ± 0.15	0.11 ± 0.15	0.15 ± 0.23	0.08 ± 0.36	0.24 ± 0.26	0.37 ± 0.28	0.43 ± 0.23	0.45 ± 0.39

Table 3.2 Objective refraction components (D; mean ± SD), in the emmetrope group. Negative eccentricities denote the temporal VF, positive eccentricities denote the nasal VF and C denotes the centre.

VF	-35°	-30°	-25°	-20°	-15°	-10°	-5°	C	5°	10°	15°	20°	25°	30°	35°
M	-0.87 ± 1.33	-0.99 ± 1.25	-0.97 ± 1.02	-1.06 ± 0.97	-1.18 ± 0.90	-1.15 ± 0.86	-1.07 ± 0.80	-1.07 ± 0.71	-1.07 ± 0.82	-1.10 ± 0.92	-1.21 ± 0.94	-1.16 ± 0.93	-1.05 ± 1.03	-0.86 ± 1.17	-0.88 ± 1.34
J_{180}	-0.98 ± 0.46	-0.74 ± 0.37	-0.61 ± 0.37	-0.40 ± 0.29	-0.32 ± 0.46	-0.16 ± 0.37	-0.09 ± 0.33	-0.04 ± 0.28	-0.08 ± 0.32	-0.21 ± 0.31	-0.32 ± 0.46	-0.50 ± 0.40	-0.72 ± 0.39	-0.89 ± 0.47	-1.05 ± 0.59
J_{45}	-0.19 ± 0.36	-0.15 ± 0.38	-0.12 ± 0.31	-0.12 ± 0.33	0.03 ± 0.28	-0.03 ± 0.28	0.02 ± 0.19	0.04 ± 0.15	0.05 ± 0.21	0.15 ± 0.16	0.11 ± 0.23	0.23 ± 0.23	0.32 ± 0.24	0.35 ± 0.34	0.40 ± 0.34

Table 3.3 Objective refraction components (D; mean ± SD), in the low myope group. Negative eccentricity represents the temporal VF, positive eccentricity represents the nasal VF and C denotes the centre.

VF	-35°	-30°	-25°	-20°	-15°	-10°	-5°	C	5°	10°	15°	20°	25°	30°	35°
M	-3.31 ± 1.40	-3.41 ± 1.29	-3.55 ± 1.26	-3.68 ± 1.12	-3.76 ± 1.13	-3.83 ± 1.06	-3.68 ± 0.99	-3.63 ± 0.90	-3.53 ± 0.89	-3.53 ± 0.90	-3.54 ± 0.90	-3.43 ± 1.03	-3.19 ± 1.08	-3.06 ± 1.34	-2.91 ± 1.61
J_{180}	-1.09 ± 0.47	-0.86 ± 0.44	-0.65 ± 0.45	-0.51 ± 0.41	-0.38 ± 0.34	-0.30 ± 0.28	-0.14 ± 0.34	-0.08 ± 0.25	-0.10 ± 0.29	-0.20 ± 0.26	-0.38 ± 0.34	-0.56 ± 0.44	-0.73 ± 0.40	-0.99 ± 0.44	-1.15 ± 0.58
J_{45}	-0.16 ± 0.40	-0.12 ± 0.35	-0.08 ± 0.29	-0.03 ± 0.24	0.07 ± 0.30	-0.03 ± 0.28	0.05 ± 0.25	0.06 ± 0.20	0.12 ± 0.25	0.19 ± 0.25	0.23 ± 0.31	0.29 ± 0.32	0.34 ± 0.34	0.40 ± 0.43	0.44 ± 0.43

Table 3.4 Objective refraction components (D; mean ± SD), in the moderate myope group. Negative eccentricities denote the temporal VF, positive eccentricities denote the nasal VF and C denotes the centre.

3.1.3.3 CORNEAL TOPOGRAPHY

Average corneal eccentricity and apical corneal radius of curvature in each refractive group are shown in Table 3.5.

	e	r_0
Emmetrope	0.53 ± 0.11	7.79 ± 0.25
Low myope	0.52 ± 0.16	7.76 ± 0.25
Moderate myope	0.51 ± 0.13	7.78 ± 0.26

Table 3.5 Eccentricity and apical radius (mm; mean ± SD) in emmetropes, low myopes and moderate myopes.

There was no significant difference in either e ($F_{(2,70)}$ = 0.553, p = 0.578) or r_0 ($F_{(2,70)}$ = 0.148, p = 0.863) between refractive groups.

3.1.4 DISCUSSION

The results demonstrate a statistically significant difference in peripheral refraction profiles between emmetropes and myopes, in agreement with previous studies (Atchison et al., 2006, Logan et al., 2004, Mutti et al., 2000b, Seidemann et al., 2002). Both emmetropes and low myopes had relatively emmetropic peripheral refraction across the horizontal meridian. Moderate myopes had significant amounts of relative hyperopia in the periphery which may reflect a more pronounced prolate ocular shape. Previous literature (Atchison et al., 2006, Logan et al., 2004) has shown that relative hyperopia in the periphery becomes more evident in myopes greater than -2.50DS which was reflected in this study.

A temporal-nasal asymmetry was found in M along the horizontal VF with greater peripheral refraction shifts in the nasal compared with temporal VF. Regional differences in scleral growth have been proposed as a cause of a peripheral refraction profile which is not symmetrical about the visual axis. Charman and Atchison (2009) suggested that the asymmetry in M is likely to be a combination of angle alpha and lack of rotational symmetry in the retinal surface as angle alpha can only partly account for the asymmetry.

In agreement with earlier studies, there was a statistical significant negative increase in J_{180} with eccentricity and asymmetry was present with the nasal VF displaying greater astigmatism (Atchison et al., 2006, Calver et al., 2007, Charman and Jennings, 2006, Mathur et al., 2009, Seidemann et al., 2002). Some studies (Atchison et al., 2006, Atchison et al., 2005b, Millodot, 1981, Seidemann et al., 2002) demonstrated a decrease in temporal-nasal asymmetry with increase in central myopia but this was not evident in our study. In contrast to some previous studies, similar J_{180} refraction profiles were seen in all three refraction groups. A possible reason for the discrepancy may be the greater degree of central myopia in subjects recruited in earlier studies; for example Millodot (1981) included myopic subjects ranging from -1.00 to -7.87D spherical equivalent and Seidemann et al's (2002) average myopic refraction was -4.75 ± 1.90D.

There was a minimal but statistically significant increase in J_{45} with field angle in accordance with other studies (Atchison et al., 2006, Atchison et al., 2005b, Calver et al., 2007). The asymmetry in astigmatism (J_{180} and J_{45}) across the VF has been attributed to tilted or translated crystalline lens, rotated cornea, misalignment from the optic axis as well as lack of symmetry of the anterior optical surfaces based on modelling schematic eyes (Atchison et al., 2006, Barnes et al., 1987, Dunne et al., 1993). Atchison et al (2006) discovered a significant correlation between angle alpha and the turning point of J_{180}, which became more temporal (VF) with larger angle alpha values. Furthermore, theoretical analysis has shown J_{180} to be approximately symmetrical about the optic axis (Charman and Atchison, 2009). These ocular

components vary considerably between individuals, which may explain the wide inter-individual variations in peripheral astigmatism seen in most studies.

Anterior optics of the eye and retinal contour together determine peripheral refraction. Although the cornea is the main contributor to the overall power of the eye, it exhibits minimal change beyond infancy and early childhood (Grosvenor and Goss, 1998, Zadnik et al., 2003, Zadnik et al., 2004). Since corneal topography over the corneal chord of interest was similar between refractive groups, it was concluded that the cornea had minimal influence on the difference in peripheral refraction found between refractive groups.

Cycloplegia was not used in this study and therefore subjects may have exercised some accommodation when viewing targets. Target vergence varied between 0.23D and 0.46D in our clinical setting (Section 2.2.3.1.6) and it has been shown that up to 2D of accommodation has very little effect on peripheral astigmatism for eccentric fixation angles up to 30° (Smith et al., 1988). Additionally, cycloplegia can introduce additional peripheral aberrations due to pupil dilation which may affect autorefraction measurements.

An attempt was made to eliminate the influence of progressing myopia on refraction results by excluding subjects who were aware of refraction changes within the past year. Although we cannot assume that all the myopes in our study were non-progressive, young adults who have an established myopic refractive error are most likely to have developed youth-onset myopia which has been found to slow or stop progressing during young adulthood (Goss et al., 1985, Grosvenor and Goss, 1999).

The results from this study confirm characteristic peripheral refraction profiles in different refractive groups. Moderate myopes were found to have relative hyperopia in the periphery supposedly reflecting a more prolate ocular shape compared to emmetropes.

3.2 COMPARISON OF PERIPHERAL REFRACTION IN DIFFERENT ETHNIC GROUPS

3.2.1 INTRODUCTION

The high prevalence of myopia repeatedly documented in the East Asian population (Fan et al., 2004, He et al., 2009, Lin et al., 2004, Saw et al., 1996, Zhao et al., 2000) is of great concern. Myopia not only carries a financial (Berdeaux et al., 2002, Javitt and Chiang, 1994, Lim et al., 2009) and social burden for the individual, but it also increases the risk of development of a number of ocular complications such as glaucoma (Grodum et al., 2001, Mitchell et al., 1999, Saw et al., 2005a), macular degeneration (Saw et al., 2005a) and various pathological retinal changes (Lai et al., 2008, Lam et al., 2005). Myopia is one of the most significant causes of blindness (Hsu et al., 2004, Iwase et al., 2006, Liang et al., 2008, Michon et al., 2002, Xu et al., 2006) (Section 1.1.4).

With previous research revealing the potential significant influence of the peripheral retina in myopia development (Hoogerheide et al., 1971, Mutti et al., 2007, Smith et al., 2005, Smith et al., 2007), it seems appropriate to investigate if there are any differences in peripheral refraction profiles between East Asians and Caucasians.

There have been some studies that investigated differences in ocular biometry between Caucasian and Asian myopic eyes (Ip et al., 2008, Logan et al., 2004, Mutti et al., 2007). However, no studies to date have compared differences in peripheral refraction profiles between Caucasian and Asians across different refractive groups. The study described in Section 3.1 was further extended to determine if there were any differences in peripheral refraction profiles between different ethnicities to explain the higher propensity of myopia development and progression in East Asian individuals compared to other ethnicities. It was hypothesised that differences in

peripheral refraction profiles will be detected between myopic East Asians and Caucasians.

3.2.2 MATERIALS AND METHODS

The same materials and methods were used as described in Section 3.1.2.

3.2.2.1 DATA ANALYSIS

Independent t-tests were performed on central refraction to confirm that East Asian and Caucasian subjects were matched in each refractive group. MANOVA at centre and ±30° allowed comparison of peripheral refraction profiles between different ethnicities in each refractive group.

ANOVA allowed comparison of corneal eccentricity and apical radius between the two ethnicities in each refractive group.

Previous studies (Radhakrishnan and Charman, 2008, Schmid, 2003b) have found increased variability and difficulty with measurements at temporal 15° which is near the location of the optic disc and have often disregarded data at this eccentricity (Atchison et al., 2006, Radhakrishnan and Charman, 2008). Thus, temporal 15° data were excluded from our analysis.

3.2.3 RESULTS

3.2.3.1 CENTRAL REFRACTION

Average objective central refractions of the East Asian and Caucasian subjects in the different refractive groups are shown in Table 3.6.

	Caucasian	n	East Asian	n
Emmetrope	0.15 ± 0.39	12; 8 F, 4 M	0.22 ± 0.35	13; 10 F, 3 M
Low myope	-1.13 ± 0.44	11; 7 F, 4 M	-1.58 ± 0.66	10; 6 F, 4 M
Moderate myope	-3.82 ± 1.00	14; 12 F, 2 M	-3.42 ± 0.81	12; 8 F, 4 M

Table 3.6 Objective central refraction (D; mean ± SD) and number of subjects. F denotes female and M denotes male

There was no significant difference in central distance refraction between East Asian and Caucasian subjects in each of the refractive groups ($t_{(23)E}$=-0.463, p=0.624; $t_{(19)LM}$=1.866, p=0.078; $t_{(24)MM}$=0.953, p=0.350). This indicated that Asian and Caucasian subjects were matched in each refractive group.

3.2.3.2 PERIPHERAL REFRACTION

There were significant differences in peripheral refraction profiles between Caucasians and East Asians when analysing both raw (F=4.686, p=0.005) and relative data (F=4.360, p=0.017). Analysing each refractive group showed no significant difference between ethnicities in raw peripheral refraction in either the emmetrope or low myope group (F_{EM}=0.254, p=0.858; F_{LM}=1.741, p=0.197). A significant difference was evident in the moderate myope group (F=4.226, p=0.017).

When analysing relative data, there were no statistically significant differences in refraction profiles between Caucasians and East Asians in either the emmetrope or low myope groups (F_E=0.241, p_E=0.788; F_{LM}=1.167, p_{LM}=0.334). However, there was a significant difference in refraction profile when analysing at centre and ±30° between Caucasian and East Asians in the moderate myope group (F=5.204, p=0.014). East Asians had a significantly greater amount of relative hyperopia at 30° in the temporal

VF ($F_{(1,25)}$= 10.571, p=0.003) but not in the nasal VF ($F_{(1,25)}$=1.368, p=0.254). RPR profiles between Caucasians and East Asians are shown in Figure 3.2.

No significant difference in J_{180} or J_{45} refraction profiles was found between Caucasians and East Asians (F_{J180}=0.298, p_{J180}=0.743; F_{J45}=0.965, p_{J45}=0.386).

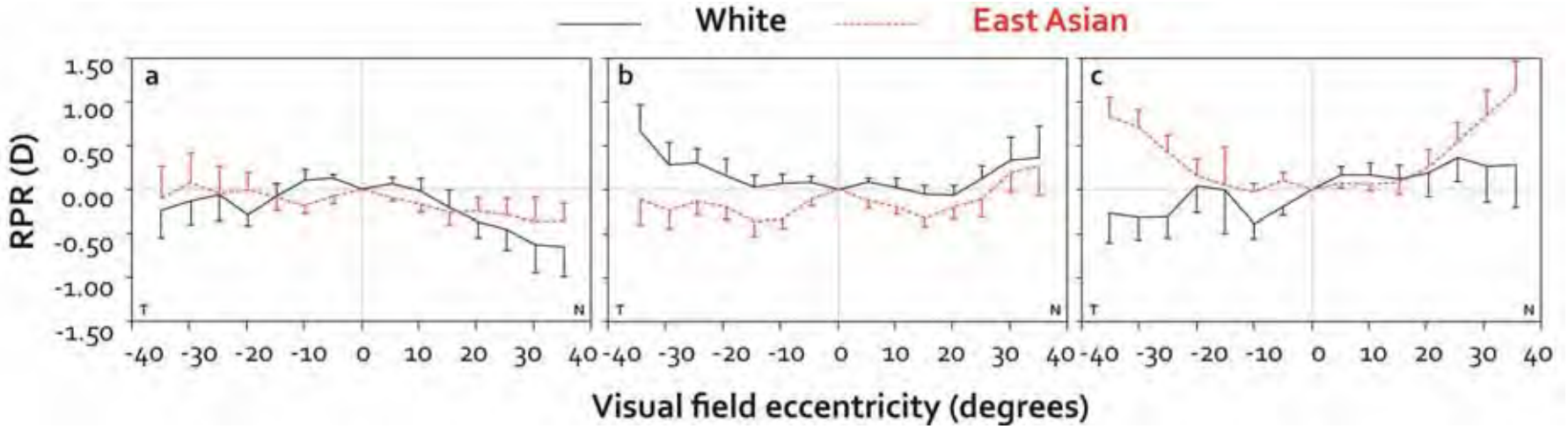


Figure 3.2 RPR profiles (D; mean) for a) emmetropes b) low myopes and c) moderate myopes. Error bars represent the standard error of the mean. Positive eccentricities denote the temporal VF while negative eccentricities denote the nasal VF.

3.2.3.3 CORNEAL TOPOGRAPHY

Average corneal eccentricity and apical radius values in each refractive group in both Caucasians and East Asians are shown in Table 3.7.

	Apical radius		Eccentricity	
	Caucasian	East Asian	Caucasian	East Asian
Emmetrope	7.84 ± 0.26	7.72 ± 0.22	0.52 ± 0.10	0.52 ± 0.18
Low myope	7.66 ± 0.17	7.87 ± 0.28	0.51 ± 0.18	0.58 ± 0.11
Moderate myope	7.81 ± 0.37	7.79 ± 0.21	0.48 ± 0.10	0.52 ± 0.13

Table 3.7 Corneal apical radius r_o (mm; mean ± SD) and eccentricity e (mean ± SD).

There were no significant differences in apical radius between Caucasians and East Asians in the three different refractive groups ($t_{(23)E}$=1.195, p=0.245; $t_{(21)LM}$=-1.977, p=0.064; $t_{MM(26)}$=-0.226, p=0.823). Similarly, there were no significant differences in corneal eccentricity between Caucasians and East Asians in the three different groups ($t_{(23)E}$=0.018, p=0.986; $t_{(21)LM}$=-1.010, p=0.327; $t_{(26)MM}$=-1.724, p=0.096).

Tangential corneal power across the central 5mm corneal chord was compared between Caucasians and East Asians and relative average values at the centre and ±2.5mm are shown in Figures 3.3a, b and c for emmetropes, low myopes and moderate myopes, respectively. Corneal tangential power across the central 5mm chord was similar between each of the three refractive groups (F=1.779, p=0.109) and across Caucasians and East Asians (F=0.859, p=0.468)

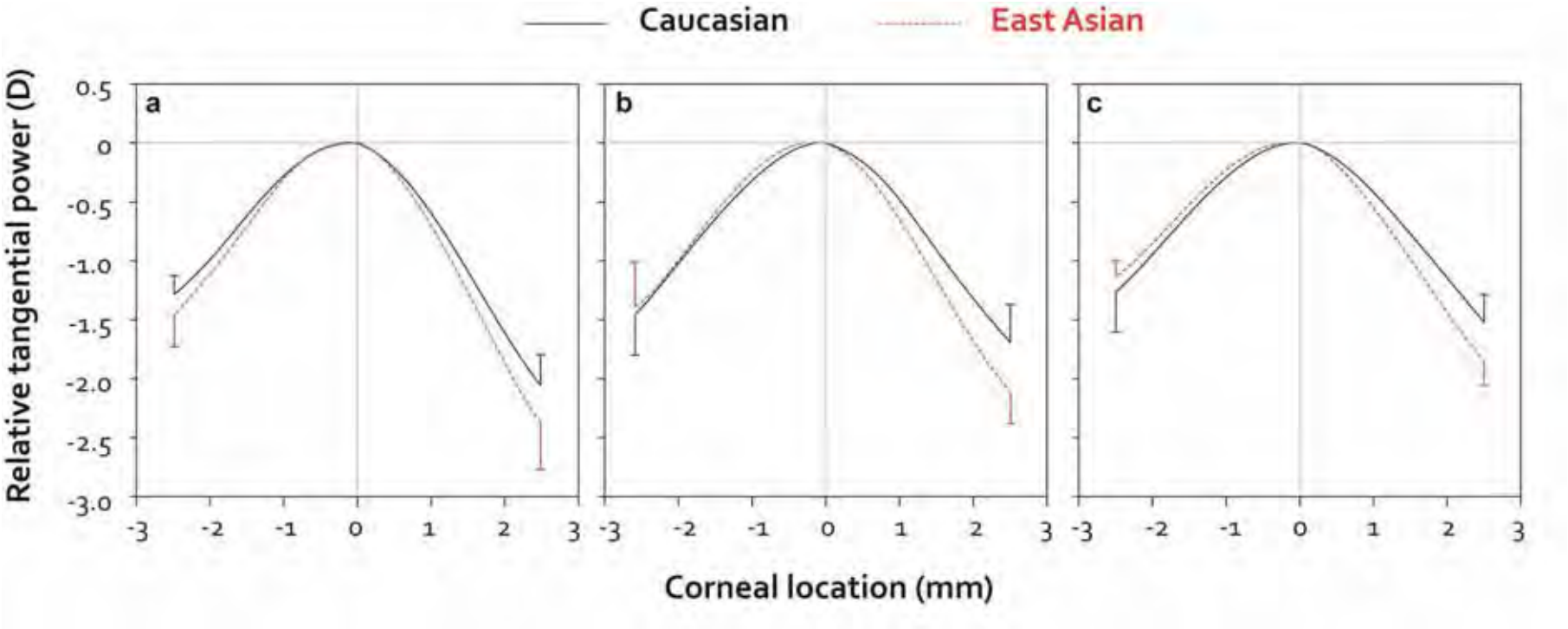


Figure 3.3 Relative tangential power (D; mean) across the central 5mm corneal chord for a) emmetropes b) low myopes and c) moderate myopes. Error bars represent the standard errors of the mean. Negative values denote the temporal cornea while positive values denote the nasal cornea.

3.2.4 DISCUSSION

Peripheral refraction profiles along the horizontal meridian were similar between Caucasians and East Asians in the emmetrope and low myope groups. Interestingly, a statistically significant difference was found in the moderate myope group. In general, moderately myopic East Asians had a greater degree of relative peripheral hyperopia, possibly corresponding to a more prolate ocular shape, when compared to Caucasian eyes of similar central refractive error. The results are consistent with previous studies (Logan et al., 2004, Mutti et al., 2007) comparing Caucasian and Asian myopic subjects in which Asian myopes were found to have greater relative peripheral hyperopia. Mutti et al (2007) demonstrated that a significant difference between Asian and Caucasian myopes was evident 3 years and 1 year before myopia onset and 1 year after onset. Furthermore, the degree of relative peripheral hyperopia in our East Asian moderate myope subjects are similar to results in a study by Chen et al (2010) who measured peripheral refraction in myopic Chinese children and adults. It must be pointed out that the criteria for refraction group categorisation is different between our study and that by Chen et al (2010). They found their results to be comparable to reports of peripheral refraction profiles in Caucasian subjects.

Corneal shape and power were found to be comparable between East Asian and Caucasian subjects in the three refractive groups over the area measured in this study, as previously reported (Ip et al., 2007). Since corneal topography over the corneal chord of interest was similar between East Asian and Caucasian moderate myopes, we conclude that it had minimal influence on the difference in peripheral refraction found.

A potential limitation of this study was that crystalline lens biometry measurements were not taken and therefore differences in peripheral refraction found in the moderate myope group may not be fully accounted for by differences in ocular shape. However, the age-related pattern of crystalline lens development beyond 10 years of age and the approximate age at which lens development ceases (Mutti et al., 1998) have been found to be similar between East Asian and Caucasian children (Zadnik et al., 2004). A recent paper from the CLEERE Study (Twelker et al., 2009) found that

although there is a statistically significant difference in the Gullstrand lens power between Caucasian and Asian children, this difference was not clinically significant (≤0.75DS). Using the child's individual refractive index has been found to be a better method for calculating lens power (calculated lens power) compared to calculating Gullstrand lens power which is the equivalent lens power calculated using Gullstrand-Emsley schematic eye values. At the age of ten, calculated lens power in addition to crystalline lens thickness and refractive index were found to be comparable between Caucasian and Asian children. Therefore differences between East Asian and Caucasian adults in lens biometry are unlikely, and consequently differences in peripheral refraction between the different ethnicities are more likely to be due to differences in retinal shape than to differences in lens biometry.

Another potential limitation of the study was that axial length measurements were not taken because these data could have been used to further confirm the possible differences in ocular shape between Caucasian and East Asian moderate myopes. As increases in axial length have been found to be sufficient to account for the myopic refraction (Atchison et al., 2004), each refractive group was matched for central refractive errors to minimise the effects of differences in axial length on the results.

3.3 CONCLUSION

Differences in peripheral refraction profiles between refractive groups were confirmed with myopes exhibiting relative hyperopia in the periphery (to a greater degree in moderate myopes) and emmetropes showing slight relative myopia. Significant difference was only found between emmetropes and moderate myopes. With further investigation, ethnic differences in peripheral refraction profile were evident in moderate myopes, with East Asians exhibiting greater amounts of relative hyperopia in the periphery compared to Caucasians with similar central refractive error.

Individuals of East Asian ethnicity have the greatest risk of developing myopia and it appears that location of residence has minimal influence as the highest prevalence of myopia is reported in East Asian individuals in both Asia and elsewhere (Fan et al., 2004, He et al., 2009, Ip et al., 2008, Kleinstein et al., 2003, Lin et al., 2004, Saw et al., 1996, Zhao et al., 2000). It is possible that differences in ocular shape inferred from differences in peripheral refraction as found in this study may explain the higher propensity for East Asian individuals to develop and progress in myopia compared with other ethnic groups. A supposedly more prolate ocular shape as inferred from peripheral refraction, which appears to be common in myopic East Asian individuals, will lead to a more hyperopic defocus in the peripheral retina which then may act as a stronger stimulus for growth in axial length. Mutti et al (2007) found relative peripheral hyperopia 1 year prior to the onset of myopia in Caucasian children and 3 years prior for Asian children. This relative peripheral hyperopia was still evident up to 5 years after the onset of myopia and was greater in Asian children. Therefore it appears that peripheral relative hyperopic defocus may be a driver for myopia development rather than being a result of myopia development. It may be that the longer duration of hyperopic defocus and more prolate ocular shape as indicated by greater hyperopic peripheral defocus may be a reason why Asian eyes seem to be much more susceptible to myopia development and progression compared to Caucasian eyes. It is possible that this greater myopic stimulus in Asians remains even after termination of myopia progression as demonstrated in non-progressing myopes in this study.

CHAPTER 4

PERIPHERAL REFRACTION AND AXIAL LENGTH

The study described in Chapter 3 confirmed characteristic peripheral refraction profiles in different refractive groups; emmetropes were found to have slight relative peripheral myopia while moderate myopes were found to have relative peripheral hyperopia. Peripheral refraction is commonly used to infer ocular shape. Relative peripheral hyperopia is believed to reflect a more prolate ocular eye shape while relative peripheral myopia is believed to indicate a more oblate eye shape (Atchison et al., 2006, Atchison et al., 2005a, Millodot, 1981, Mutti et al., 2000b, Schmid, 2003b, Seidemann et al., 2002, Smith et al., 1988, Stone and Flitcroft, 2004).

Differences in peripheral refraction were evident between Caucasian and East Asian moderate myopes as discussed in Chapter 3. Compared to Caucasians of similar central refractive error, East Asians were found to have greater relative hyperopia in the periphery possibly reflecting a more prolate ocular shape. It was proposed that the apparent difference in ocular shape inferred from peripheral refraction could be a reason why East Asians are at greater risk of development and progression of myopia. The more prolate ocular shape that was apparent in East Asians as inferred from peripheral refraction was proposed as a myopiogenic factor.

Ray tracing (Atchison and Smith, 2000) has suggested that peripheral refraction is able to accurately reflect ocular shape. However eye modelling studies have shown that this may be an oversimplification and not an accurate portrayal of ocular shape (Dunne, 1995, Logan et al., 1995). Schmid (2003b), using an optical low coherence reflectometer in 63 children subjects aged 7-15 years, was able to show that there was significant correlation between relative peripheral axial length and relative M at 15° in the temporal retina. However, measurements were taken at only 3 locations on the retina. More recently, Schmid (2011) measured retinal contour using the same technique at 20° in the superior, inferior, nasal and temporal retina in 140 children

subjects aged 7-11 years. He found the retina was steepest temporally, followed by nasally then inferiorly and flattest superiorly.

Animal studies have demonstrated significant correlations between axial length and peripheral refraction. Form deprivation induces axial myopia as well as changes in ocular shape and corresponding peripheral refraction in infant rhesus monkeys (Huang et al., 2009). Hemi-field form deprivation produces corresponding regionally selective myopic changes and associated changes in peripheral refraction (Smith et al., 2009a).

The first part of this chapter describes a pilot study evaluating the repeatability of peripheral axial length measurements determined by the IOLMaster. The second half of this chapter sought to determine any relationship between peripheral axial length measurements and corresponding peripheral refraction measurements. The study aimed to validate the use of peripheral refraction as a descriptor of ocular shape.

4.1 CLINICAL EVALUATION OF THE IOLMASTER

4.1.1 INTRODUCTION

The IOLMaster (Zeiss, Germany) is a PCI, also known as a low coherence reflectometer, capable of measuring corneal curvature, axial length and anterior chamber depth. It has been found to be comparable to traditional ultrasound methods of axial length measurement in both children (Carkeet et al., 2004, Chan et al., 2006) and adults (Lam et al., 2001, Santodomingo-Rubido et al., 2002, Sheng et al., 2004). The IOLMaster has the advantage of possessing higher resolution (±0.01mm) compared to ultrasound (±0.15mm) in addition to being a non-contact instrument. The IOLMaster is traditionally used to obtain central axial length measurements.

Relative peripheral hyperopia, possibly reflecting a more prolate ocular shape, has been proposed as a potential myopiogenic factor. Therefore there is great interest in developing reliable methods to describe ocular shape. However the instruments which have been traditionally used to measure ocular shape such as MRI scans and CT scans are expensive and not readily available. Thus an inexpensive and non-invasive alternative method is sought.

The IOLMaster, which typically is used to measure central axial length, can be modified to take peripheral axial length measurements (Macfadden et al., 2007, Mallen and Kashyap, 2007). In the study described below, the IOLMaster was clinically evaluated for repeatability of peripheral axial length measurements. It was hypothesised that the IOLMaster will be able to take repeatable peripheral axial length measurements with similar repeatability levels as reported for central axial length measurements.

4.1.2 MATERIALS AND METHODS

4.1.2.1 STUDY DESIGN

Five central axial length measurements were taken and averaged after which one drop of 1% Cyclopentolate was instilled into both eyes. One drop of 1% Cyclopentolate will cause a maximum mydriasis (average 6.5 to 7.5mm) after 20 to 30 minutes (Frazier and Jaanus, 2008). 1% Cyclopentolate was chosen as it is a superior cycloplegic agent compared to Tropicamide providing effective mydriasis and cycloplegia (Lovasik, 1986, Macfadden et al., 2007). 40 minutes after Cyclopentolate instillation, five axial length measurements were taken at centre and peripherally at 25° in the temporal and nasal VF. Subjects were then instructed to return in approximately a week at the same time of day for a second measurement session. One drop of 1% Cyclopentolate was instilled into both eyes again and central and peripheral axial length and autorefraction measurements were taken from the same eye as the first visit.

Measurements were taken only in the right eye unless it did not meet the inclusion criteria as described in Section 4.1.2.2, in which case the left eye was used.

4.1.2.2 SUBJECTS

Ten subjects (age range 18 – 38 years; 6 M, 4 F) were recruited for this study. Approval from the institutional Human Research Ethics Advisory panel (Approval number HREA 10059) was obtained before study commencement. All subjects gave their informed written consent to participate in the study after being informed about the nature and possible consequences of study participation. Subjects were screened prior to enrolment and found to be in good ocular health and free from ocular disease. To be eligible for the study, subjects were required to be non-RGP wearers, and SCL wearers were instructed to cease lens wear for at least 24 hours before measurements were to be taken.

Subjects were screened for suitability for cycloplegia through IOP measurements and observation of the anterior chamber angle. Cyclopentolate can cause elevation of IOP in primary open angle glaucoma sufferers and precipitate acute glaucoma attacks (Frazier and Jaanus, 2008, Jones and Hodes, 1991). Therefore, those individuals with pressures equal to or greater than 21mmHg or Van Herrick ratios of less than 0.3 were excluded from the study.

4.1.2.3 MEASUREMENT TECHNIQUES

4.1.2.3.1 CENTRAL AXIAL LENGTH

Central axial length measurements are taken with the subject fixating on the central target presented by the IOLMaster. An image of the eye appears on the monitor and the IOLMaster is adjusted such that the central and 6 peripheral spots are centred on the cross hairs within the pupil. The IOLMaster is aligned so that all spots and iris are in best focus as shown in Figure 4.1. Five consecutive measurements were taken from the right eye and averaged. Measurements with a signal to noise ratio of less than 2 were disregarded.

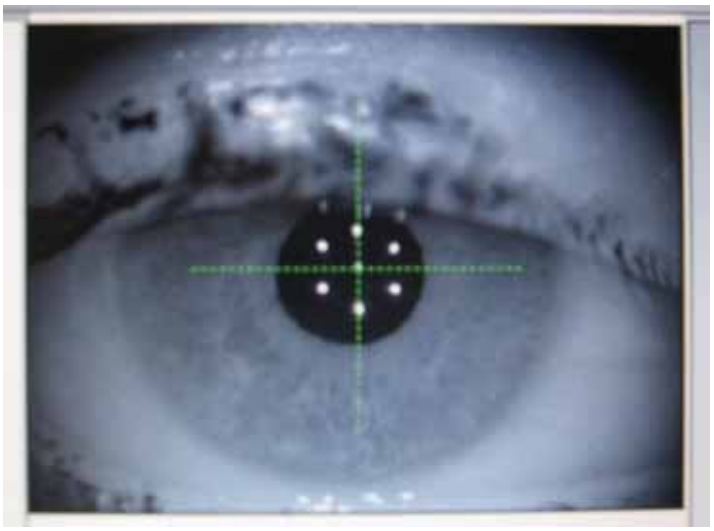


Figure 4.1 Central and peripheral spots and cross hairs displayed on the IOLMaster monitor used for alignment for central axial length measurements.

4.1.2.3.2 PERIPHERAL AXIAL LENGTH

The IOLMaster is traditionally used to measure central axial length whereby the beam has approximate normal incidence with the optical surfaces of the eye. With oblique measurements, it is likely that the measurement beam is not normal to the eye's optical surfaces which will result in deviation of the beam passage through the eye. In order to take peripheral axial length measurements, dilation is required for maximum pupil size. Subsequent to pupil dilation, subjects were instructed to fixate on a peripheral target that was placed at 25° in the temporal and nasal VF along the horizontal meridian. There are two methods of taking off-axis measurements as described by Atchison and Charman (2011). The corneal-direction method involves directing the beam in a direction that is incident normally to the corneal surface. The incident beam will be directed at the centre of curvature of the anterior corneal surface. Theoretical investigation by Atchison and Charman (2011) determined this to give reasonable estimates of the retinal shape up to field angles of approximately 30°. The pupil-direction method involves directing the beam towards the centre of the entrance pupil. Due to pupil aberration, an oblique beam will not pass through the centre of the entrance pupil and over-estimation of retinal radius of curvature will result.

During alignment on the human eye, the pupil appeared as an oval on the monitor and difficulty taking measurements normal to the cornea was encountered. However, repeatable measurements were able to be taken when the measurement beam was directed between the central alignment spot and the temporal pupil margin as shown in Figure 4.2. Five axial length measurements were taken and averaged. Measurements with a signal to noise ratio of less than 2 were disregarded.

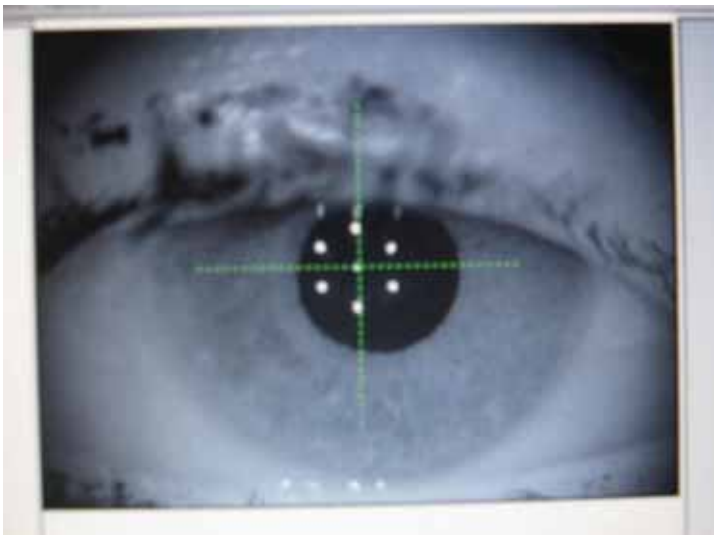


Figure 4.2 Oval entrance pupil of the right eye during nasal gaze and alignment spots on the monitor of the IOLMaster for peripheral axial length measurements. The central spot is aligned to bring it into best focus.

4.1.2.4 DATA ANALYSIS

Repeatability of peripheral axial length measurements was assessed as suggested by Bland and Altman (1999) and as described in Section 2.3.2.1.2.

4.1.3 RESULTS

The mean objective central refraction is shown in Table 4.1.

	M	J_{180}	J_{45}
Objective distance refraction	-0.09 ± 1.13	-0.09 ± 0.18	0.15 ± 0.25D

Table 4.1 Objective central refraction (D; mean ± SD).

The repeatability of central, nasal and temporal axial length measurements are shown in Bland-Altman plots in Figure 4.3a, b and c respectively. The differences between measurements taken at two separate sessions are shown in Table 4.2. Nasal measurements had the poorest repeatability with a 95% limits of agreement range between -0.23 to 0.29mm. Student t-tests determined no significant difference from zero in the differences in measurements taken on two separate sessions (t_C=-1.922, p=0.087; t_N=1.595, p=0.145; t_T=0.294, p=0.775).

	Mean difference*	95% Limits of agreement**
Centre	-0.02 ± 0.03	-0.05 to 0.04mm
Nasal 25°	0.06 ± 0.12	-0.23 to 0.29mm
Temporal 25°	0.01 ± 0.07	-0.13 to 0.13mm

Table 4.2 Difference between axial length measurements (mm; mean ± SD) taken on two separate sessions at centre and 25° in the nasal and temporal VF.

**Mean difference = Mean first session axial length – mean second session axial length*

***95% limits of agreement = mean difference ± 1.96 x SD of the differences*

Approximately 0.35mm increase in axial length corresponds to 1D of myopia (Atchison et al., 2004) and all second measurements were within 0.35mm of the first.

Intra-session repeatability was found to be acceptable with SD of measurements in one session of 0.03, 0.12 and 0.07mm for central, nasal and temporal axial length measurements with the IOLMaster. The repeatability coefficients were 0.05 mm, 0.23 mm and 0.13mm for central, nasal and temporal axial length measurements respectively.

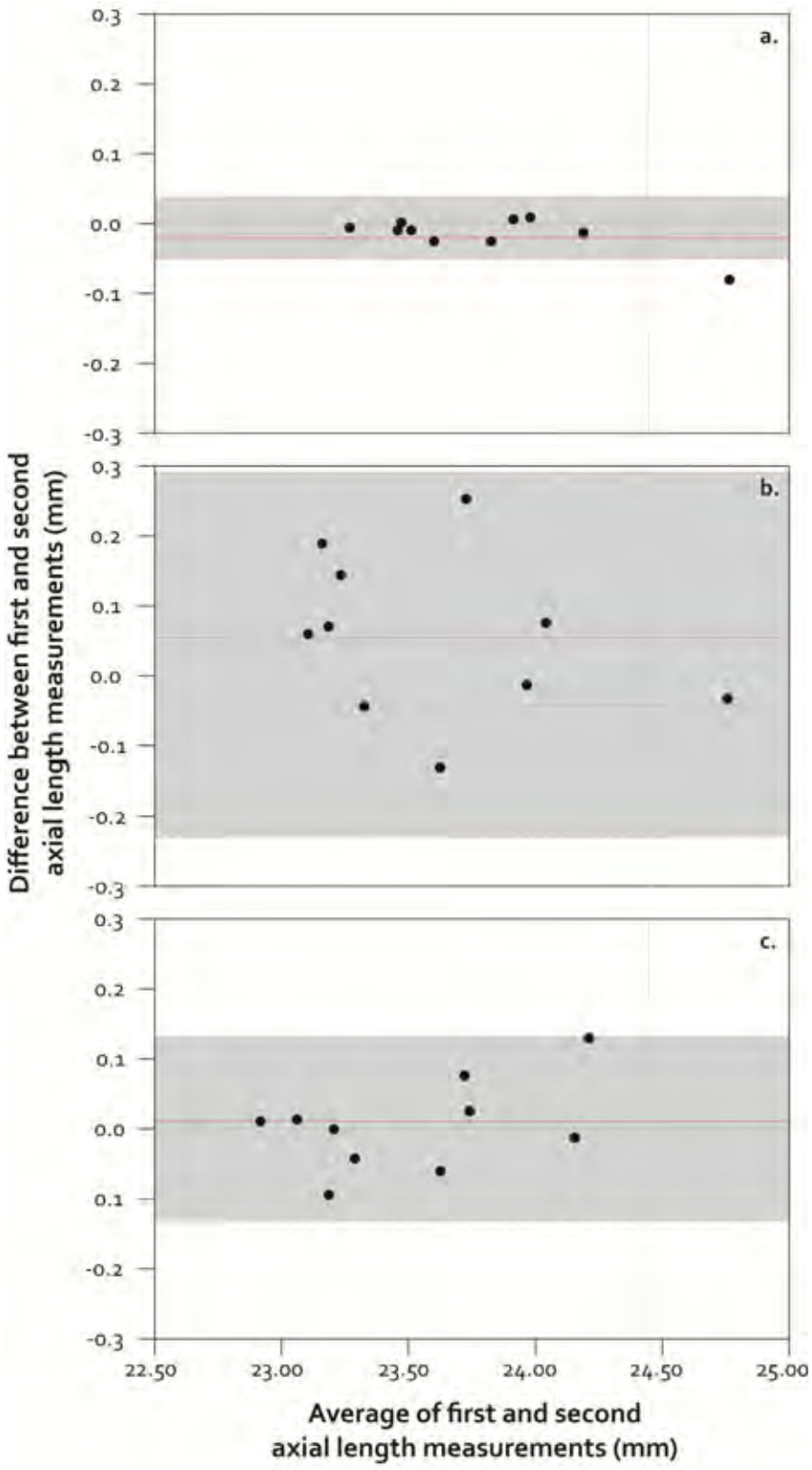


Figure 4.3 Average of repeated axial length measurements taken at a) centre, b) nasal 25° and c) temporal 25° plotted against their difference (mm).

Mean difference (bias) is indicated by the solid red line and the upper and lower dotted lines indicate 95% limits of agreement

Furthermore, there was no significant effect of cycloplegia on central axial length measurements with no bias (t=0.169, p=0.869) evident between two measurements taken during separate sessions (Figure 4.4). The repeatability coefficient was 0.08mm.

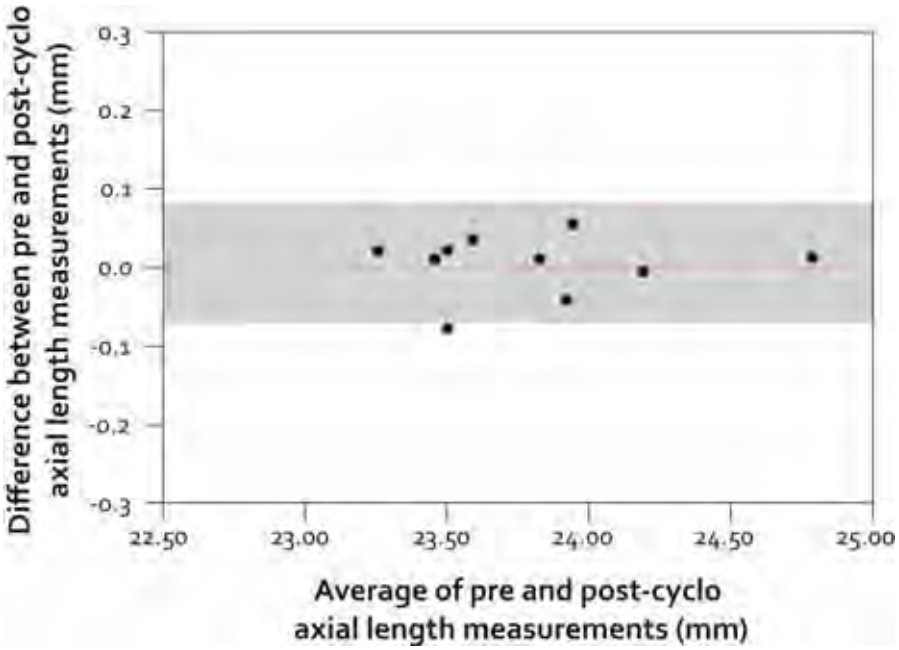


Figure 4.4 Average of central axial length taken with and without cycloplegia against their difference (mm).

Mean difference (bias) is indicated by the solid red line and the upper and lower dotted lines indicate 95% limits of agreement

4.1.4 DISCUSSION

The IOLMaster is a PCI which is traditionally used to measure central axial length. Modifications of the instrument have allowed peripheral axial length measurements to be taken (Macfadden et al., 2007, Mallen and Kashyap, 2007).

Alignment problems were encountered with peripheral axial length measurements in this study. As theoretically investigated by Atchison and Charman (2011), the corneal-direction method has been demonstrated to be the superior technique. However, difficulty was encountered when trying this alignment method on real human eyes.

Therefore alignment was manipulated such that measurements were taken between the central alignment spot and pupil margin where repeatable alignment was possible. However this method will cause deviations of the measurement beam and therefore it is unknown exactly where on the retina axial length measurements are being taken. This is a limitation of the method employed in this study.

Bland-Altman analysis determined no significant differences in measurements taken at all locations during two separate sessions and no significant effect of cycloplegia on measurements. Acceptable repeatability of both central and peripheral axial length measurements was demonstrated in this study. Repeatability coefficients of 0.05 mm, 0.23 mm and 0.13mm were found with repeated central, nasal and temporal axial length measurements respectively. Poorer repeatability in peripheral locations may be due to poor fixation or coincidence with the optic nerve head. The IOLMaster will be able to detect approximately 0.14D, 0.66D and 0.37D of refractive change at the centre, 25° in the nasal and 25 ° in the temporal retina respectively if it is assumed that 0.35mm increase in axial length approximates to 1D of myopia (Atchison et al., 2004).

Pupil dilation is required for peripheral axial length measurements and only one study to date has investigated the effect of cycloplegia on axial length measurements. Similar to results in our study, Sheng et al (2004) found no significant effect of cycloplegia on measurements. The effect of cycloplegia could only be investigated along the visual axis as insufficient pupil size during pre-cycloplegia would not allow peripheral axial length measurements.

Recently, Read et al (2010b) found an increase in axial length with accommodation. During accommodation, prominent changes occur in the anterior eye. The anterior and posterior curvatures of the crystalline lens steepen resulting in increased crystalline lens thickness. There is also an anterior movement of the anterior lens surface and subsequent shortening of the anterior chamber depth (Drexler et al., 1997, Garner and Yap, 1997, Kirschkamp et al., 2004). Posterior pole changes have also been reported. Taking into consideration these ocular changes with accommodation, Read et al (2010b) found a mean increase in axial length in both emmetropes and myopes of 5.2 ± 11.2µm and 7.4 ± 18.9µm for a 3D and 6D accommodative stimulus

respectively. Drexler et al (1998) also found similar transient increases in axial length with accommodation in emmetropes and myopes, exhibiting an increase of 12.7µm and 5.2µm respectively. On the other hand, Woodman et al (2010) found the opposite with greater axial elongation measured in their early onset myopic and progressing myopic subjects compared to their emmetropic subjects. This trend was also detected by Mallen et al (2006) but with a substantially greater increase in axial length of 37µm and 58µm in emmetropes and myopes respectively with a 6D accommodative stimulus. These transient changes in axial length with accommodation for up to 30 minutes were found to return to baseline at the end of a 10 minute regression period (Woodman et al., 2010). Transient changes in axial length with accommodation were assumed to not occur in this study as subjects were required to accommodate for periods of less than a minute.

For peripheral axial length measurements, subjects are required to rotate their eyes to fixate on an eccentric target. The effect of eye rotation has also been investigated using the IOLMaster in a group of 24 young adult subjects (Macfadden et al., 2007). These authors reported that eye rotation created a less prolate ocular shape in myopes while having no effect in either hyperopes or emmetropes. EOMs generate substantial amounts of force as demonstrated by changes in corneal topography after 15 minutes of convergence tasks (Read et al., 2010a), and following EOM surgery (Collins et al., 1981, Hainsworth et al., 1999). Therefore it is not surprising that eye rotation might affect ocular shape. However, recent studies have demonstrated that peripheral refraction, which is believed to relatively accurately reflect ocular shape, did not change with short periods of 2.5 minutes (Radhakrishnan and Charman, 2008) or 3 minutes (Mathur et al., 2009) of oblique viewing out to 30° in the horizontal meridian with cycloplegia. The study described in this chapter did not require eye rotation for longer than 3 minutes.

It must also be noted that the IOLMaster calculates axial length using an average refractive index. With peripheral axial length measurements, the optical path of the infrared light emitted by the IOLMaster through the crystalline lens becomes longer with greater oblique viewing and average refractive index becomes a relatively poor

representation of the gradient refractive index property of the crystalline lens. Therefore it is expected that the IOLMaster will over-estimate peripheral axial lengths (Mallen and Kashyap, 2007). Although the IOLMaster may tend to overestimate peripheral axial length measurements, it was found to be able to take repeatable measurements with the modified alignment technique.

4.2 PERIPHERAL REFRACTION AND AXIAL LENGTH AT CORRESPONDING RETINAL LOCATIONS

4.2.1 INTRODUCTION

Peripheral refraction has been commonly used to infer ocular shape with relative peripheral hyperopia supposedly reflecting a more prolate ocular eye shape while relative peripheral myopia is believed to indicate a more oblate eye shape (Atchison et al., 2006, Atchison et al., 2005a, Millodot, 1981, Mutti et al., 2000b, Schmid, 2003b, Seidemann et al., 2002, Smith et al., 1988, Stone and Flitcroft, 2004). Peripheral refraction is non-invasive, inexpensive and a readily available technique which may be able to give information on the shape of the eye.

Schmid (2003b) has demonstrated significant correlation between relative peripheral axial length and relative M at 15° in the temporal retina using an optical low coherence reflectometer. The pilot study described in the first section of this chapter demonstrated acceptable repeatability of both central and peripheral axial length measurements taken by the IOLMaster. The following study aims to investigate if there is any relationship between ocular shapes determined by peripheral refraction and by PCI in order to verify the use of peripheral refraction as an indicator of ocular shape. It is hypothesised that ocular shape inferred from peripheral refraction will be comparable to ocular shape measured by the IOLMaster.

4.2.2 MATERIALS AND METHODS

4.2.2.1 STUDY DESIGN

One drop of 1% Cyclopentolate was instilled into both eyes. Axial length measurements were taken centrally and peripherally at 25° in the temporal and nasal VF 40 minutes after drop instillation. Subsequently, autorefraction measurements were taken at centre and at 25° in the nasal and temporal VF along the horizontal meridian.

Measurements were taken only in the right eye unless it did not meet the inclusion criteria (Section 4.2.2.2) in which case the left eye was used.

4.2.2.2 SUBJECTS

Sixty-one adult subjects (age range 19 to 31 years; 28M, 33F) were enrolled in this study. Approval from the institutional Human Research Ethics Advisory panel (Approval number HREA 10059) was obtained before study commencement. All subjects gave their informed written consent to participate in the study after being informed about the nature and possible consequences of study participation. Subjects were screened prior to enrolment and found to be in good ocular health and free from ocular disease. To be eligible for the study, subjects were required to be non-RGP wearers, and SCL wearers were instructed to cease lens wear for at least 24 hours before measurements were to be taken. Central refraction was required to be between +4.00DS and -4.00DS with ≤-1.50DC.

Subjects were stratified into three groups depending on their objective central refraction. Those with M values between +4.00D and +0.49D were placed in the hyperope group, between <+0.50D and -0.49DS in the emmetrope group and between <-0.50DS and -4.00 into the myope group.

Subjects were screened for suitability for cycloplegia as described in Section 4.1.2.2.

4.2.2.3 MEASUREMENT TECHNIQUES

4.2.2.3.1 CENTRAL AND PERIPHERAL AXIAL LENGTH

Five axial length measurements were taken and averaged at centre and at 25° in the nasal and temporal retina as described in Section 4.1.2.3.1 and Section 4.1.2.3.2 respectively.

4.2.2.3.2 CENTRAL AND PERIPHERAL REFRACTION

Objective central refraction was measured with the Shin-Nippon NVision-K 5001 autorefractor as described in Section 2.2.2.1.

Five peripheral refraction measurements at 25° in the nasal and temporal VF were taken and averaged as described in Section 2.2.3.1. Alignment was modified such that peripheral refraction measurements were taken between the central alignment spot and pupil margin to maintain consistency with peripheral axial length measurements taken with the IOLMaster.

4.2.2.4 DATA ANALYSIS

Repeated-measures ANOVA was performed to describe the horizontal peripheral refraction profile while MANOVA at centre and ±25° allowed comparison of peripheral refraction profiles between different refractive groups.

Peripheral axial length was calculated from simple eye calculations using peripheral refraction data. Initially, the power of the eye along the visual axis (F_C) was calculated using central axial length and Gullstrand's No.1 schematic eye data in the following equation;

$$F_C = RI/AL_C$$

where AL_C is central axial length and RI is the average refractive index of the eye (1.336). Determining equivalent peripheral eye power will allow determination of the focal length of the image plane in the periphery (Figure 4.5). An assumption is made that equivalent peripheral eye power is equal to central eye power. To determine the corresponding peripheral retinal position, relative refraction difference at the corresponding peripheral position was added to central eye power (Figure 4.5) using the following equations:

$$\mathbf{M_{REL} = M_{N/T} - M_C}$$

$$\mathbf{F_{N/T} = F_C + M_{REL}}$$

where M_{REL} is the relative difference in refractive error at the corresponding peripheral location, M_N is the peripheral refractive error in the nasal VF, M_T is the peripheral refractive error in temporal VF, M_C is central refractive error and $F_{N/T}$ is peripheral eye power.

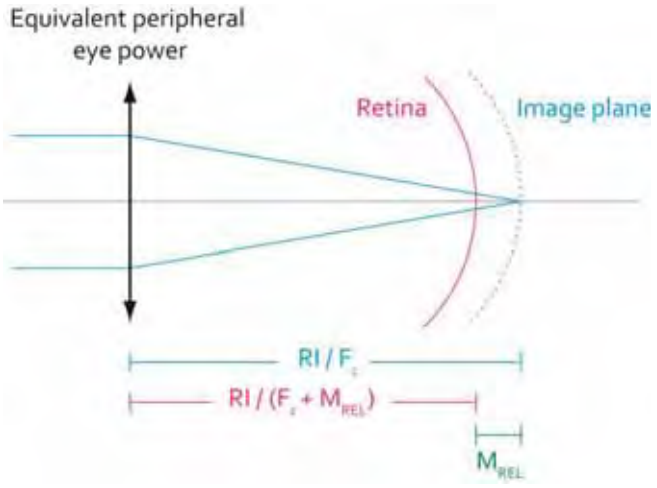


Figure 4.5 Difference in calculation between peripheral axial length and image focal length.

Axial length in the peripheral location was then calculated from the following equation:

$$\mathbf{AL_{N/T} = RI/F_{N/T}}$$

Linear regression analysis was performed on axial length calculated from peripheral refraction measurements and directly measured by the IOLMaster at both the nasal

and temporal retina. The two techniques were compared using Bland-Altman plots (Bland and Altman, 1999).

The shape of the retinal surface from axial length measurements derived from peripheral refraction was analysed in each refractive group by RM-ANOVA. MANOVA allowed comparison of ocular shape between refractive groups.

4.2.3 RESULTS

The mean objective central refraction in each refractive group is shown in Table 4.3.

Objective distance refraction	M	J_{180}	J_{45}	n
Hyperope	1.12 ± 0.77	-0.10 ± 0.19	0.09 ± 0.11D	22; 8 M, 14 F
Emmetrope	0.07 ± 0.31	-0.03 ± 0.16	0.08 ± 0.12D	15; 9 M, 6 F
Myope	-2.20 ± 1.25	-0.02 ± 0.31	0.04 ± 0.22D	24; 11 M, 13 F

Table 4.3 Objective central refraction (D; mean ± SD) and number of subjects. F denotes female and M denotes male.

Peripheral M refraction profiles in each refractive group are shown in Figure 4.6. All refractive groups had significant amounts of relative peripheral hyperopia ($F=10.634$, $p<0.001$). However, no significant differences in M refraction profiles were detected between the refractive groups ($F=1.221$, $p=0.306$).

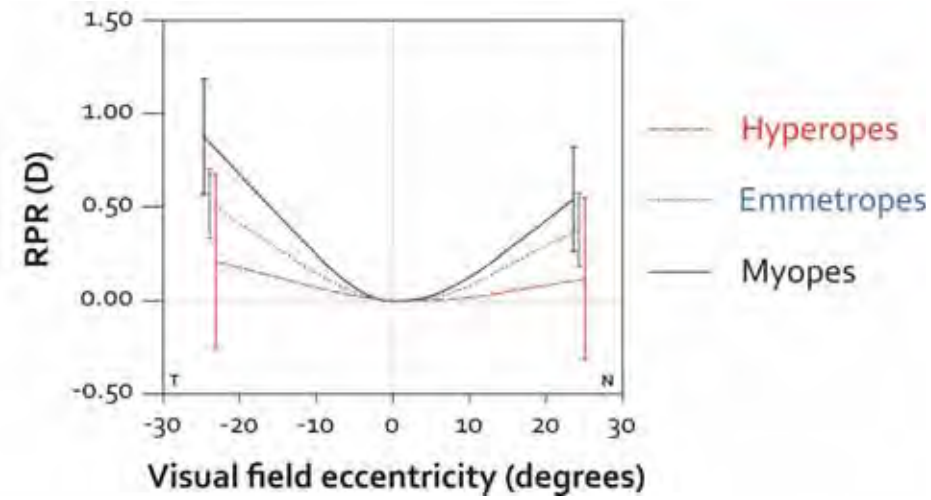


Figure 4.6 Relative peripheral M profile (D; mean) along the horizontal meridian in hyperopes, emmetropes and myopes. Error bars represent the standard error of the mean. Negative eccentricity denotes the temporal VF while positive eccentricity denotes the nasal VF.

Mean nasal and temporal axial lengths measured with the IOLMaster and derived from peripheral refraction are shown in Table 4.4.

	IOLMaster axial length			Axial length calculated from peripheral refraction	
	Centre	25° Nasal	25° Temporal	25° Nasal	25° Temporal
Hyperope	23.25 ± 0.65	23.08 ± 0.63	23.00 ± 0.67	23.17 ± 0.67	23.21 ± 0.67
Emmetrope	23.70 ± 0.69	23.47 ± 0.70	23.28 ± 0.64	23.48 ± 0.78	23.54 ± 0.72
Myope	24.56 ± 1.02	24.31 ± 1.22	23.96 ± 1.01	24.19 ± 1.29	24.33 ± 1.12

Table 4.4 Central, nasal and temporal axial length measurements measured by the IOLMaster and calculated from peripheral refraction (mm; mean ± SD).

Analysing direct measurements of axial length from the IOLMaster, ocular shapes were found to differ between refraction groups ($F_{(4,116)}$=3.486, p=0.010). Nasal and temporal axial lengths were significantly shorter compared to centre (p_N<0.001; p_T<0.001) in hyperopes and no temporal-nasal asymmetry was found (p=0.143). Similarly, nasal and temporal axial lengths were significantly shorter compared to centrally (p_N<0.001; p_T<0.001) in emmetropes and temporal-nasal asymmetry was evident (p=0.006) with the temporal retina being shorter than the nasal retina. Both nasal and temporal axial lengths were significantly shorter compared to the centre in myopes (p_N=0.026; p_T=0.004) and the temporal retina was significantly shorter than the nasal retina resulting in asymmetry (p<0.001) (Figure 4.7).

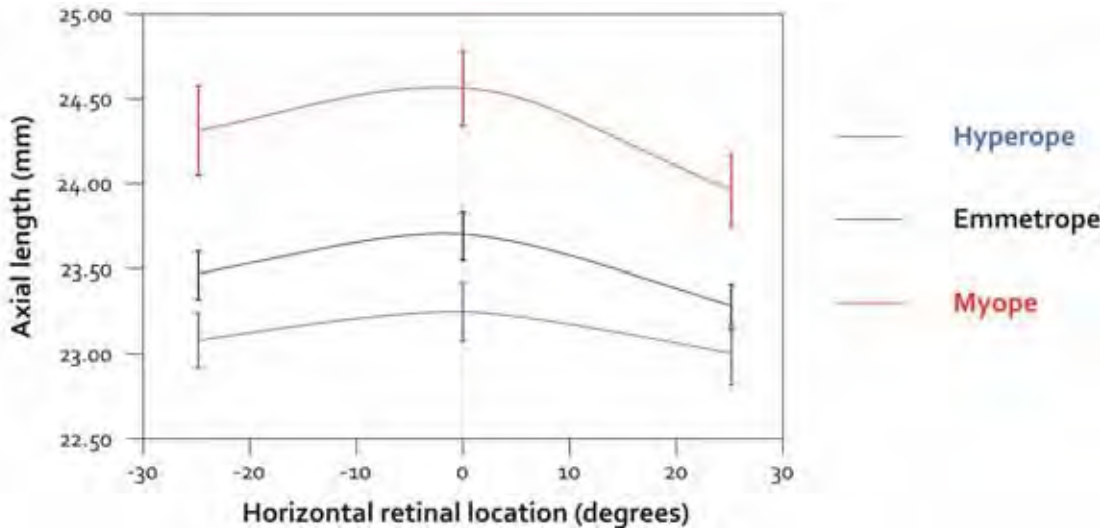


Figure 4.7 Measured central and peripheral axial length (mm; mean) in hyperopes, emmetropes and myopes using the IOLMaster. Error bars represent the standard error of the mean. Negative retinal locations denote the nasal retina (or temporal VF) while positive retinal locations denote the temporal retina (or nasal VF).

Myopes had significantly longer axial lengths centrally (p_h<0.001; p_e=0.001), nasally (p_h=0.001; p_e=0.008) and temporally (p_h=0.002; p_e=0.014) compared to hyperopes and emmetropes. Emmetropes and hyperopes had comparable axial lengths centrally, nasally and temporally (p=0.320; p=0.620; p=0.860).

There were no statistically significant differences between measured and calculated axial lengths at both nasal and temporal retina in hyperopes and myopes and in the nasal retina in emmetropes. A significant difference in axial length measurements between the two methods was found in the temporal retina in emmetropes. Differences between measured and calculated peripheral axial length from centre are shown in Table 4.5. Overall, direct measurements of peripheral axial length by the IOLMaster tended to be shorter than those determined by refraction.

	Hyperopes		Emmetropes		Myopes	
	N	T	N	T	N	T
IOLMaster	-0.17 ± 0.12	-0.26 ± 0.14	-0.23 ± 0.20	-0.41 ± 0.25	-0.25 ± 0.41	-0.60 ± 0.37
Peripheral refraction	-0.09 ± 0.37	-0.05 ± 0.40	-0.21 ± 0.40	-0.16 ± 0.40	-0.37 ± 0.41	-0.23 ± 0.46
p-value	0.347	0.150	0.706	<0.001	0.427	0.657

Table 4.5 Differences between peripheral and central axial length (mm; mean ± SD) in the nasal and temporal retina in the different refractive groups as determined by the IOLMaster and peripheral refraction. N denotes the nasal retina while T denotes the temporal retina.

**Mean difference = Mean peripheral axial length – mean central axial length*

Differences between calculated and measured nasal and temporal axial lengths in each refractive group are shown in Table 4.6. Compared to the nasal retina, the difference between calculated and measured axial length was larger in the temporal retina in all refractive groups.

	Hyperopes		Emmetropes		Myopes	
	N	T	N	T	N	T
Mean difference	0.09 ± 0.41	0.21 ± 0.45	0.02 ± 0.39	0.26 ± 0.46	-0.11 ± 0.33	0.37 ± 0.46

Table 4.6 Difference between measured and calculated axial length (mm; mean ± SD) in the nasal and temporal retina in the different refractive groups. N denotes the nasal retina while T denotes the temporal retina.

**Mean difference = Mean calculated axial length – mean measured axial length*

Bland-Altman plots revealed that axial length directly calculated from peripheral refraction was similar to that directly measured by the IOLMaster in the nasal retina (average difference of -0.01 ± 0.38). Axial length calculated from peripheral refraction underestimated axial length by an average of 0.29 ± 0.45mm in the temporal retina (Figure 4.8) compared to direct measurements by the IOLMaster.

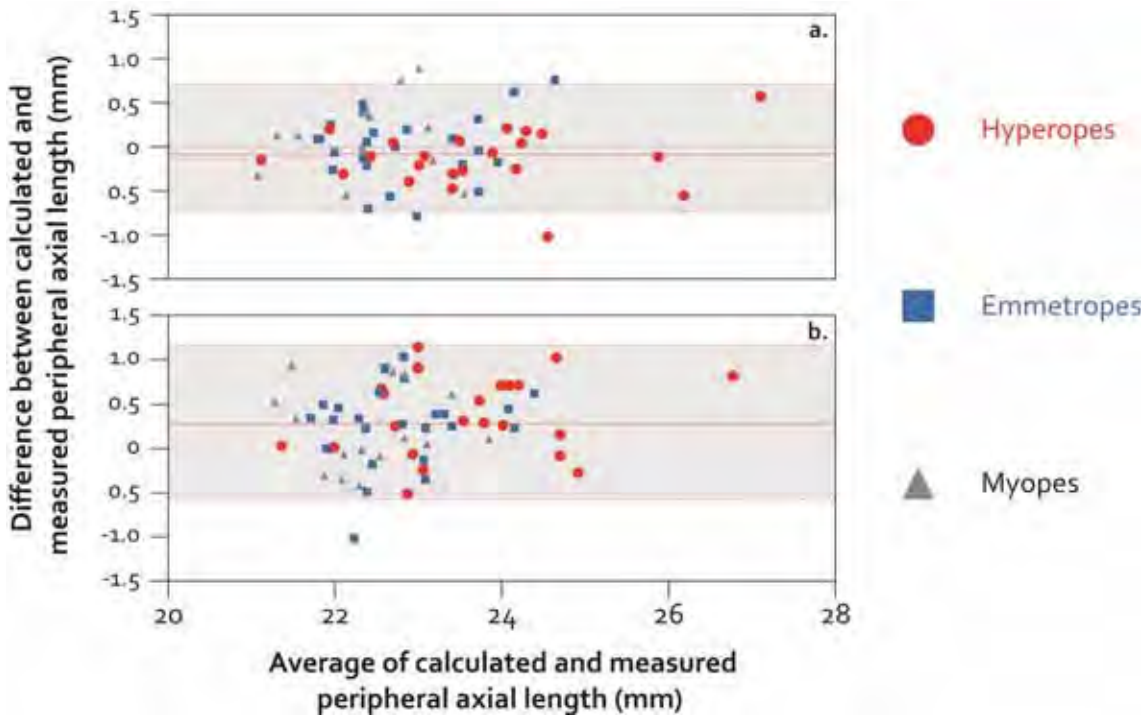


Figure 4.8 Average of calculated and measured axial length in the a) nasal and b) temporal retina plotted against their difference (mm).

Mean difference (bias) is indicated by the solid red line and the upper and lower dotted lines indicate 95% limits of agreement

4.2.4 DISCUSSION

Measuring ocular shape has assumed particular interest with growing evidence that a more prolate ocular shape as inferred from peripheral refraction can potentially increase the risk of development of myopia (Charman, 2006, Charman and Radhakrishnan, 2010, Seidemann et al., 2002, Smith, 2011, Wallman and Winawer, 2004). Hoogerheide et al (1971) first demonstrated a general trend of relative hyperopia or a more prolate ocular shape in young adult pilots who later developed myopia. Mutti et al (2007) similarly revealed relative hyperopic peripheral refraction in myopic children up to 2 years before onset of central myopia. The study described in Chapter 3 also demonstrated more relative peripheral hyperopia in East Asian myopes, who are at greater risk of development and progression of myopia, compared to Caucasian myopes of similar central refractive error. This implied that

East Asian myopes have a more prolate ocular shape compared to Caucasians of similar refractive error.

M measured in the peripheral retina has been used to infer ocular shape. The image shell is assumed to be spherical (Stone and Flitcroft, 2004). An emmetropic eye generally possesses a spherical globe hence the spherical image shell will typically coincide with the retina resulting in an emmetropic central and peripheral refractive state. A hyperopic eye is generally assumed to be more oblate in shape and in this situation the spherical image shell will sit in front of the peripheral retina resulting in a relative peripheral myopic state. Conversely, the myopic eye is often assumed to be more prolate in shape such that the spherical image shell will sit behind the retina resulting in relative peripheral hyperopia (Stone and Flitcroft, 2004) (Section 1.2.4.1).

As described in the chapter introduction, there have been conflicting reports on the use of peripheral refraction as a method of describing ocular shape. Therefore the study described in this chapter sought to determine if direct measurement of ocular shape was comparable to that inferred from peripheral refraction.

Direct measurements of axial length revealed nasal and temporal axial lengths to be shorter compared to centre indicating a relatively prolate ocular shape in agreement with previous studies (Schmid, 2003a, Schmid, 2003b, Schmid, 2011). Schmid (2011) found the temporal retina to be the steepest out of the 4 retinal locations investigated and this study similarly demonstrated a shorter axial length and hence steeper temporal retina compared to the nasal retina.

Peripheral axial length calculated from peripheral refraction was shorter compared to centre also inferring a relatively prolate ocular shape. The differences in peripheral and central axial length were most pronounced in myopes followed by emmetropes then hyperopes as determined by both direct and calculated methods. This indicated that myopes had the most prolate ocular shape. Overall, peripheral refraction tended to generate similar axial lengths as direct measurements in the nasal retina (average difference of -0.01 ± 0.38) while axial length calculated from peripheral refraction underestimated axial length by an average of 0.29 ± 0.45mm in the temporal retina. Axial length determined from refraction suggested that the nasal retina was steeper

than the temporal retina which disagrees with direct measurements which measured the temporal retina to be steeper than the nasal retina. This may be attributable to the crude calculations used to calculate peripheral axial length. The power of the eye is likely to be similar between different refractive groups. However the calculations assumed decreased eye power for myopes merely due to longer central axial lengths.

Another limitation in the methodology used is the choice of alignment method for peripheral axial length measurements which was discussed Section 4.1.4. As measurements were not taken normal to the corneal surface, the measurement beam is likely to have deviated within the eye (Atchison and Charman 2011). To allow for comparison, peripheral refraction measurements were taken with the same alignment technique as peripheral axial length measurements. Although measurement wavelengths are different between the IOLMaster and Shin-Nippon NVision-K 5001 autorefractor, it is unlikely this difference would be of significance. It was assumed that the measurement beam emitted from the autorefractor and IOLMaster would deviate in a similar manner as comparable alignment criteria were used with the two instruments.

The IOLMaster calculates axial length using an average refractive index which becomes a poorer representation of the ocular refractive index with oblique viewing. The optical path of the infrared light emitted from the IOLMaster through the crystalline lens becomes longer with more oblique viewing and the gradient refractive index property of the crystalline lens is not taken into account with eccentric measurements. Similarly, peripheral axial length calculated from peripheral refraction values also assumes a simple eye model and does not take into account changes in refractive index or individual variations of various ocular components. Taking topographic maps of the cornea and applying this information to calculation of peripheral axial length would have strengthened this study. The IOLMaster utilises diode laser light with a wavelength of 780nm while the Shin-Nippon NVision-K 5001 autorefractor uses an infrared ring of wavelength 850nm. As previously mentioned, another possible reason for the differences between techniques may be the difference in wavelength of light used in each of the two instruments although the difference is small.

MRI has been used for studying various aspects of ocular anatomy including measuring ocular shape (Atchison et al., 2004, Atchison et al., 2005a, Cheng, 1991, Cheng et al., 1992). High-resolution slice images of the eye can be obtained along any desired meridian and used to calculate the dimensions of the eye. Recent developments have allowed generation of novel colour-coded 3D images of the entire eye from 2D ocular MRI scans (Singh et al., 2006). Although MRI facilitates direct 3D measurements of the shape of the eye independent of parameter assumptions (Atchison et al., 2004), it is an expensive technique which is not readily available. Furthermore, the repeatability of scan locations is another limitation to be considered. Atchison et al (2005a) fitted nonrotationally symmetrical ellipsoids to the retinal surface of images derived from MRI and revealed oblate ocular shapes in both their emmetropic and myopic subjects. Myopic eyes were longest axially, then vertically and shortest horizontally. Myopic eyes tended to be more elongated in all meridians compared to emmetropic eyes, particularly axially. However, there was great variability of ocular shapes amongst myopic subjects (Atchison et al., 2004, Cheng et al., 1992).

Other less widely used techniques include radiography and CT scans. X-rays of 15 myopic eyes similarly demonstrated that axial length typically exceeds both vertical and horizontal diameters (Deller et al., 1947). CT scans of 255 eyes revealed that most myopes possess prolate eyes, emmetropes have either spherical or oblate eyes while hyperopes display mostly oblate eyes (Wang et al., 1994). The discrepancy in results between different studies highlights the variable nature of ocular shape. CT scans and X-rays also carry similar disadvantages to MRI. Therefore, a technique or instrument which is easily assessable and inexpensive has been sought.

In our study, peripheral refraction was found to be relatively hyperopic in all refractive groups, which disagrees with the characteristic peripheral refraction profiles described by numerous studies. A possible reason for the discrepancy is the small difference between central refractive error means in the refractive groups (+1.12 ± 0.77, +0.07 ± 0.31 and -2.20 ± 1.25 for hyperopes, emmetropes and myopes, respectively). Furthermore, refraction was measured out to only ±25°. However myopes were found

to have the greatest relative peripheral hyperopia followed by emmetropes and hyperopes, indicating that myopes may have the most prolate ocular shape and hyperopes the least, and this trend has been demonstrated in previous studies (Atchison et al., 2004, Atchison et al., 2005a, Schmid, 2003b, Stone and Flitcroft, 2004). Peripheral refraction is governed not only by ocular shape, but also by ocular surface asphericity, the gradient refractive index of the crystalline lens and ocular surface misalignment. All these parameters vary considerably between individuals and are likely to result in large individual variations in peripheral refraction measurements and thus may have contributed to the atypical peripheral refraction profile findings.

Axial length derived from peripheral refraction was found to be comparable to direct measurements in the nasal retina while it underestimated axial length by an average of 0.29 ± 0.45mm in the temporal retina. The discrepancy in measurements using the two methods in the temporal retina may be due to assumptions made in the calculations used to derived axial length. Although direct measurement of ocular shape with techniques such as MRIs, CT-scans and X-rays may provide a more accurate description of ocular shape, inferring ocular shape from peripheral refraction is more desirable due to ease of use and the cost-effective nature of the method. Incorporation of other ocular parameters, such as corneal topography, may improve axial length calculations.

4.3 CONCLUSIONS

The IOLMaster is able to produce repeatable peripheral axial length measurements, and cycloplegia had no significant effect on axial length measurements taken along the visual axis. Comparison of peripheral axial length determined by the IOLMaster and derived from peripheral refraction showed comparable results in the nasal retina. Calculations based on peripheral refraction tended to under-estimate axial length in the temporal retina relative to the IOLMaster. However, both techniques indicated that ocular shapes in the refractive groups investigated were relatively prolate with myopes showing the most and hyperopes showing the least prolate shape. This suggests that the assumption that peripheral refraction reflects ocular shape may not be an oversimplification (Dunne, 1995, Logan et al., 1995). Further investigation of assumptions made for the calculation of peripheral axial length and refinement of methodology will allow improvement of the calculations used to derive ocular shape from peripheral refraction. However, due to the ease of use and cost-effective nature of peripheral refraction measurements with a readily available open-field autorefractor, it will remain as a commonly used technique to acquire basic information about ocular shape.

CHAPTER 5

PERIPHERAL REFRACTION CHANGES WITH OK AND RGP LENS WEAR

The results from Chapter 4 demonstrated that describing ocular shape from peripheral refraction is a simple method but carries many assumptions. However, the advantages of cost effectiveness and ease of use of the autorefractor to describe ocular shape out-weigh other expensive techniques such as MRI and CT scans which are independent of confounding ocular parameters.

Peripheral refraction has been found to be relatively hyperopic in East Asian myopic children supposedly reflecting a more prolate ocular shape (Chen et al., 2010, Mutti et al., 2007). Motivation for investigation of peripheral refraction in East Asian children arises from the alarming myopia prevalence rates reported over the past decade. Reports of up to 80% of the 18 year old population being myopic have been recorded in East Asia (He et al., 2004, He et al., 2009, Lin et al., 2004). Growing trends are also apparent in Western countries with estimates of close to 40% of the United States population aged between 20 to 59 years having myopia greater than -1.0D (Vitale et al., 2008).

With growing evidence from both human (Hoogerheide et al., 1971, Mutti et al., 2007) and animal studies (Liu and Wildsoet, 2011, Smith et al., 2005, Smith et al., 2007, Smith et al., 2009b), it has been hypothesised that inducing a myopic defocus onto the retinal periphery of myopic individuals could possibly slow down or even stop the progression of myopia (Charman and Radhakrishnan, 2010, Smith, 2011, Wallman and

---

The first section of this chapter has been published: KANG, P., SWARBRICK, H. 2011. Peripheral refraction in children wearing orthokeratology and gas-permeable lenses. *Optom Vis Sci* 2011; 88: 476-82

Winawer, 2004). OK is an effective form of myopia correction which has been shown to modify the state of defocus on the peripheral retina in myopic adults (Charman et al., 2006, Queirós et al., 2010). However, the effects of OK lenses on peripheral defocus have not been investigated in myopic children. Moreover, the corneal topography and peripheral refraction effects during the initial days of OK treatment have not been ascertained.

The study described in this chapter endeavoured to confirm reports of peripheral refraction profiles in East Asian myopic children. The chapter also aimed to elucidate the effect of RGP and OK lenses on peripheral refraction to determine if the effects of OK lenses in children were similar to those reported on adults. Furthermore, the second part of this chapter describes in detail the time course of changes in corneal topography and peripheral refraction in myopic adults wearing OK lenses.

5.1 PERIPHERAL REFRACTION IN CHILDREN WEARING OK AND RGP LENSES

5.1.1 INTRODUCTION

Peripheral refraction profiles have been frequently described in adults in different refractive groups. As described in Chapter 3, distinctive refraction profiles along the horizontal meridian are found in individuals with different refractive errors. Hyperopes and emmetropes typically have relative myopia in the periphery, with hyperopes possessing greater degrees of relative peripheral myopia. Relative peripheral hyperopia is often measured in myopes.

There have been a few studies which have investigated peripheral refraction in children, particularly those who are myopic. Mutti et al (2000b) measured peripheral refraction at 30° in the nasal VF and found that emmetropic and hyperopic children had relative myopia of -0.41 ± 0.75D and -1.09 ± 1.02D in the periphery respectively. Relative peripheral hyperopia of +0.80 ± 1.29D was measured in myopic children with mean central M of -2.84 ± 2.09D. Chen et al (2010) found +0.86 ± 0.72D of relative hyperopia at 32° in the nasal VF and +0.44 ± 1.04D at 32° in the temporal VF in myopic children with mean central M of -4.09 ± 0.81D.

A longitudinal study by Mutti et al (2007) found that emmetropic children who in the future became myopic were found initially to have relative myopia in the periphery but then became relatively hyperopic in the periphery up to 2 years before the onset of axial myopia. Stable peripheral refraction profiles were discovered after the onset of myopia. Mutti et al (2007) suggested a two-phase process in ocular growth, the first stage leading up to the onset of myopia and a second more stable stage after the onset. This stability in peripheral refraction was unexpected as continued axial elongation and possible change in overall ocular shape was revealed.

OK is a procedure in which RGP lenses with a reverse geometry design are worn overnight to temporarily alter corneal curvature. The predominant corneal

topography change is the temporary flattening of the central cornea which corrects mild to moderate degrees of central myopic refraction. OK lenses alter refraction within the central ±10° (Charman et al., 2006) to ±20° (Queirós et al., 2010) VF in adults. As a result, the peripheral refractive status changes from relative hyperopia to relative myopia compared to central refraction.

The purpose of the first study reported in this chapter was to confirm peripheral refraction profiles in myopic children and investigate whether changes in peripheral refraction profiles after OK lens wear in children were similar to changes reported in adults (Charman et al., 2006, Queirós et al., 2010). It was hypothesised that myopic children will demonstrate relative peripheral hyperopia, and that peripheral refraction will become relatively myopic with OK lenses, similar to reports in myopic adults wearing OK lenses.

5.1.2 MATERIALS AND METHODS

5.1.2.1 STUDY DESIGN

This study was conducted under the auspices of a larger clinical trial, the Myopia Control Study, investigating the effects of OK and RGP lenses on the progression of myopia in myopic Asian children.

The Myopia Control Study was a 12 month prospective study in which myopic children subjects were randomly fitted with an OK lens in one eye for overnight wear and a conventional RGP lens in the other eye for daily wear. Central and peripheral refraction and topography maps were captured at baseline and after 3 months of lens wear, in the morning typically within 2 hours after removal of overnight OK lenses, and approximately 15 minutes after removal of daily wear RGP lenses.

5.1.2.2 SUBJECTS

Sixteen child subjects of East Asian ethnicity with progressive myopia were enrolled (age range 11 to 16 years; 7 M, 9 F). Approval from the institutional Human Research Ethics Committee (Approval number HREC 07032) was obtained before study commencement. All subjects and guardians gave their informed written consent to participate in the study after being informed about the nature and possible consequences of study participation. Subjects were screened before enrolment and found to be in good ocular health and free from ocular disease. Inclusion criteria required that subjects were non-RGP wearers and SCL wearers were instructed to cease CL wear for at least 24 hours. Central refraction was between -1.00DS and -4.00DS with ≤-1.50DC.

5.1.2.3 LENSES

Subjects were fitted with an OK lens (BE or BE-A; Capricornia Contact Lens, Brisbane) in one eye to be worn on an overnight basis, with no lens wear during the day. The eye assigned to wear the OK lens was determined by coin toss. Total lens diameter (TD) for the BE OK lenses was 11mm with a 6mm optic zone diameter (OZD) while the BE-A lenses had a TD of 10.6mm with a OZD of 6mm. The other eye was assigned to wear a conventional alignment fit RGP lens (J-Contour; Capricornia; 10.6mm TD) for daily wear. Both lenses were fabricated from Boston XO_2 material (Dk ISO/Fatt 141).

5.1.2.4 LENS FITTING PROTOCOL

OK trial lenses were selected through software provided by the lens manufacturer based on baseline corneal apical radius and weighted corneal sagittal height derived from corneal topography maps taken with the corneal topographer (Medmont E300, Medmont Pty Ltd, Melbourne, Australia). Appropriate OK lenses were manufactured dependent on the outcome of the overnight wear of trial lenses.

Standard RGP lenses (J-Contour; Capricornia) were ordered based on trial lenses that achieved clinically acceptable alignment fits, verified with standard rigid contact lens fitting techniques using sodium fluorescein.

5.1.2.5 LENS CLEANING AND WEARING PROTOCOL

Lenses were cleaned, rinsed and stored in new CL cases with Boston Advance rigid lens cleaner (Bausch & Lomb), Sensitive Eyes saline (Bausch & Lomb) and Boston Advance conditioning solution (Bausch & Lomb) prior to being issued to subjects. Each subject was instructed on insertion and removal of the lenses as well as cleaning and maintenance. Subjects were also educated on unbinding lenses if the OK lens was adherent on awakening. Subjects were asked to remove the OK lens on awakening and insert the RGP on the contra-lateral eye. Written instructions were given to each subject.

5.1.2.6 MEASUREMENT TECHNIQUES

5.1.2.6.1 CENTRAL AND PERIPHERAL REFRACTION

Objective central refraction was measured with the Shin-Nippon NVision-K 5001 autorefractor as described in Section 2.2.2.1.

Five peripheral refraction measurements at 10°, 20°, 30° and 35° in the nasal and temporal VF were taken and averaged as described in Section 2.2.3.1.

5.1.2.6.2 CORNEAL TOPOGRAPHY

The E300 videokeratoscope (Medmont Pty Ltd, Melbourne, Australia) was used to capture corneal topography, with data analysed using Medmont Studio 4, version 4.12.2. Four images of each eye were obtained at each visit and data for Flat K, Steep

K and corneal apical radius (r_0) were extracted from the corneal topography maps and averaged.

5.1.2.7 DATA ANALYSIS

ANOVA was carried out on central refraction and paired t-tests on corneal topography data to compare parameters before and after lens wear.

Repeated-measures ANOVA was used to analyse refraction across the horizontal meridian and doubly MANOVA was performed to assess for changes in peripheral refraction profile over time.

5.1.3 RESULTS

5.1.3.1 BASELINE VARIABLES

There was no significant difference at baseline between the OK and RGP eyes in terms of central refractive error or corneal topography (Table 5.1 and 5.2).

	OK	RGP	p value
M	-2.37 ± 1.10	-2.43 ± 0.91	0.865
J_{180}	0.19 ± 0.30	0.12 ± 0.23	0.461
J_{45}	0.05 ± 0.20	0.10 ± 0.11	0.340

Table 5.1 Central refraction (D; mean ± SD) at baseline, for OK and RGP lens-wearing eyes.

	OK	RGP	p value
Flat K	42.87 ± 1.12	42.90 ± 1.17	0.945
Steep K	44.35 ± 1.19	44.23 ± 1.37	0.803
r_o	7.79 ± 0.20	7.79 ± 0.22	0.987

Table 5.2 Flat and Steep K (D; mean ± SD) and corneal apical radius r_o (mm; mean ± SD) at baseline, for OK and RGP lens-wearing eyes.

5.1.3.2 CENTRAL REFRACTION

OK lenses significantly reduced central myopia from -2.37 ± 1.10D to -0.54 ± 0.95D after three months of wear ($p<0.001$) whereas there was no significant change in astigmatism (Table 5.3). There was no significant change in central M, J_{180} or J_{45} after three months in the eye assigned for RGP lens wear (Table 5.3).

	OK		RGP	
	Change	**p value**	**Change**	**p value**
M	1.83 ± 1.18	<0.001	-0.15 ± 0.45	0.209
J_{180}	-0.07 ± 0.20	0.158	-0.06 ± 0.23	0.322
J_{45}	-0.07 ± 0.20	0.184	0.01 ± 0.11	0.686

Table 5.3 Change (3 months – baseline) in central refraction (D; mean ± SD) after 3 months of RGP and OK lens wear.

5.1.3.3 PERIPHERAL REFRACTION

At baseline, in the eye assigned for OK lens wear, M along the horizontal meridian was myopic out to ±35° (Table 5.4). M at 20°, 30° and 35° in the temporal VF (F_{T20}=7.155, p_{T20}=0.017; F_{T30}=19.790, p_{T30}<0.001; F_{T35}=17.660, p_{T35}=0.001) and at 30° and 35° in the nasal VF (F_{N30}=7.831, p_{N30}=0.014; F_{N35}=8.975, p_{N35}=0.009) were significantly hyperopic relative to central M (Figure 5.1a). Temporal-nasal asymmetry was evident only at ±20° (F=6.335, p=0.024) (Figure 5.1a). No significant difference in M profiles was found between the eye assigned for OK and RGP lens wear at baseline (F=0.979, p=0.484). M was significantly hyperopic relative to central refraction in the RGP lens wearing eye (Figure 5.2a).

OK lenses caused a significant change in peripheral refraction after 3 months of lens wear (F=6.495, p=0.011). There was a hyperopic shift in absolute M at 10°, 20° and 30° in the temporal VF and also at 10° and 20° in the nasal VF (Table 5.4). There was an increase in myopia at 35° in the nasal VF (Table 5.4). This caused the relative peripheral hyperopia evident at baseline to change to relative peripheral myopia. Peripheral refraction was significantly myopic at all positions in the nasal VF (F_{N10}=7.588, p=0.015; F_{N20}=16.576, p=0.001; F_{N30}=18.004, p=0.001; F_{N35}=22.108, p<0.001) (Figure 5.1a). Temporal-nasal asymmetry after OK lens wear was evident at ±20°, ±30 and ±35° (F_{20}=14.060, p_{20}=0.002; F_{30}=16.298, p_{30}=0.001; F_{35}=9.178, p_{35}=0.008) (Figure 5.1a).

The eye assigned for RGP lens wear demonstrated no significant change in peripheral M after 3 months of lens wear (Figure 5.2a).

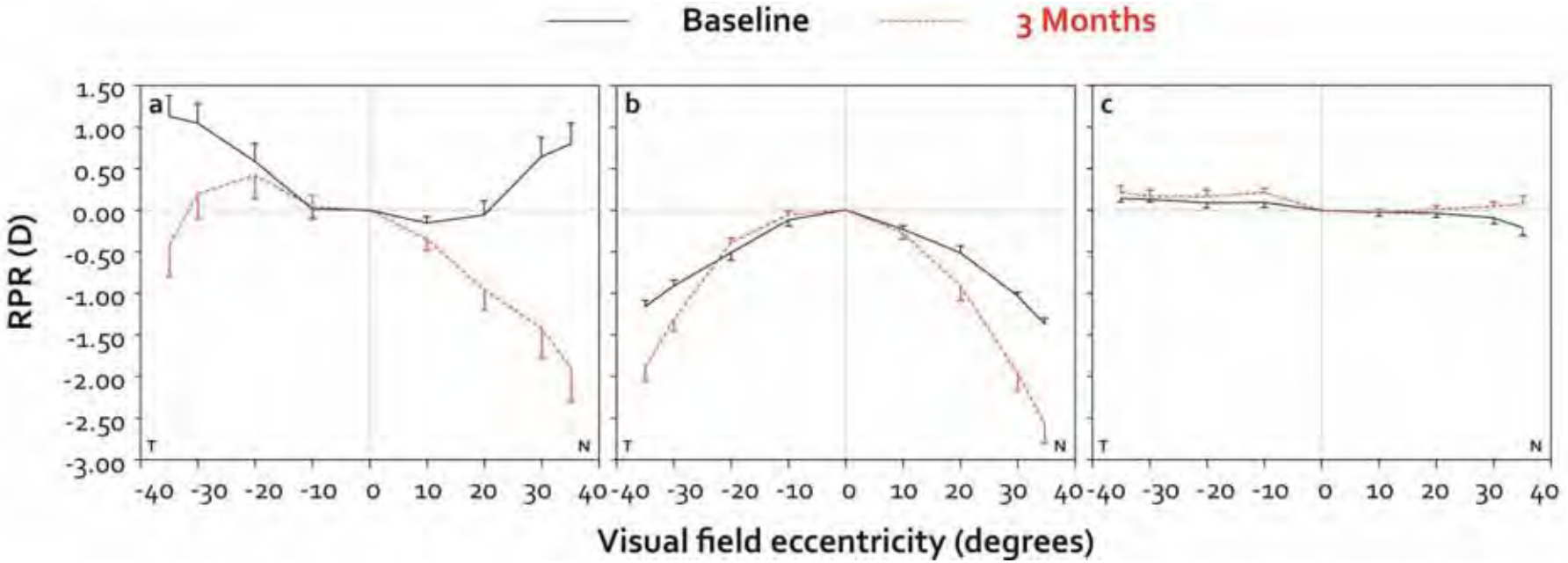


Figure 5.1 RPR profiles (D; mean) for a) M b) J_{180} and c) J_{45} before and after OK lens wear. Error bars represent the standard error of the mean. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

Position	35°T	30°T	20°T	10°T	C	10°N	20°N	30°N	35°N
Baseline	-1.23 ± 1.23	-1.31 ± 1.28	-1.77 ± 1.52	-2.35 ± 1.10	-2.37 ± 1.17	-2.49 ± 1.17	-2.41 ± 1.24	-1.70 ± 1.19	-1.56 ± 1.20
3 Months	-0.95 ± 1.57	-0.32 ± 1.43	-0.12 ± 1.59	-0.48 ± 1.08	-0.54 ± 0.95	-0.87 ± 1.16	-1.47 ± 1.33	-1.95 ± 1.54	-2.42 ± 1.59
p value	0.319	<0.001	<0.001	<0.001	<0.001	<0.001	0.008	0.436	0.018

Table 5.4 M (D; mean ± SD) along the horizontal meridian at baseline and after 3 months of OK lens wear. T denotes the temporal VF, N denotes the nasal VF and C denotes the centre.

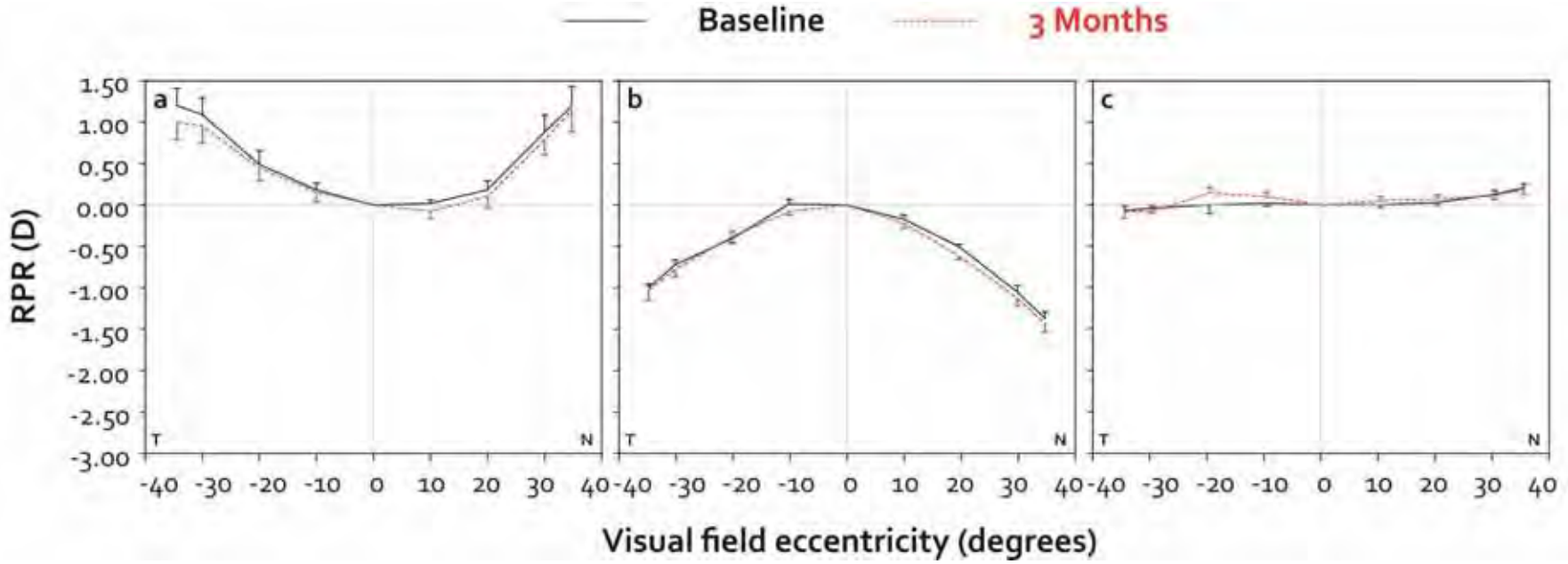


Figure 5.2 RPR profiles (D; mean) for a) M b) J_{180} and c) J_{45} before and after RGP lens wear. Error bars represent the standard error of the mean. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

At baseline, in the eye assigned for OK lens wear, J_{180} was increasingly negative at all eccentricities except at temporal 10° (F=2.926, p=0.108). Asymmetry was found at ±10° and at ±35° (F_{10}=5.289, p_{10}=0.036; F_{35}=5.436, p_{35}=0.034) with more astigmatism in the nasal VF. No significant difference in baseline J_{180} profile was found between the OK and RGP lens wearing eyes (F=0.813, p=0.610).

Three months of OK lens wear significantly altered J_{180} peripheral refraction profile (F=4.372, p=0.032). OK lenses induced a negative increase at 30° and 35° in the temporal VF and also at 20°, 30° and 35° in the nasal VF (F_{T30}=11.632, p_{T30}=0.004; F_{T35}=21.951, p_{T35}<0.001; F_{N20}=9.663, p_{N20}=0.007; F_{N30}=28.579, p_{N30}<0.001; F_{N35}=31.099, p_{N35}<0.001). Asymmetry was found after OK lens wear with greater amounts of astigmatism in the nasal VF (F_{10}=8.420, p_{10}=0.011; F_{20}=8.456, p_{20}=0.011; F_{30}=7.202, p_{30}=0.017; F_{35}=5.885, p_{35}=0.028) (Figure 5.1b).

There was a negative increase in J_{45} with eccentricity at baseline in the eye assigned for OK lens wear, with J_{45} being significantly more positive in value at temporal 30° and 35° (F=9.969, p=0.007; F=13.155, p=0.002) and more negative at nasal 35° (F=7.038, p=0.018) (Figure 5.1c). On the contrary, a positive increase in J_{45} with eccentricity was found at baseline in the eye assigned for RGP lens wear. However, this apparent difference in baseline J_{45} profiles between the OK and RGP lens wearing eyes did not reach statistical significance (F=2.214, p=0.062). Furthermore, OK lenses caused no change in J_{45} refraction profile (F=2.405, p=0.130) (Figure 5.1c).

The eye assigned for RGP lens wear exhibited no significant change in either astigmatism component after 3 months of lens wear (Figure 5.2b and c).

5.1.3.4 CORNEAL TOPOGRAPHY

OK lenses significantly flattened the central cornea as highlighted by changes in both Flat and Steep K and corneal apical radius (Table 5.5). Conversely no significant change in corneal topography was noted after 3 months of RGP lens wear (Table 5.5).

	OK		RGP	
	Change	p value	Change	p value
Flat K	-1.37 ± 0.87	<0.001	0.13 ± 0.70	0.438
Steep K	-1.52 ± 0.92	0.001	0.17 ± 0.63	0.296
r_o	0.33 ± 0.22	<0.001	-0.31 ± 0.15	0.416

Table 5.5 Change between baseline and 3 months of RGP and OK lens wear in Flat and Steep K (D; mean ± SD) and corneal apical radius r_o (mm; mean ± SD).

5.1.4 DISCUSSION

OK is not a new procedure but has become an established form of effective myopia correction with improvements in designs, lens materials and instrumentation (Swarbrick, 2006). OK not only provides individuals with clear unaided vision throughout the day, it also potentially offers myopia control (Cho et al., 2005, Walline et al., 2009) due to the changes in peripheral refraction that are induced by OK lens wear (Charman et al., 2006, Queirós et al., 2010).

Results from this study are in agreement with previous studies that have investigated peripheral refraction in myopic children (Chen et al., 2010, Mutti et al., 2007, Mutti et al., 2000b, Schmid, 2003b). M was found to be relatively hyperopic in the periphery from 20° in the temporal VF and from 30° in the nasal VF. Mutti et al (2000b) measured peripheral refraction at only 30° in the nasal VF and found relative hyperopia (spherical equivalent) of 0.80 ± 1.29D in 820 children aged between 5 to 14 years participating in the Orinda Longitudinal Study of Myopia (OLSM). Chen et al (2010) found +0.86 ± 0.72D of relative hyperopia at 32° in the nasal VF and 0.44 ± 1.04D at 32° in the temporal VF. We found relative hyperopia of 0.67 ± 0.95D at 30° in the nasal VF and 1.06 ± 0.96D at 30° in the temporal VF. Temporal-nasal M asymmetry was evident at 20° and this phenomenon has been demonstrated in

numerous studies (Charman and Jennings, 2006, Charman et al., 2006, Chen et al., 2010, Logan et al., 2004). Regional differences in scleral expansion have been suggested as a possible cause of this asymmetry (Logan et al., 2004, Schmid, 2003b, Seidemann et al., 2002). Temporal-nasal asymmetries in eye shapes have been demonstrated in modelling studies of the human eye (Logan et al., 2004, Singh et al., 2006). Charman and Atchison (2009) suggested that the asymmetry in M is likely to be a combination of angle alpha and lack of rotational symmetry in the retinal surface as angle alpha can only partly account for the asymmetry.

OK lens wear caused significant reduction of central myopia from -2.37 ± 1.17D to -0.54 ± 0.95D (Table 5.3). Peripheral M was found to be similar to the centre at all positions in the temporal VF while significantly myopic at all eccentricities in the nasal VF (Table 5.4 and Figure 5.1a). It is possible that the peripheral myopic defocus after OK which may result from the relatively unchanged peripheral corneal shape may act to slow eye growth and hence myopia progression in children.

The asymmetry in correction across the horizontal meridian may be due to temporal decentration of the OK lenses which has been previously reported (Alharbi and Swarbrick, 2003, Owens et al., 2004), and flatter nasal corneal curvature (Sheridan and Douthwaite, 1989) may be responsible for the decentration. Charman et al (2006) found that OK lenses primarily induce refractive changes within the central ±10° and cause little change beyond this point. Queirós et al (2010) similarly found myopia reduction within the central ±20°. Our study found similar results with a significant hyperopic shift in refraction between 30° temporal and 20° nasal VF while myopic defocus was induced at 30° and 35° in the nasal VF (Table 5.4).

In agreement with previous studies, J_{180} was found to increase negatively in both the nasal and temporal VF at baseline in both eyes. Asymmetry was evident with J_{180} being negatively greater in the nasal VF (Atchison et al., 2006, Atchison et al., 2005b, Calver et al., 2007, Gustafsson et al., 2001, Seidemann et al., 2002). Astigmatism is measured in reference to the fovea and the asymmetry is believed to arise from the angle between the eye's optic axis and visual axis (angle alpha) (Atchison et al., 2006, Seidemann et al., 2002). Theoretical analysis has shown J_{180} to be approximately

symmetrical about the optic axis (Charman and Atchison, 2009). Asymmetry has also been attributed to asymmetries, rotation or misalignment in the curvature of anterior optical surfaces (Barnes et al., 1987, Charman, 2005, Dunne et al., 1993). The human cornea, which is the strongest refractive surface of the eye, is not symmetrical (Sheridan and Douthwaite, 1989) and is likely to contribute to the asymmetry common in peripheral refraction measurements (Atchison et al., 2006, Charman, 2005).

J_{45} had a negative correlation with VF angle at baseline in the eye assigned for OK lens wear (Figure 5.1c). However, this was not significantly different to the J_{45} profile for the RGP lens wearing group which demonstrated a positive trend (Figure 5.2c). Although the J_{45} profiles were similar, it is unclear why a negative correlation in J_{45} was found in the eye assigned for OK lens wear whereas the opposite was evident in the eye assigned for RGP lens wear. The assignment of OK and RGP lenses was random. The dioptric range of J_{45} values across the horizontal meridian is small (range from -0.172D to 0.183D) and the difference in trends may be due to high variability in peripheral refraction (Schmid, 2003b) and ocular shape (Atchison et al., 2004, Singh et al., 2006) commonly seen in human eyes.

OK lenses negatively increased J_{180} corresponding with results from previous studies (Charman et al., 2006, Queirós et al., 2010). Queirós et al (2010) found a negative increase beyond 20° in both the temporal and nasal VF and similarly we found a negative increase from 30° in the temporal VF and 20° in the nasal VF. Refraction measurements at 30° in the temporal and nasal VFs correspond to refraction measurements taken at approximately 1.12mm on the temporal cornea and 2.38mm on the nasal cornea (Appendix A), which typically lie inside the OK treatment zone. Therefore, the increase in astigmatism seen after OK lens wear can be due to changes in optical properties (curvature and refractive index) in the cornea after lens wear, and in some instances measurements may be captured inadvertently on the steepened mid-peripheral cornea for those with smaller treatment zones (Queirós et al., 2010). Charman et al (2006) noted that the general trend seen with OK lenses was for a

reduction of the positive linear trend in J_{45} although this was not demonstrated in our study or by Queirós et al (2010).

A slowing in the axial length growth and myopia progression has been reported with OK lens wear (Cho et al., 2005, Walline et al., 2009). Walline et al (2009) suggested that the steepening ring in the mid-peripheral cornea may cause the peripheral retina to experience a myopic defocus which in turn may slow down the rate of myopia progression. Conventional forms of myopia correction, such as spectacle lenses, correct central myopia while creating a hyperopic focus on the peripheral retina (Lin et al., 2010, Tabernero et al., 2009). OK may slow down axial growth and myopia progression by correcting central myopia while leaving the peripheral retina myopic as demonstrated in this study. Cho et al (2005) proposed that higher order aberrations induced by OK lens wear may be a stimulus for the slowing of eye growth. However, the exact mechanism underlying reduced myopia progression with OK lenses is unknown. This is an active area of research.

As described in Chapter 4, peripheral refraction is believed to reflect ocular shape. There is debate on whether the relatively hyperopic defocus is simply a reflection of the prolate (or less oblate) ocular shape commonly seen in myopes (Atchison et al., 2006, Schmid, 2003b, Seidemann et al., 2002) rather than being a myopiogenic factor (Collins et al., 1995, Smith, 2011, Wallman and Winawer, 2004). Mutti et al (2007) have demonstrated that children who became myopic had significantly higher amounts of relative peripheral hyperopia before the onset of central myopia in addition to longer axial lengths. It has been argued that the increasing relative hyperopia may be due to the increasing prolate ocular eye shape evident before the onset of myopia and that this defocus may be driving myopia progression seen in these children. If the eye becomes more prolate with increasing myopia, a larger amount of relative peripheral hyperopia is expected. This potentially would act as an even stronger stimulus of axial length growth and myopia development. However, Mutti et al (2007) discovered stability in relative peripheral hyperopia in myopic children from the year of onset of myopia through to 5 years after onset despite increases in central myopia and axial length. Furthermore, it is unknown what causes

myopia progression to slow down or stop in mid to late adolescence despite the persistence of relative peripheral hyperopia. It may be that peripheral relatively hyperopic visual signals have reached a balance with the visual signals sent from the myopic fovea (Wallman and Winawer, 2004) and hence stopped axial elongation even in the presence of relative peripheral hyperopia.

In this study peripheral refraction measurements were taken in the naked eye without OK and RGP lenses in place. Thus in effect the measurements were taken in the OK lens-wearing eye with correction, while the RGP eye was measured without correction for myopia. The question therefore arises whether RPR in the RGP eye would have been altered during wear of the RGP lens. Shen et al (2010) found that, compared to the naked eye, RGP lenses on average eliminated almost all relative hyperopia evident in the periphery and increased J_{180} refraction. J_{45} was unaffected by CL wear. Only one out of the nine subjects in Shen's study had a central M refraction close to our average central M value; most of their subjects were significantly more myopic. Refraction was measured out to only ±30° and was found to be hyperopic by approximately 0.50D in the periphery in this one subject. RGP lenses reduced this hyperopia only in the nasal VF. Furthermore the RGP lenses fitted by Shen et al (2010) were of a different design to the lenses used in our study.

Despite the possibility that RGP lenses may have altered peripheral refraction during wear, we were primarily interested in demonstrating whether overnight OK lens wear induced changes in peripheral refraction as well as corneal topography. In this context, the RGP lens-wearing eye acted as a control, and no changes in corneal topography or peripheral refraction could be demonstrated during the 3 months of RGP lens wear. On the other hand, significant changes in the peripheral refraction profile and corneal topography were found in the OK lens-wearing eyes.

A potential limitation of this study is that cycloplegia was not used and therefore subjects may have exercised some accommodation during refraction measurements. The eye assigned for OK lens wear was corrected during measurements while the eye assigned for RGP lens wear was uncorrected. This could cause differences in accommodation during measurements and may account for some differences in

peripheral refraction between eyes. Target vergence varied between 0.23 to 0.46D in our clinical setting as discussed in Section 2.2.3.1.6 and it has been shown that up to 2D of accommodation has little effect on peripheral astigmatism for eccentricities of up to ±30° (Smith et al., 1988). Cycloplegia can also introduce peripheral aberrations due to pupil dilation which may affect autorefraction measurements. Additionally examiners were not masked. However with the type of data collection such as corneal topography and refraction, it is not possible to mask examiners. The measurement techniques used in this study (corneal topography and autorefraction) are objective techniques with automatic data capture and the fact that examiners were unmasked would not be likely to influence collected data.

5.2 TIME COURSE OF EFFECTS OF OK

Many have described rapid on-axis effects of OK (within a day) as well as OK effects on corneal topography and refraction over a longer period of time. Sridharan and Swarbrick (2003) demonstrated improvements in VA within only 10 mins of lens wear. Corneal curvature and refractive changes predominantly occur over the first few days of OK lens wear (Alharbi and Swarbrick, 2003, Soni et al., 2003, Stillitano et al., 2007, Wang et al., 2003a) and stability is usually apparent after 7 to 10 nights of OK lens wear (Alharbi and Swarbrick, 2003, Soni et al., 2003).

Only two studies have investigated off-axis changes in peripheral refraction with OK and peripheral refraction changes with OK treatment have been described after 7 and 14 days of lens wear (Charman et al., 2006) and after at least 1 month of OK lens wear (Queirós et al., 2010). The study described in the first part of this chapter also only described corneal topography and peripheral refraction changes after three months of OK lens wear in myopic children. These studies failed to describe the time course of changes in corneal topography and peripheral refraction during the initial critical period of treatment with OK.

The purpose of this study was to describe the time course of changes in both peripheral refraction and corneal topography in myopic adults wearing OK lenses. This will enhance our understanding of the effects of OK lenses on para-central corneal refractive power and peripheral refraction change. It is hypothesised that peripheral refraction and corneal topography change will be most prominent during the first day of OK treatment and that the rate of change in peripheral refractive and topography effect reduces with longer wear, similar to reports on changes in central refraction and apical corneal radius.

5.2.1 METHODS AND MATERIALS

5.2.1.1 STUDY DESIGN

Adult subjects were fitted with OK lenses in both eyes for overnight wear. Peripheral refraction and corneal topography maps were taken at baseline and after 1, 4, 7 and 14 days of OK lens wear, in the morning typically within 2 hours after lens removal. All measurements were taken in the right eye.

5.2.1.2 SUBJECTS

Nineteen adult subjects (age range 18-38; 12M, 7F) were enrolled. This study followed the tenets of the Declaration of Helsinki and approval was obtained from the institutional Human Research Ethics Committee (Approval number HREC 07032) before study commencement. All subjects gave their informed written consent to participate in the study after being informed about the nature and possible consequences of study participation. Subjects were screened before enrolment and found to be in good ocular health and free from ocular disease. Subjects were non-RGP wearers and SCL wearers were instructed to cease lens wear at least 24 hours prior to study commencement. Central refraction was required to be between -1.00DS and -4.00DS with ≤-1.50DC.

5.2.1.3 LENSES

Subjects were fitted with OK lenses (BE; Capricornia Contact Lens, Brisbane) to be worn on an overnight basis, with no lens wear during the day. TD for the BE OK lenses was 11mm with a 6mm OZD. Lenses were fabricated from Boston XO_2 material (Dk ISO/Fatt 141) and worn for 2 weeks.

5.2.1.4 LENS FITTING PROTOCOL

OK trial lenses were selected using software provided by the lens manufacturer which nominated trial lenses based on baseline corneal apical radius and weighted corneal sagittal height derived from the corneal topographer (Medmont E300, Medmont Pty Ltd, Melbourne, Australia). Appropriate OK lenses were manufactured dependent on the outcome of overnight trial lens wear.

5.2.1.5 LENS CLEANING AND WEARING PROTOCOL

Lenses were cleaned, rinsed and stored in new CL cases with Boston Advance rigid lens cleaner (Bausch & Lomb), Sensitive Eyes saline (Bausch & Lomb) and Boston Advance conditioning solution (Bausch & Lomb) prior to being issued to subjects. Each subject was instructed on insertion and removal of the lenses as well as cleaning and maintenance. Subjects were also educated on unbinding lenses if the OK lens was adherent on awakening. Subjects were instructed to remove lenses on awakening. Written instructions were also given to each subject.

5.2.1.6 MEASUREMENT TECHNIQUES

5.2.1.6.1 CENTRAL AND PERIPHERAL REFRACTION

Objective central refraction was measured with the Shin-Nippon NVision-K 5001 autorefractor as described in Section 2.2.2.1.

Five peripheral refraction measurements at 10°, 20°, 30° and 35° in the nasal and temporal VF were taken and averaged as described in Section 2.2.3.1.

5.2.1.6.2 CORNEAL TOPOGRAPHY

The Medmont E300 videokeratoscope was used to capture corneal topography, with data analysed using Medmont Studio 4, version 4.12.2. Four images of each eye were obtained at each visit and data for axial radius of curvature and corneal sagittal height were extracted from the corneal topography maps, and averaged for calculation of corneal refractive power at specified locations along the horizontal corneal meridian, as described in Appendix B.

5.2.1.7 DATA ANALYSIS

Corneal refractive power was calculated along a 4.3mm horizontal chord assuming a refractive index of 1.3375 (Appendix B). Simple ray tracing determined corneal locations at which each eccentric peripheral refraction measurement was centered and taken (Appendix A).

Paired t-tests were carried out on central refraction and corneal topography data to compare parameters before and after lens wear.

Repeated-measures ANOVA was used to analyse both refraction and corneal refractive power across the horizontal meridian and doubly MANOVA was performed to assess for changes in peripheral refraction and corneal refractive power profile over time.

5.2.2 RESULTS

5.2.2.1 BASELINE VARIABLES

Central refraction and corneal power at baseline and after 2 weeks of OK lens wear are shown in Table 5.6.

	M	J_{180}	J_{45}	Corneal refractive power
Baseline	-2.33 ± 1.15	-0.04 ± 0.21	0.06 ± 0.20	43.13 ± 1.30
OK	-0.20 ± 1.10	-0.02 ± 0.29	0.21 ± 0.36	41.19 ± 1.55

Table 5.6 Central refraction (D; mean ± SD) and corneal refractive power (D; mean ± SD) at baseline and after OK lens wear.

There was a significant hyperopic shift in central M ($t_{(16)}$=-5.154, p<0.001) and a reduction in corneal power (or corneal flattening) ($t_{(16)}$=14.818, p<0.001) after 2 weeks of OK lens wear. However, there was no difference in J_{180} and J_{45} apparent with OK lens wear ($t_{(16)J180}$=-0.486, p=0.633; $t_{(16)J45}$=-2.005, p=0.062).

5.2.2.2 PERIPHERAL REFRACTION

At baseline, M was myopic at all positions along the horizontal meridian. M at 35° in the temporal VF ($F=4.806$, $p=0.044$) and M at all positions in the nasal VF were significantly more hyperopic compared to centre ($F_{(1,16)N10}=7.445$, $p=0.015$; $F_{(1,16)N20}=9.665$, $p=0.007$; $F_{(1,16)N30}=10.949$, $p=0.004$; $F_{(1,16)N35}=15.281$, $p=0.001$).

There was a significant change in M over the course of 14 days of OK treatment at all positions except at 35° in the temporal VF and 20° in the nasal VF. Although doubly MANOVA analysis detected significant change, post hoc t-tests revealed no significant change in M with OK lens wear at 30° in the nasal VF. At all other positions, the general trend was a hyperopic shift in M except at 35° in the nasal VF where there was instead a myopic shift in M (Figure 5.3). From Figure 5.3, it appears that the most significant change in M occurs between baseline and day 1 and the effect becomes less dramatic between subsequent days. The statistics and p values for this analysis are shown in full in Appendix C2.

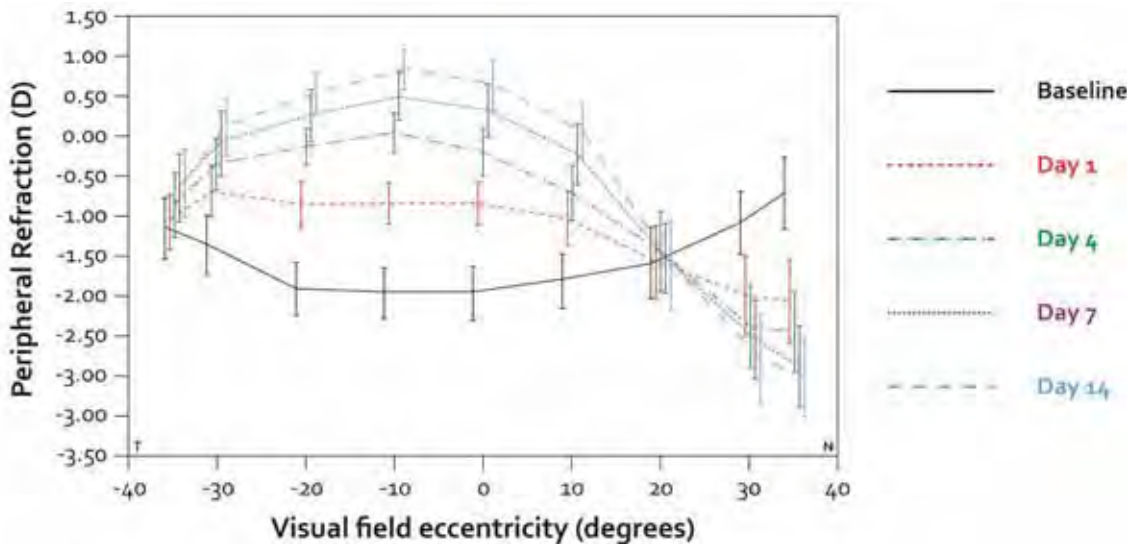


Figure 5.3 Raw M peripheral refraction profiles (D; mean) at baseline and days 1, 4, 7 and 14 of OK lens wear. Error bars represent the standard error of the mean and have been offset for clarity. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

At baseline, J_{180} was significantly more negative at all positions compared to centre ($p<0.001$) except at 10° in the temporal VF ($F_{(1,16)}=0.119$, $p=0.735$).

J_{180} profile significantly changed with OK ($F=2.585$, $p<0.001$). J_{180} did not change from baseline at 10° and 20° in the temporal VF ($F=72.368$, $p=0.063$; $F=0.691$, $p=0.601$) or at centre ($F=0.835$, $p=0.508$). At all other positions, there was a negative shift in J_{180} which became greater with longer OK treatment. From Figure 5.4, it is apparent that similar to M, the greatest change in J_{180} occurred between baseline and Day 1. The statistics and p values for this analysis are shown in full in Appendix C3.

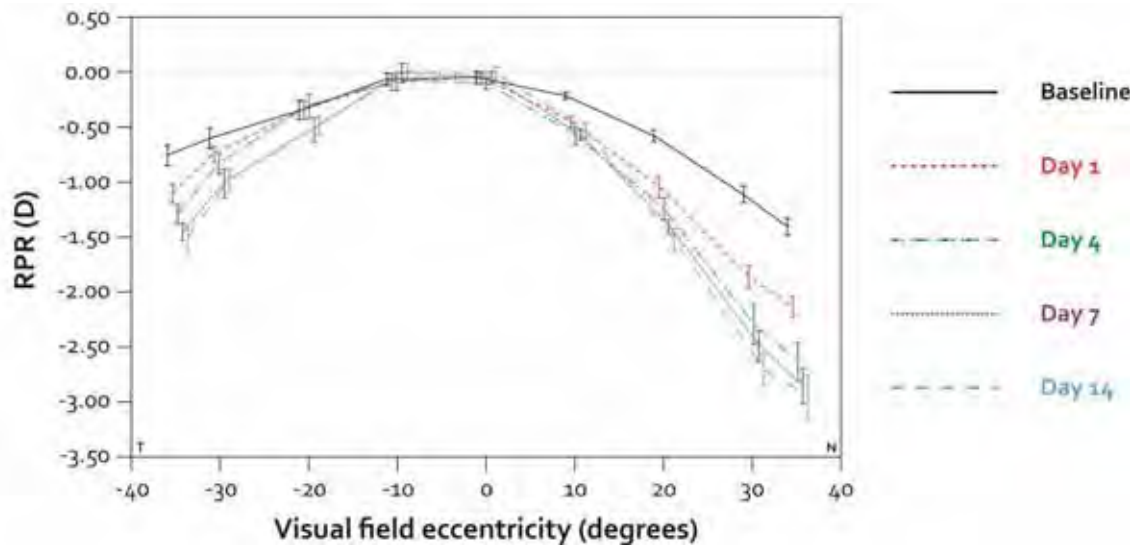


Figure 5.4 Raw J_{180} peripheral refraction profiles (D; mean) at baseline and days 1, 4, 7 and 14 of OK lens wear. Error bars represent the standard error of the mean and have been offset for clarity. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

At baseline, J_{45} was negative compared to centre at 35° in the temporal VF ($F_{(1,16)}$=6.038, p=0.026) and more positive at 20°, 30° and 35° in the nasal VF compared to centre ($F_{(1,16)N20}$=10.170, p=0.006; $F_{(1,16)N30}$=21.960, p<0.001; $F_{(1,16)N35}$=35.787, p<0.001). There was a positive linear relationship between J_{45} and eccentricity as shown in Figure 5.5. OK lens wear caused no significant change in J_{45} profile from baseline (F=1.103, p=0.327) (Figure 5.5).

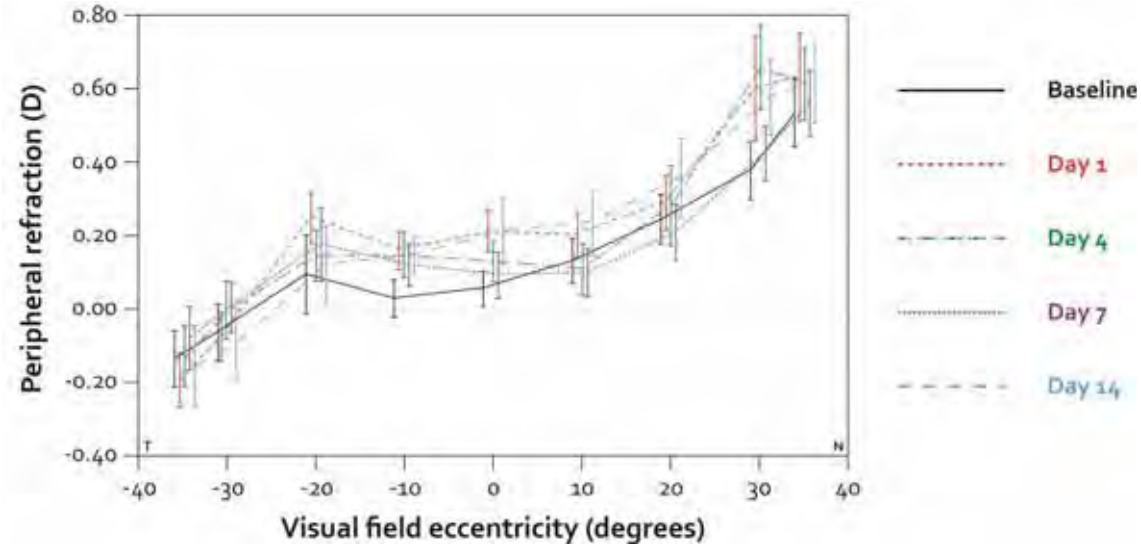


Figure 5.5 Raw J_{45} peripheral refraction profiles (D; mean) at baseline and days 1, 4, 7 and 14 of OK lens wear. Error bars represent the standard error of the mean and have been offset for clarity. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

5.2.2.3 CORNEAL REFRACTIVE POWER

At baseline, corneal refractive power was significantly greater (or steeper) at 0.5mm on the temporal cornea and 0.1mm on the nasal cornea compared to centre (0.5mm on the nasal cornea) ($F_{(1,16)0.5T}$=6.111, p=0.025; $F_{(1,16)0.1N}$=40.413, p<0.001). At all other positions on the nasal cornea, refractive power was significantly less (or flatter) compared to centre (0.5mm on the nasal cornea) (p<0.001).

OK caused significant change in corneal refractive power at all positions along the horizontal corneal chord ($F=2.667$, $p<0.001$). The general trend was a reduction in corneal power or flattening of the cornea at all positions except at 2.4mm and 2.8mm on the nasal cornea where there was increase in corneal refractive power or steepening of the cornea (Figure 5.6). The statistics and p values for this analysis are shown in full in Appendix C4.

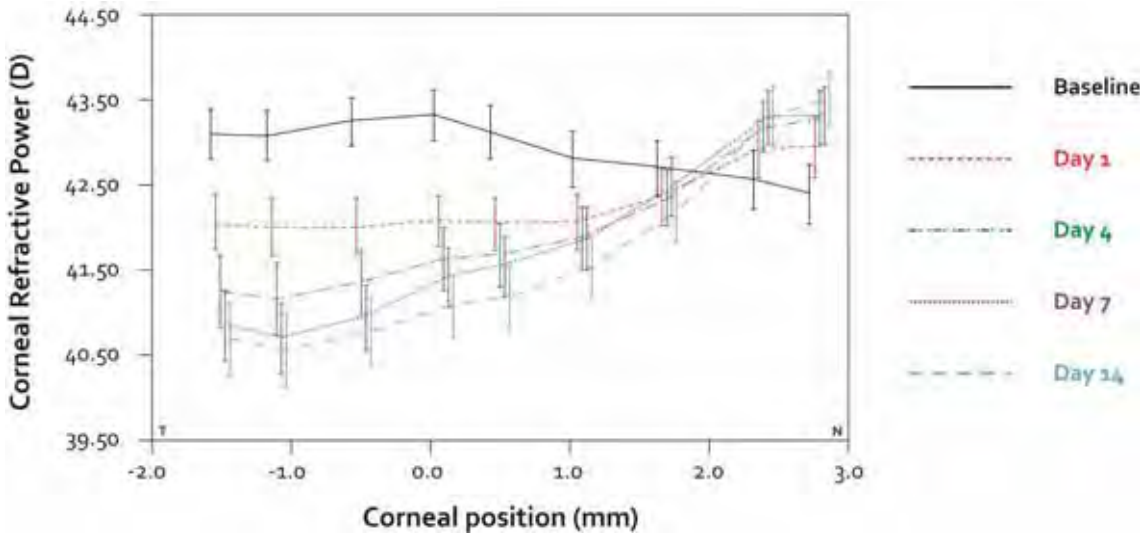


Figure 5.6 Corneal refractive power (D; mean) at baseline and days 1, 4, 7 and 14 of OK lens wear. Error bars represent the standard error of the mean and have been offset for clarity. Negative values denote the temporal cornea while positive values denote the nasal cornea.

5.2.3 DISCUSSION

OK caused a significant hyperopic shift in M across the horizontal meridian except at 20° in the nasal VF where there was no change and at 30° and 35° in the nasal VF where there was instead a myopic shift. J_{180} increased negatively in the periphery while no change in J_{45} was apparent with OK lens wear. These changes are similar to reported changes in children as described in the first section of this chapter and to published reports in myopic adults wearing OK (Charman et al., 2006, Queirós et al., 2010).

The greatest change in M and J_{180} appeared to occur during the first day of OK lens wear and changes during the subsequent days of OK treatment were not as pronounced. Correspondingly, the most appreciable change in corneal refractive power across the horizontal corneal chord occurred during the first night of OK lens wear and subsequent changes were less dramatic. These refractive and corneal topographic changes are consistent with published reports on changes in apical corneal radius and central refraction with OK. The most prominent change has been found to occur between 1-7 days of OK lens wear with stability reached after 7 to 10 days (Alharbi and Swarbrick, 2003, Nichols et al., 2000, Soni et al., 2003, Sorbara et al., 2005). The asymmetry in refractive and cornea topographic changes across the horizontal meridian may be due to temporal decentration of the OK lenses which has been previously reported (Alharbi and Swarbrick, 2003, Owens et al., 2004). A flatter nasal corneal curvature (Sheridan and Douthwaite, 1989) may be responsible for the lens decentration.

Charman et al (2006) measured peripheral refraction changes after 7 and 14 days of OK lens wear. They also found the greatest change in all refraction components occurred before 7 days of OK lens wear and only minimal change occurred between 7 and 14 days of OK treatment (Figure 5.7).

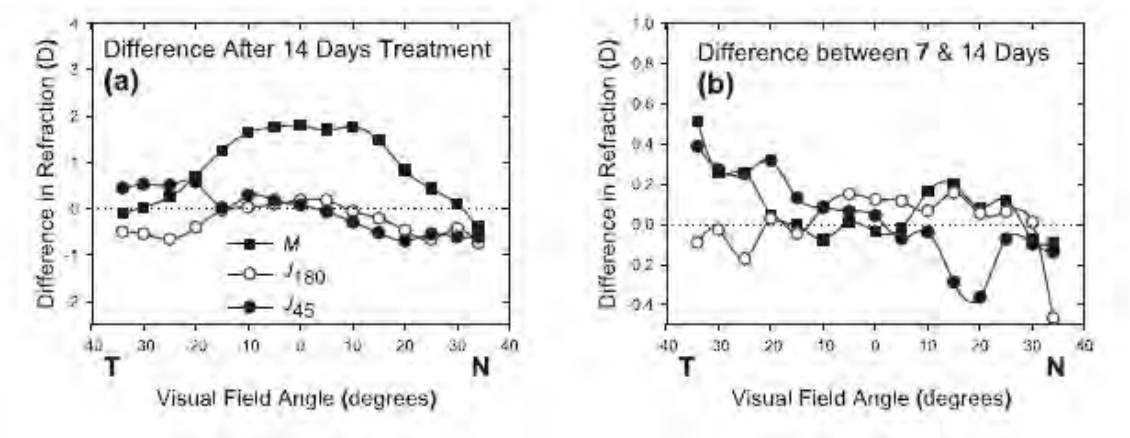


Figure 5.7 Changes from baseline in M, J_{180} and J_{45} (D; mean) after 14 days of OK (left) and difference in M, J_{180} and J_{45} between day 7 and 14 of OK treatment (right). The filled squares represent M, open circles represent J_{180} and filled circles represent J_{45} (Reproduced from Charman, W. N., Mountford, J., Atchison, D. A. & Markwell, E. L. Peripheral refraction in orthokeratology patients. *Optom Vis Sci,* 83, 641-8. Copyright (2006), with permission from Lippincott Williams & Wilkins).

It is apparent that the time course of changes in both corneal refractive power and peripheral refraction changes across the horizontal meridian after OK lens wear behaves in a similar way to reported time course of changes in apical radius and central refraction after OK. Most changes occur during the first 1-7 days of lens wear after which stability is reached.

5.3 CONCLUSION

The results from this study confirm previous reports on peripheral refraction in myopic children. Prior to lens wear, relative hyperopia was found at and beyond 20° in the temporal VF and 30° in the nasal VF. OK lenses corrected myopia in the centre and at all positions in the temporal VF while leaving the nasal VF myopic. This study demonstrates that changes in RPR after OK lens wear are similar in children as reported in adults (Charman et al., 2006, Queirós et al., 2010). Furthermore, both para-central corneal refractive power and peripheral refraction changes occurring during the course of OK treatment appear to be consistent with reported time course of changes in apical radius and central refraction.

Myopic defocus in the periphery apparent during OK treatment could act to negate the potential peripheral myopiogenic defocus apparent in most myopic eyes with conventional refractive correction. This may be a potential mechanism for myopia control with OK. Further longitudinal investigation is required to monitor peripheral refraction and axial length changes in myopic children in order to verify whether manipulation of peripheral defocus is able to slow down myopia progression.

CHAPTER 6

MANIPULATION OF PERIPHERAL REFRACTION WITH OK

The study described in chapter 5 confirmed relatively hyperopic peripheral refraction profiles in myopic children. It has been suggested that the eye responds to this hyperopic defocus by increasing in axial length in order to bring the peripheral retina in focus with the peripheral image (Charman, 2005, Charman, 2006, Charman and Radhakrishnan, 2010, Seidemann et al., 2002). Therefore correcting this relative peripheral hyperopia or inducing myopia onto the peripheral retina of myopic individuals have been proposed as methods of eliminating this potential myopiogenic factor inherent in most myopic eyes (Charman and Radhakrishnan, 2010, Smith, 2011, Wallman and Winawer, 2004). Peripheral refraction is highly variable due to variability of ocular components which contribute to peripheral refraction. Thus the same change in optical defocus is not appropriate for all myopic individuals and ideally, peripheral refraction manipulation for potential myopia control should be customised.

The results from chapter 5 demonstrated the ability of OK lenses to modify peripheral refraction in myopic children. OK corrected myopia at the centre of the VF in addition to all positions in the temporal VF but left the nasal VF myopic, similar to reports in adults (Charman et al., 2006, Queirós et al., 2010). Furthermore, the most significant para-central corneal refractive power and peripheral refraction changes appeared to occur after the first day of OK lens wear and stability was apparent after about 7 days of OK lens wear.

To be able to design OK lenses that induce specified changes in peripheral defocus appropriate for an individual, an understanding of the relationship between corneal topography change and manifest refraction is required. The first part of this chapter describes a study investigating corneal topography change and corresponding peripheral refraction change induced by OK lenses. With this knowledge, the second

half of this chapter continues to explore if specified changes in corneal topography can be imposed by manipulating different OK lens parameters.

6.1 CORRELATION BETWEEN CHANGES IN CORNEAL TOPOGRAPHY AND PERIPHERAL REFRACTION

6.1.1 INTRODUCTION

OK is a procedure involving overnight wear of reverse geometry design rigid contact lenses which modify anterior corneal curvature to temporarily correct mild to moderate degrees of myopia (Swarbrick, 2006). The relationship between changes in corneal topography and manifest refraction after OK has been investigated along the visual axis (Chan et al., 2010, Mountford, 1997). However, no other locations on the cornea have been explored to investigate this relationship. The purpose of this study is to gain a better understanding and extrapolate any relationships between para-central corneal refractive power change and corresponding peripheral refraction change after OK lens wear. This will ultimately give vital information for future development of OK lenses which can be customised to induce individualised peripheral refraction modifications. It was hypothesised that changes in corneal topography will be reflected in changes in refraction at all corresponding locations along the horizontal meridian.

6.1.2 METHODS AND MATERIALS

The same overall study design, measurement techniques and subjects were used as described in Section 5.2.1.

6.1.2.1 DATA ANALYSIS

Corneal refractive power was calculated along a 4.3mm horizontal chord (Appendix B). Simple ray tracing determined corneal locations at which each eccentric peripheral refraction measurement was centred and taken (Appendix A).

Paired t-tests were carried out on central refraction and corneal topography data to compare parameters before and after lens wear.

Repeated-measures ANOVA was used to analyse refraction across the horizontal meridian and doubly MANOVA performed to assess for changes in peripheral refraction profile between baseline and after 14 days of OK lens wear.

Linear regression analysis allowed extrapolation of relationships between the amount of para-central corneal refractive power change and corresponding peripheral refraction change.

6.1.3 RESULTS

6.1.3.1 BASELINE VARIABLES

Central refraction and corneal power at baseline and after 2 weeks of OK lens wear are reported in Section 5.2.2.1.

6.1.3.2 PERIPHERAL REFRACTION

Peripheral refraction profiles of raw M, J_{180} and J_{45} at baseline and during the course of 14 days of OK lens wear are illustrated in Section 5.2.2.2.

14 days of OK caused peripheral refraction to become relatively myopic compared to the centre at 30° and 35° in the temporal VF ($F_{(1,18)\,T30}$=5.469, p=0.031; $F_{(1,18)\,T35}$=13.381, p=0.002) and all positions in the nasal VF ($F_{(1,18)N10}$=37.881, p<0.001; $F_{(1,18)N20}$=51.972,

$p<0.001$; $F_{(1,18)N30}=83.620$, $p<0.001$; $F_{(1,18)N35}=97.934$, $p<0.001$). Asymmetry was evident at ±20° ($p=0.004$), ±30° ($p<0.001$) and ±35° ($p=0.001$). The relative M profile is shown in Figure 6.1a.

OK caused a negative increase in J_{180} at all positions except at centre, and at 10° and 20° in the temporal VF causing J_{180} profile to be more negative at 30° and 35° in the temporal VF ($F_{(1,18)T30}=5.954$, $p=0.025$; $F_{(1,18)T35}=40.291$, $p<0.001$) and all positions in the nasal VF ($F_{(1,18)N10}=17.664$, $p=0.001$; $F_{(1,18)N20}=67.258$, $p<0.001$; $F_{(1,18)N30}=137.915$, $p<0.001$; $F_{(1,18)N35}=67.791$, $p<0.001$). The relative J_{180} profile is shown in Figure 6.1b.

OK did not cause a significant change in J_{45} across the horizontal VF ($F=1.484$, $p=0.273$). The relative J_{45} profile is shown in Figure 6.1c.

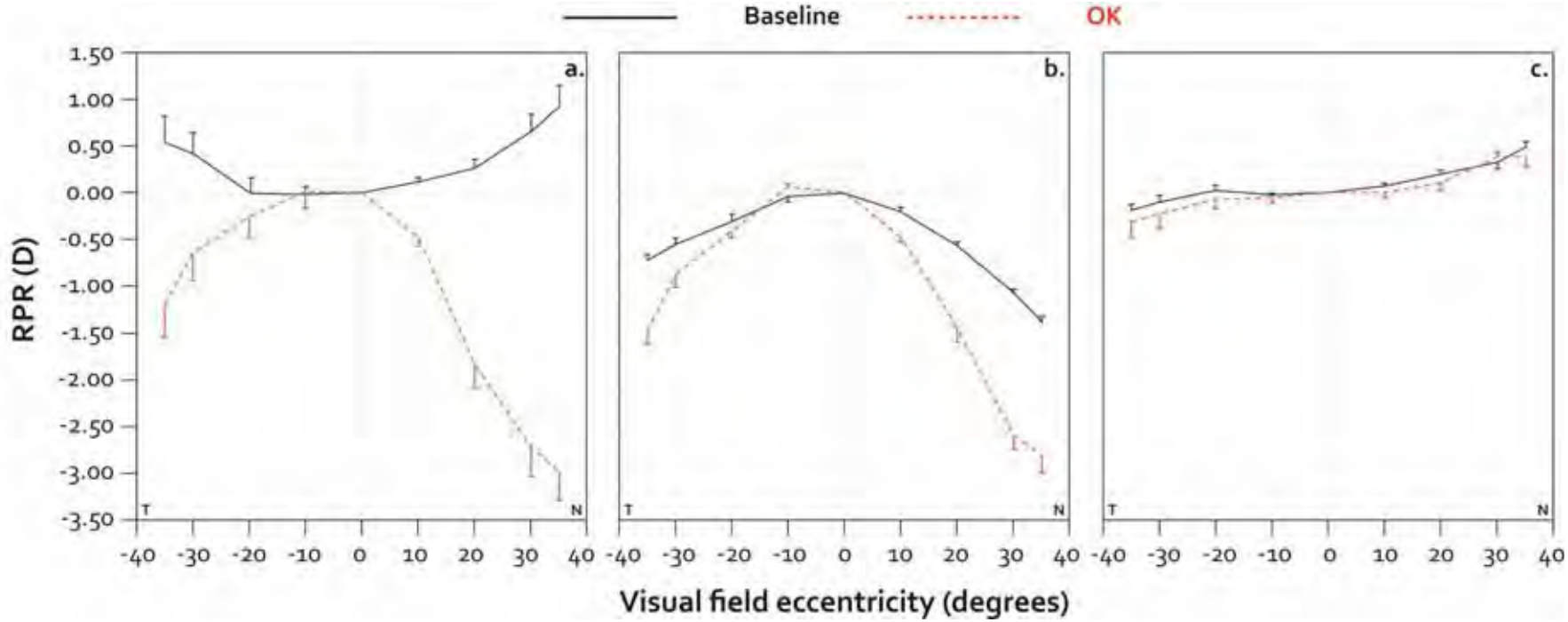


Figure 6.1 RPR profiles for a) M b) J_{180} and c) J_{45} (D; mean) at baseline and after OK lens wear. Error bars represent the standard error of the mean. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

6.1.3.3 CORNEAL REFRACTIVE POWER

Corneal refractive powers at baseline and during the course of 14 days of OK lens wear have been reported in Section 5.2.2.3. Corneal refractive power significantly changed at all positions with OK (Table 6.1).

6.1.3.4 CORRELATION BETWEEN REFRACTION AND CORNEAL REFRACTIVE POWER CHANGE

There was a significant correlation between corneal refractive power change and peripheral refraction change at all locations except at 30° and 35° in the temporal VF and 10°, 20° and 30° in the nasal VF (Figure 6.2). A decrease in corneal refractive power was coupled with a hyperopic shift in M. Corneal refractive power change overestimated manifest M change at all locations except at centre and nasal 10° where there was underestimation (Table 6.3). There was no significant difference in the amount of corneal refractive power change and corresponding peripheral refraction change at 10° in the temporal VF, centre and at 10° and 20° in the nasal VF (Table 6.2).

	-1.5/-35°	-1.1/-30°	-0.5/-20°	0.1/-10°	0.5/C	1.1/10°	1.7/20°	2.4/30°	2.8/35°
Baseline	43.00 ± 1.21	42.98 ± 1.20	43.12 ± 1.18	43.19 ± 1.24	43.01 ± 1.27	42.74 ± 1.29	42.64 ± 1.31	42.51 ± 1.34	42.35 ± 1.38
OK	40.70 ± 1.64	40.57 ± 1.69	40.69 ± 1.59	40.95 ± 1.52	41.08 ± 1.51	41.47 ± 1.46	42.09 ± 1.46	43.19 ± 1.40	43.39 ± 1.33
p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table 6.1 Corneal refractive power (D; mean ± SD) at baseline and after 14 days of OK lens wear at corresponding corneal (mm) and visual field (degrees) positions. Negative values denote the temporal cornea while positive values denote the nasal cornea (mm). Negative values denote the temporal VF, positive values denote the nasal VF and C denotes the centre.

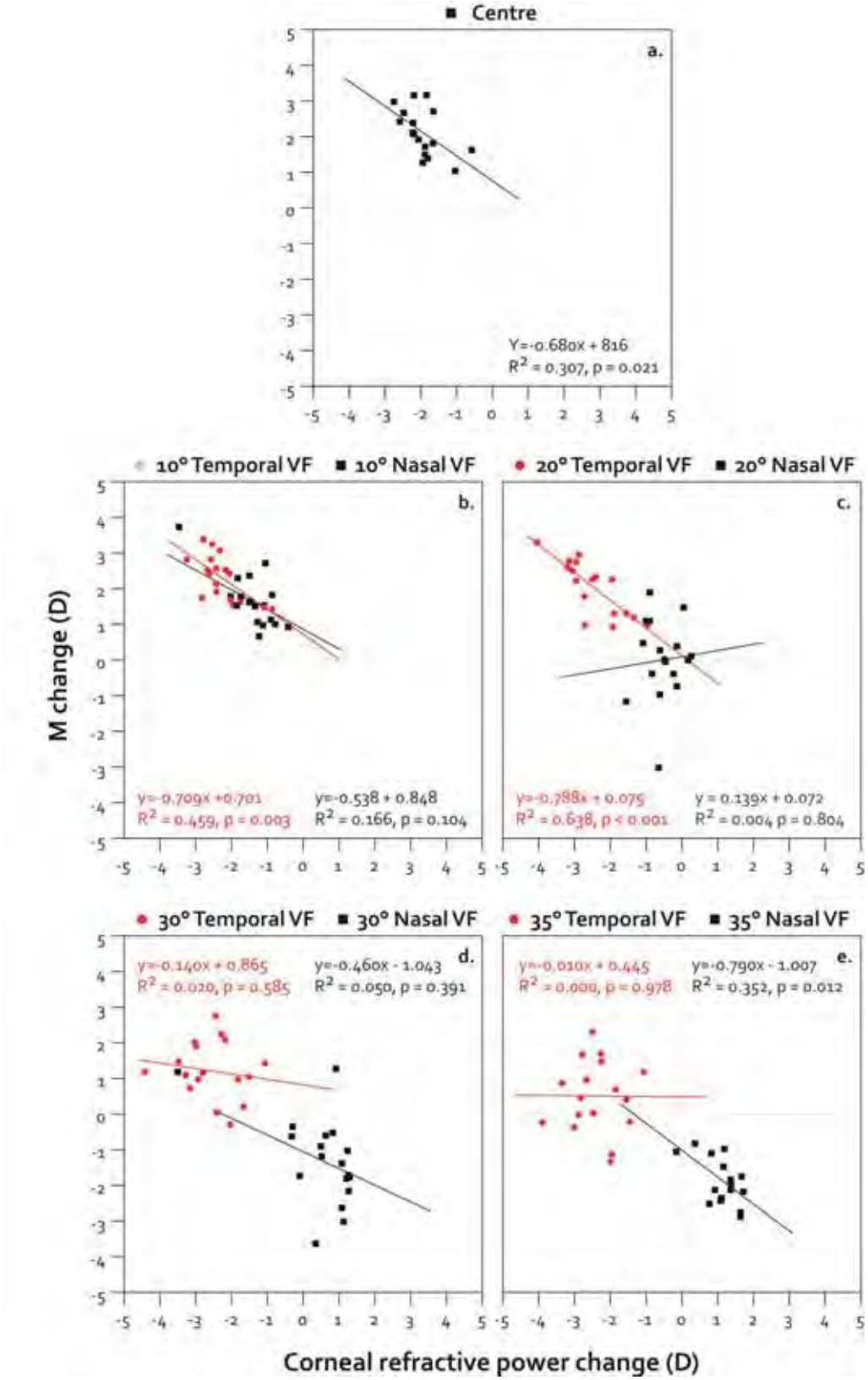


Figure 6.2 Relationship between corneal refractive power change and M change at a) centre, b) ±10°, c) ±20°, d) ±30° and e) ±35° VF.

	-1.5/-35°	-1.1/-30°	-0.5/-20°	0.1/-10°	0.5/C	1.1/10°	1.7/20°	2.4/30°	2.8/35°
M change	0.47 ± 1.00	1.22 ± 0.80	2.02 ± 0.76	2.29 ± 0.63	2.13 ± 0.66	1.53 ± 0.56	0.00 ± 1.13	-1.39 ± 1.13	-1.87 ± 0.66
Corneal change	-2.41 ± 0.72	-2.53 ± 0.83	-2.46 ± 0.77	-2.25 ± 0.60	-1.94 ± 0.54	-1.27 ± 0.42	-0.51 ± 0.49	0.75 ± 0.55	1.10 ± 0.49
Difference	1.94 ± 1.23	1.31 ± 1.07	0.45 ± 0.49	0.05 ± 0.50	0.19 ± 0.58	0.26 ± 0.55	0.51 ± 1.26	0.64 ± 1.14	0.78 ± 0.54
p value	<0.001	<0.001	0.002	0.712	0.184	0.067	0.113	0.035	<0.001

Table 6.2 Corneal refractive power change and peripheral refraction change (D; mean ± SD) after OK at corresponding locations and absolute difference between these two values (D; mean ± SD). Negative values denote the temporal VF, positive values denote the nasal VF and C denotes the centre.

Difference = |Corneal refractive power change| – |refractive error change| (D)

6.1.4 DISCUSSION

Baseline characteristics and changes in peripheral refraction and corneal refractive power across the horizontal meridian with OK lens wear have been discussed in Section 5.2.3.

The aim of this study was to investigate the relationships between peripheral refraction change and corneal refractive power change at numerous locations along the horizontal corneal meridian. Mountford (1997) investigated changes in both central refraction and apical corneal power (ACP) after OK and found high correlation between the two parameters ($\Delta Rx = 0.92\Delta ACP + 0.15D$; $R^2 = 0.91$) indicating an almost 1:1 relationship. A more recent study by Chan et al (2010) found that although there was a significant correlation between achieved myopia reduction and ACP change ($\Delta M = 0.91\Delta ACP + 0.57D$; $r = 0.78$), corneal power underestimated refractive error change by an average of 0.34 ± 0.57D. Different methodologies and corneal topographers used were proposed as explanations for difference in relationships found. A significant relationship between ACP and refractive error change was also revealed in this study ($\Delta M = 0.68\Delta ACP + 0.82D$; $R^2 = 0.31$). ACP underestimated refractive power by an average of 0.19 ± 0.58D. The same topographer (Medmont E300) was used in both the current study and that by Chan et al (2010). Possible reasons for the discrepancy include differences in study methodology whereby Chan et al (2010) compared ACP change derived from the topography map with residual non-cycloplegic subjective refraction whereas this study compared ACP change to residual non-cycloplegic objective refraction. Furthermore corneal refractive power was extracted from 0.5mm on the nasal cornea (along the visual axis) rather than at the corneal apex (the position at which apical radius is measured) as this was calculated to be the position at which the autorefractor would be centred to take central refraction measurements. Additionally, the current study was prospective while Chan et al's (2010) study was retrospective. These differences in study design could also contribute to the difference in underestimation found between the two studies, although this was clinically insignificant (<0.25D).

There were statistically significant correlations between corneal refractive power change and peripheral refractive error change at only half the investigated locations (Figure 6.2). A decrease in corneal refractive power was coupled with a hyperopic increase in manifest refraction at corresponding locations (Table 6.2). Differences in corneal refractive power change and peripheral refraction change was similar only at centre, 10° in the temporal VF and at 10° and 20° in the nasal VF. At all other positions, the amount of change in corneal refractive power and corresponding change in peripheral refraction with OK were significantly different.

At 20°, 30° and 35° in the temporal VF there was decrease in corneal power (-2.46 ± 0.77D, -2.53 ± 0.83D and -2.41 ± 0.72D respectively) reflected by a disproportionate small hyperopic shift in peripheral refraction (2.02 ± 0.76, 1.22 ± 0.80D and 0.47 ± 1.00D respectively). At 20° in the nasal VF, there was a decrease in corneal power (-0.51 ± 0.49D) with no significant change in peripheral refraction (0.00 ± 1.13D). Conversely at 30° in the nasal VF, there was a small increase in corneal refractive power (0.75 ± 0.55D) with a corresponding larger myopic shift in M (-1.39 ± 1.13D). It is unclear why stronger relationships were not evident at these locations. Average refractive index of n=1.3375 is adopted by the Medmont topographer and changes in the refractive index and thickness of cornea after OK could be a potential source of error contributing to the poor relationships found. Peripheral refraction measurements with the autorefractor are averaged over a 2.3mm diameter area and hence may not reflect the refractive value at the point of interest at which corneal refractive power was extracted. Furthermore, as measurements are taken obliquely, it is likely that peripheral refraction measurements would not have been taken at the exact same position on the retina compared to baseline measurements due to optical changes induced by OK. Relatively complex peripheral ray tracing would be required to determine exactly which parts of the retina correspond to refraction measurements taken before and after OK lens wear.

As demonstrated in Chapter 4, ocular shape can possibly be inferred from peripheral refraction and has also been found to be highly variable amongst individuals (Atchison et al., 2004, Schmid, 2003b, Singh et al., 2006). Thus required changes in peripheral

defocus in order to correct or induce myopia onto the peripheral retina will vary amongst individuals. Current bifocal SCLs which have been used to induce myopic defocus in the periphery are available in limited peripheral power parameters (Anstice and Phillips, 2011) which may not be suitable for all individuals. Individualised changes in peripheral defocus may be the best mode of potential myopia control (Charman and Radhakrishnan, 2010, Smith, 2011, Wallman and Winawer, 2004). This study demonstrates that there are significant relationships between corneal refractive power change and refractive error change at some para-central corresponding locations. A larger sample size is required to confirm the results of this study and inclusion of anterior corneal curvature data such as apical corneal radius instead of assumptions used may determine reasons why some locations demonstrate stronger relationships than others. The statistical power achieved in this study was only 0.49. To be able to achieve a power of 0.8, another 20 subjects are required. Peripheral ray tracing would also strengthen the results of this study.

6.2 OK PARAMETERS AND PERIPHERAL REFRACTION

6.2.1 INTRODUCTION

With the growing speculation of potential myopia control with peripheral defocus manipulation, there is now a demand for optical devices that will induce myopic defocus or correct the refractive error in the peripheral retina of myopes while correcting central myopia. Currently multifocal SCLs with limited set parameters are commercially available including the Anti-Myopia Contact Lens (AMCL; developed by the Brien Holden Vision Institute, Sydney, Australia) and MiSight® lens (Coopervision; New York, USA). Because of the high individual variability of peripheral refraction, lenses which can induce individualised peripheral refraction changes are required.

OK lenses have traditionally been used for correcting myopia and only recently have been found to potentially reduce myopia progression compared to other means of myopia correction (Cho et al., 2005, Kakita et al., 2011, Swarbrick et al., 2010, Walline et al., 2003). It has been proposed that the changes in peripheral defocus induced by OK lenses could underlie the anti-myopiogenic effect evident with OK lens wear (Charman et al., 2006, Walline et al., 2009). However there has been no investigation to determine if OK can be used to induce targeted changes in peripheral defocus. The effect of changing OK lens parameters on peripheral refractive error is unknown. This study aimed to investigate the effects of changes in OZD and peripheral tangent in OK lenses on peripheral refraction in myopic individuals.

The BE OK lenses used in the studies reported in this thesis use a tangent in the periphery of the OK lens to distribute the pressure of the lens over a wide area (for comfort) in addition to aiding centration. The peripheral tangent is defined by the cone angle (Ø) as well as the point of corneal contact, P (Figure 6.3).

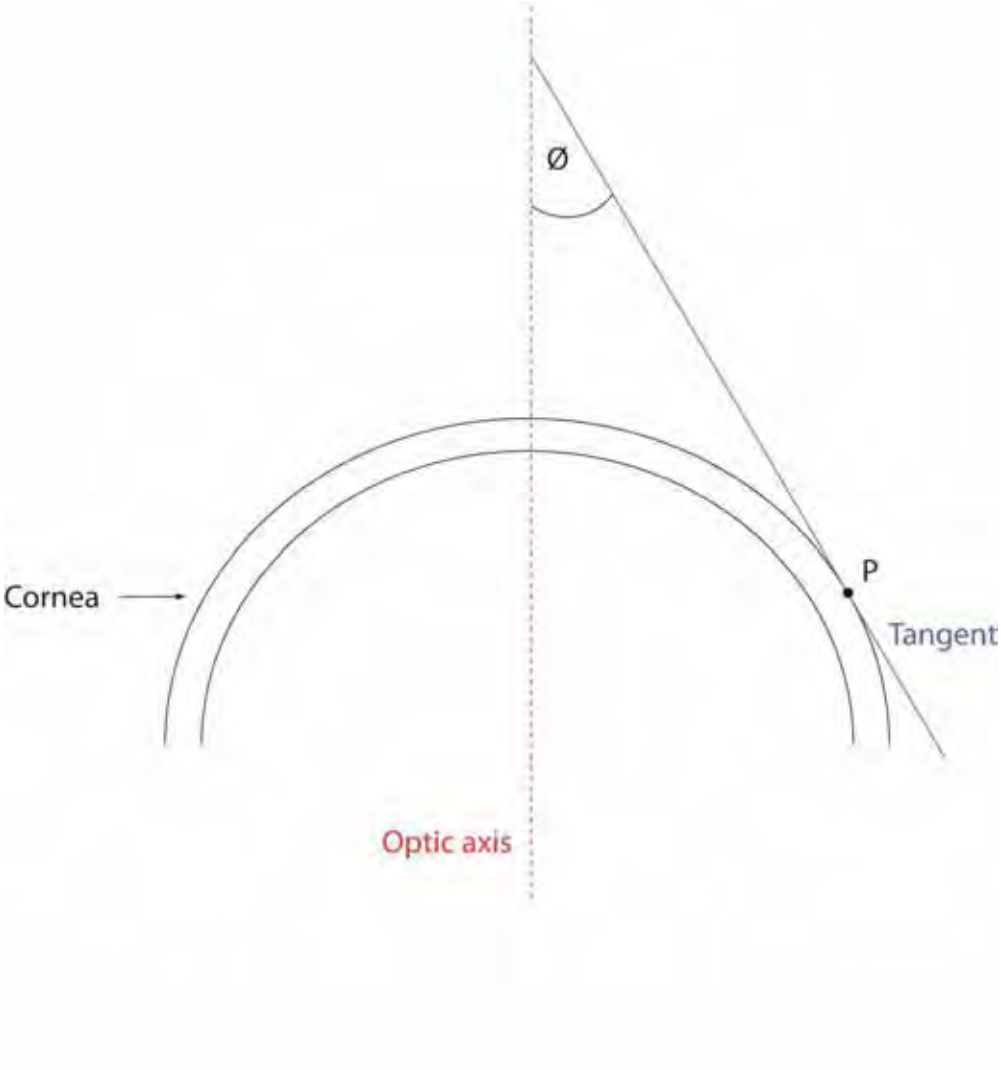


Figure 6.3 Diagram of the formation of the tangent from the cone angle (Ø) and point of contact (P) between the OK lens and cornea (Adapted from Mountford et al, 2004).

Standard BE lenses have ¼ tangent which means that they are constructed such that the tangent meets the cornea at along ¼ of its width. The lenses can be modified such that the point of contact is set at either 1/3 or 1/2 of the tangent width. As shown in Figure 6.4, as P is moved further along the width of the tangent, Ø becomes smaller and thus the chord of contact between the cornea and OK lens correspondingly becomes larger.

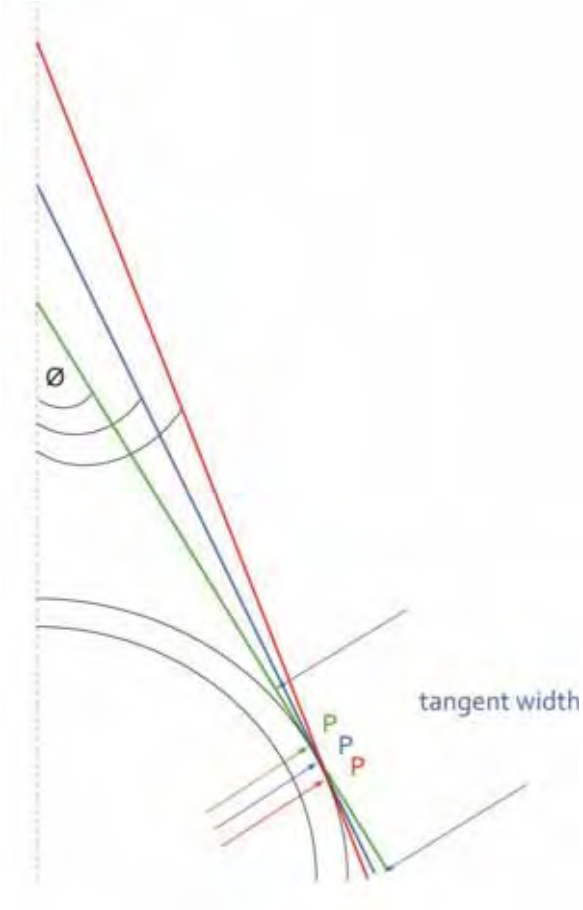


Figure 6.4 Illustration of change in peripheral lens tangent and corresponding change in Ø. The green line represents the point of contact along ¼ of the tangent width, the blue line represents point of contact along 1/3 of the tangent width and the red line represents the point of contact along a ½ of the tangent width

It was hypothesised that a smaller OZD would create a smaller zone of central refractive correction and a steeper tangent would increase the amount of para-central corneal steepening which in turn would increase the amount of myopia induced in the periphery.

6.2.2 METHODS AND MATERIALS

6.2.2.1 STUDY DESIGN

The study was divided into two lens wearing phases. During the first phase (Phase 1), subjects were fitted with standard OK lenses in both eyes for overnight wear. Central and peripheral refraction and corneal topography measurements were taken at baseline (baseline 1) and after 1, 4, 7 and 14 days of lens wear. Subjects were then instructed to cease lens wear for at least 2 weeks for a wash out period. Subsequently, subjects were asked to return for the second lens wearing phase (Phase 2) where they were refitted with another set of OK lenses where one eye was randomly chosen to wear an OK lens with a smaller OZD and the other eye fitted with a lens with a steeper peripheral tangent. Once again the same measurements were taken at baseline (baseline 2) and after 1, 4, 7 and 14 days of overnight lens wear.

6.2.2.2 SUBJECTS

Seventeen subjects (age range 18-38; 10M, 7F) were enrolled. This study followed the tenets of the Declaration of Helsinki and approval from the institutional Human Research Ethics Committee (Approval number HREC 08270) was obtained before study commencement. All subjects gave their informed written consent to participate in the study after being informed about the nature and possible consequences of study participation. Subjects were screened before enrolment and found to be in good ocular health and free from ocular disease. Inclusion criteria required that subjects were non RGP wearers and SCL wearers were instructed to cease CL wear for at least 24 hours prior to study commencement. Central refraction was between -1.00DS and -4.00DS with ≤-1.50DC.

6.2.2.3 LENSES

Subjects were fitted with two lenses in each eye, a pair of lenses for each of the lens-wearing phases. Lenses used in Phase 1 of this study are standard BE OK lenses. The eyes were randomly selected to wear lenses with altered OZD or tangent in either the right or left eye in Phase 2 of the study.

OZD comparison	Phase 1 - OZD of 6mm, ¼ tangent in periphery
	Phase 2 - OZD of 5mm, ¼ tangent in periphery
Tangent comparison	Phase 1 - OZD of 6mm, ¼ tangent in periphery
	Phase 2 - OZD of 6mm, ½ tangent in periphery

All lenses had a TD of 11mm and were fabricated from Boston XO_2 material (Dk ISO/Fatt 141).

6.2.2.4 LENS FITTING PROTOCOL

The parameters used in Phase 1 of the study were selected from OK trial lenses which were chosen using software provided by the lens manufacturer. Trial lenses were determined from baseline corneal apical radius and weighted corneal sagittal height derived from the corneal topographer (Medmont E300, Medmont Pty Ltd, Melbourne, Australia). Appropriate OK lenses were manufactured dependent on the outcome of overnight lens wearing trials.

For Phase 2 of the study, corneal topography maps were sent to the manufacturer to produce OK lenses with the same fitting overall characteristics as the first lens but including either the OZD or tangent modification. Changing the OZD and tangent required other lens parameters to also be modified in order to maintain the same sagittal height as lenses used in Phase 1. Any changes in corneal topography or peripheral refraction between Phase 1 and Phase 2 for each eye would then be a reflection of either OZD or tangent change.

6.2.2.5 LENS CLEANING AND WEARING PROTOCOL

Lenses were cleaned, rinsed and stored in new CL cases with Boston Advance rigid lens cleaner (Bausch & Lomb), Sensitive Eyes saline (Bausch & Lomb) and Boston Advance conditioning solution (Bausch & Lomb) prior to being issued to subjects. Each subject was instructed on insertion and removal of the lenses as well as cleaning and maintenance. Subjects were also educated on unbinding lenses if the OK lens was adherent on awakening. Subjects were asked to remove the OK lens on awakening. Written instructions were also given to each subject.

6.2.2.6 MEASUREMENT TECHNIQUES

6.2.2.6.1 CENTRAL AND PERIPHERAL REFRACTION

Central objective refraction was measured with the Shin-Nippon NVision-K 5001 autorefractor as described in Section 2.2.2.1.

Five peripheral refraction measurements at 10°, 20°, 30° and 35° in the nasal and temporal VF were taken and averaged as described in Section 2.2.3.1.

6.2.2.6.2 CORNEAL TOPOGRAPHY

The Medmont E300 videokeratoscope was used to capture corneal topography, with data analysed using Medmont Studio 4, version 4.12.2. Four images of each eye were obtained at each visit and data for axial radius of curvature and sagittal height were extracted from the corneal topography maps, averaged and used to calculate corneal refractive power along the horizontal corneal meridian as described in Appendix B.

6.2.2.7 DATA ANALYSIS

Corneal refractive power was calculated along a 4.3mm horizontal chord (Appendix B). Simple ray tracing determined corneal locations at which each eccentric peripheral refraction measurement was centred (Appendix A).

Paired t-tests were carried out on central refraction and corneal topography data to compare parameters before and after lens wear.

Repeated-measures ANOVA was used to analyse refraction and corneal topography across the horizontal meridian and doubly MANOVA performed to assess for changes in peripheral refraction and corneal topography profile with OK lens wear and to analyse the effects of change in both OZD and tangent.

The diameter of the corneal flattening zone after OK lens wear or treatment zone diameter (TZD) is defined as the horizontal chord between the points of no change in refractive power from the baseline corneal topography (Mountford, 2004a). The maps that were closest to the average of the 4 taken at each session were selected. The point of intersection of no change between two corneal refractive power maps at baseline and after 14 days of OK lens was identified to determine TZD. Paired t-test was performed to compare TZD size between OK with a 6mm OZD (Phase 1) and a 5mm OZD (Phase 2).

6.2.3 RESULTS

6.2.3.1 OZD COMPARISON

6.2.3.1.1 BASELINE VARIABLES

Central refraction and corneal refractive power at the commencement of Phase 1 (baseline 1) and at the commencement of Phase 2 after washout (baseline 2), in the eye wearing lenses comparing OZD are shown in Table 6.3.

	Refraction			Corneal refractive power
	M	J_{180}	J_{45}	
Baseline 1	-2.17 ± 1.24	0.09 ± 0.25	0.06 ± 0.19	43.25 ± 1.29
Baseline 2	-2.06 ± 1.28	0.07 ± 0.20	0.06 ± 0.17	43.24 ± 1.31

Table 6.3 Central refraction (D; mean ± SD) and central corneal refractive power (D; mean ± SD) at baseline 1 and baseline 2.

There were no significant differences in refraction components between baseline 1 and 2 ($F_{(1,16)M}$=4.159, p=0.058; $F_{(1,16)J180}$=0.164, p=0.691; $F_{(1,16)J45}$=0.001, p=0.978). Furthermore, there was no significant difference in central corneal refractive power between baseline 1 and 2 ($t_{(16)}$=0.083, p=0.935).

6.2.3.1.2 PERIPHERAL REFRACTION

M was myopic at all positions along the horizontal meridian at both baseline 1 and 2 (Table 6.4). M was relatively more hyperopic at 30° and 35° in the temporal VF ($F_{(1,16)T30}$=4.563, p=0.048; $F_{(1,16)T35}$=6.852, p=0.019) and at 10°, 30° and 35° in the nasal VF ($F_{(1,16)N10}$=5.631, p=0.031; $F_{(1,16)N30}$=6.944, p=0.018; $F_{(1,16)N35}$=8.673, p=0.010) at baseline 1. Similarly, M was relatively more hyperopic compared to centre at 30° and 35° in the temporal VF ($F_{(1,16)T30}$=9.101, p=0.008; $F_{(1,16)T35}$=11.251, p=0.009) and at 30° and 35° in the nasal VF ($F_{(1,16)N30}$=8.579, p=0.010; $F_{(1,16)N35}$=9.989, p=0.006) at baseline 2. There was no difference in M along the horizontal meridian between baseline 1 and 2 (F=0.527, p=0.0.637).

J_{180} was significantly more negative compared to the centre at all positions ($p<0.05$) except at 10° in the temporal VF at both baseline 1 and 2 ($F_{(1,16)BL1}$=0.10, p=0.920; $F_{(1,16)BL2}$=0.00, p=0.993. Furthermore, there was no difference detected in J_{180} profiles between baseline 1 and 2 (F=0.184, p=0.990).

No significant variation in J_{45} compared to the centre across the horizontal meridian was detected at baseline 1 ($F_{(1.430,22.882)}$=0.903, p=0.388) or baseline 2 ($F_{(1.671,26.737)}$=3.134, p=0.068). Additionally, there was no significant difference in J_{45} profiles between baseline 1 and 2 (F=0.847, p=0.598).

The RPR profiles for M, J_{180} and J_{45} at baseline 1 and 2 are shown in Figure 6.5 a, b and c respectively.

	-35°	-30°	-20°	-10°	C	10°	20°	30°	35°
Baseline 1	-1.68 ± 1.31	-1.82 ± 1.25	-2.15 ± 1.26	-2.28 ± 1.24	-2.17 ± 1.24	-2.06 ± 1.28	-1.98 ± 1.43	-1.63 ± 1.63	-1.45 ± 1.84
Baseline 2	-1.68 ± 1.39	-1.72 ± 1.34	-2.00 ± 1.35	-2.15 ± 1.33	-2.06 ± 1.28	-1.94 ± 1.34	-1.95 ± 1.29	-1.67 ± 1.53	-1.69 ± 1.69

Table 6.4 Objective M (D; mean ± SD) along the horizontal meridian at baseline 1 and 2. Negative eccentricities denote the temporal VF, positive eccentricities denote the nasal VF and C denotes the centre.

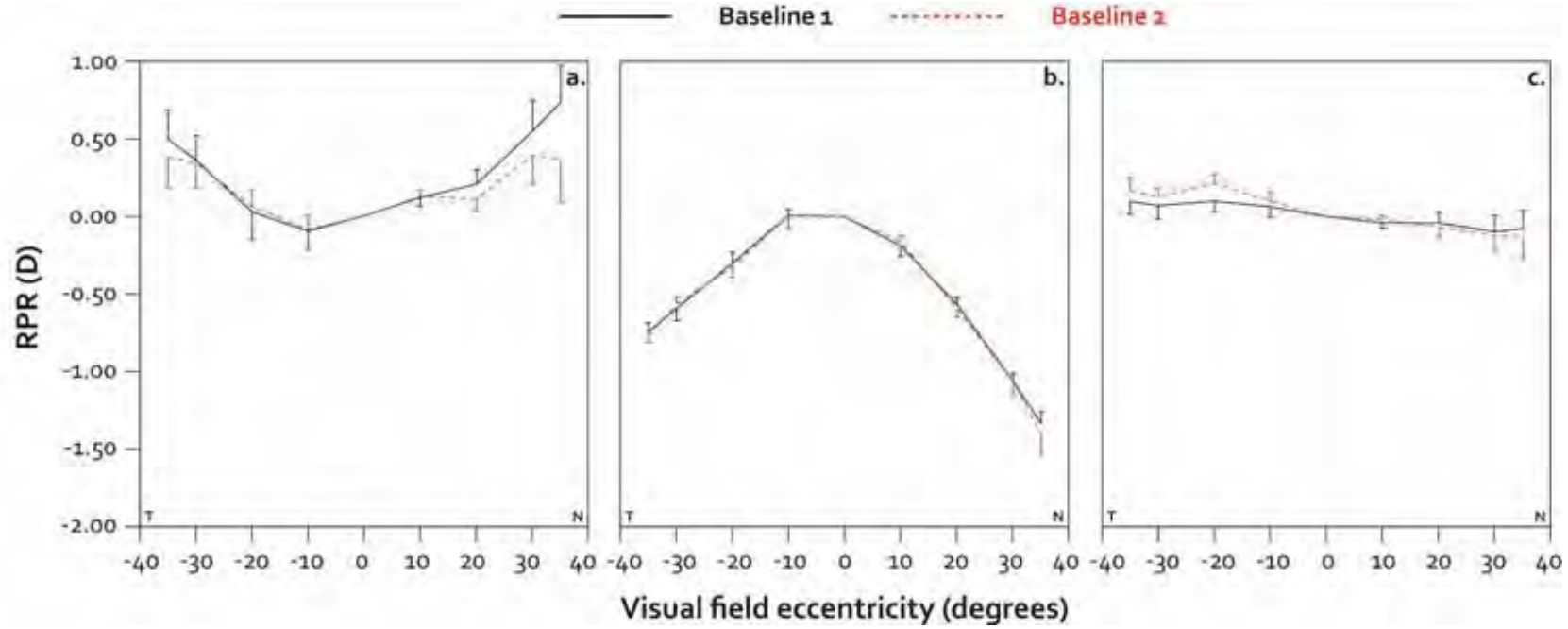


Figure 6.5 RPR profiles (D; mean) for a) M b) J_{180} and c) J_{45} at baseline 1 and 2. Error bars represent the standard error of the mean. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

In phase 1 of the study, peripheral M profile changed from baseline 1 with a 6mm OZD OK lens ($F=2.856$, $p<0.001$) (Figure 6.6). No significant change in M from baseline was evident at 30° or 35° in the temporal VF ($F_{T30}=2.146$, $p=0.127$; $F_{T35}=1.338$, $p=0.277$) or at 20° in the nasal VF ($F=1.778$, $p=0.139$). Although doubly MANOVA analysis detected significant change, post hoc t-tests revealed no significant change in M from baseline with OK lens wear at 30° in the nasal VF ($p>0.05$). The general trend at all other positions except at 35° in the nasal VF was a hyperopic shift in M which increased with longer periods of OK lens wear. At 35° in the nasal VF, there was a myopic shift in M (Figure 6.6). The statistics and p values for this analysis are shown in full in Appendix C5.

There was no significant difference in change in raw peripheral M profile between 6mm (Phase 1) and 5mm (Phase 2) OZD OK lenses ($F=1.111$, $p=0.307$) (Figure 6.6).

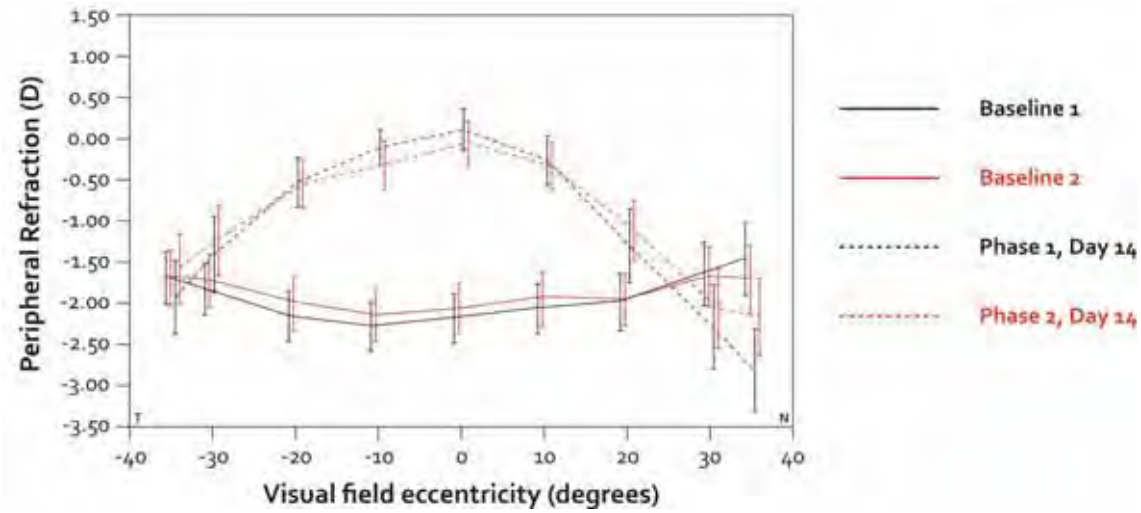


Figure 6.6 Raw M peripheral refraction profiles (D; mean) along the horizontal meridian at baseline 1 and 2 and after 14 days of OK lens wear with a 6mm (Phase 1) and a 5mm (Phase 2) OZD. Error bars represent the standard error of the mean and have been offset for clarity. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

Furthermore, there was no significant difference in relative M profile shapes with a 6mm OZD OK lens (Phase 1) or a 5mm OZD OK lens (Phase 2) ($F=1.245$, $p=0.172$) (Figure 6.7).

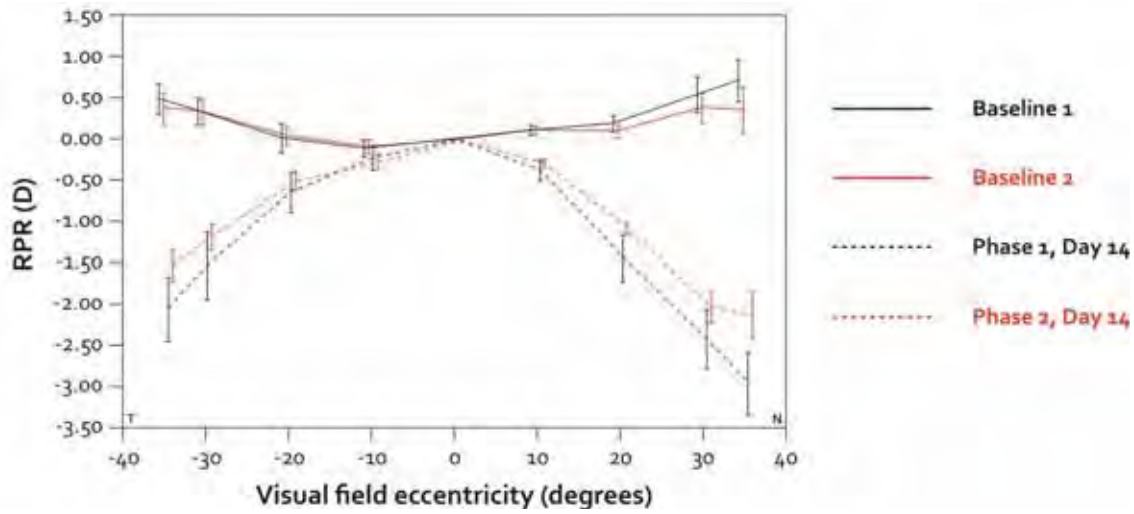


Figure 6.7 Relative peripheral M profiles (D; mean) along the horizontal meridian at baseline 1 and 2 and after 14 days of OK lens wear with a 6mm (Phase 1) and a 5mm (Phase 2) OZD. Error bars represent the standard error of the mean and have been offset for clarity. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

In phase 1 of the study, J_{180} profile significantly changed with a 6mm OZD OK lens ($F=2.718$, $p<0.001$) (Figure 6.8). No significant change was evident in J_{180} at 10° in the temporal VF and centrally with OK lens wear ($F_{J180}=0.398$, $p=0.725$; $F_c=1.008$, $p=0.411$). J_{180} experienced change with OK lens wear at all other positions and the general trend was a negative increase which became greater with longer duration of lens wear. The statistics and p values for this analysis are shown in full in Appendix C6.

The change in J_{180} profile was similar between a 6mm OZD OK lens (Phase 1) and a 5mm OZD OK lens (Phase 2) ($F=1.131$, $p=0.281$) as shown in Figure 6.8.

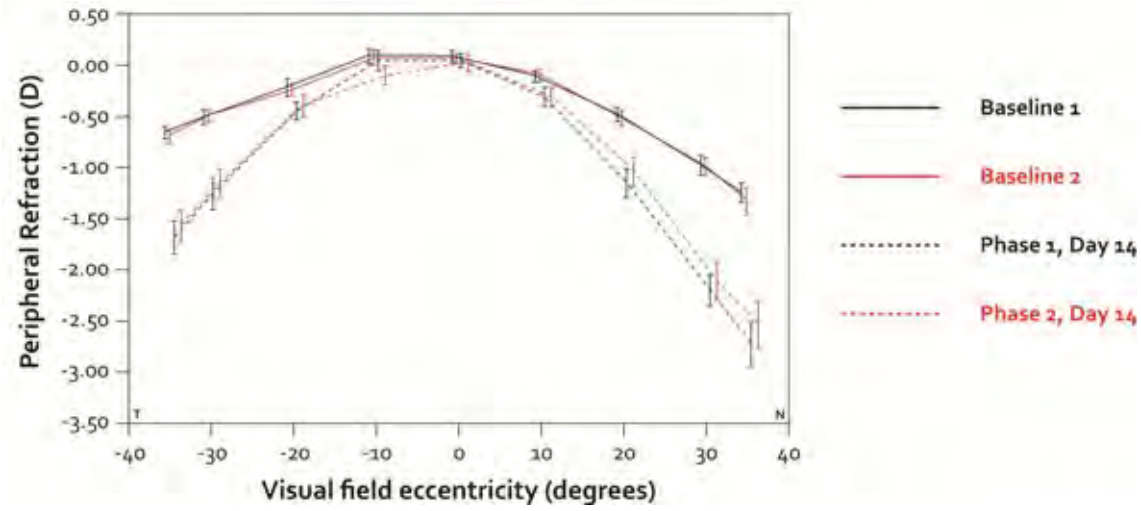


Figure 6.8 Raw J_{180} peripheral refraction profiles (D; mean) along the horizontal meridian at baseline 1 and 2 and after 14 days of OK lens wear with a 6mm (Phase 1) and a 5mm (Phase 2) OZD. Error bars represent the standard error of the mean and have been offset for clarity. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

J_{45} did not change with OK lens wear (F=1.090, p=0.344) (Figure 6.9) and the J_{45} profile was similar between a 6mm OZD OK lens (Phase 1) and a 5mm OZD OK lens (Phase 2) (F=0.890, p=0.655).

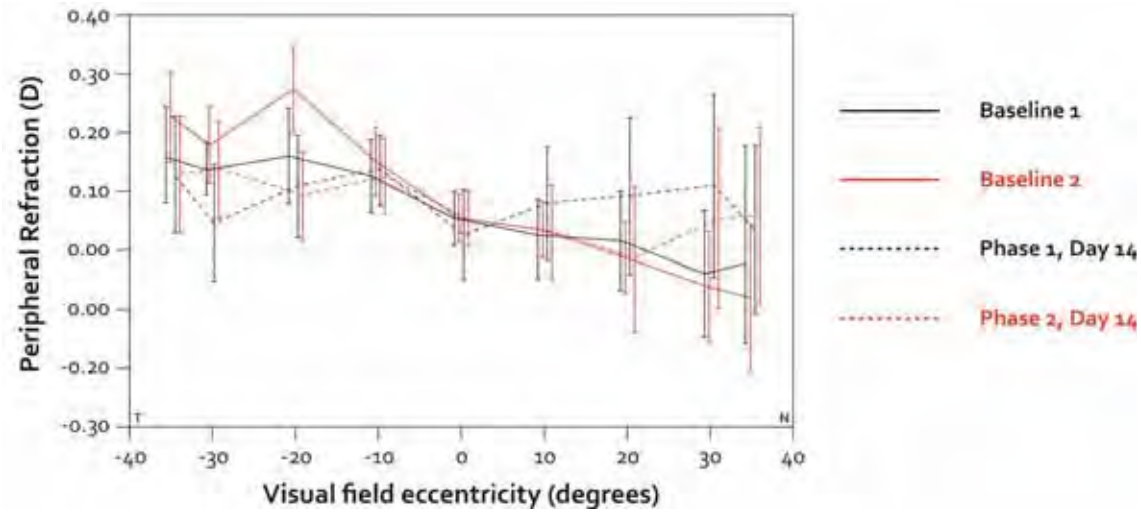


Figure 6.9 Raw J_{45} peripheral refraction profiles (D; mean) along the horizontal meridian at baseline 1 and 2 and after 14 days of OK lens wear with a 6mm (Phase 1) and a 5mm (Phase 2) OZD. Error bars represent the standard error of the mean and have been offset for clarity. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

6.2.3.1.3 CORNEAL TOPOGRAPHY

At baseline 1, corneal refractive power became significantly weaker ($p<0.05$) with eccentricity except at 0.1mm in the temporal cornea and 1.1mm on the nasal cornea where refractive power was similar to centre (0.5mm nasal)($F_{T0.1}=0.606$, $p=0.448$; $F_{N1.1}=0.060$, $p=0.810$). Furthermore, there was no significant difference in corneal topography between baseline 1 and 2 ($F=0.314$, $p=0.953$) (Figure 6.10).

There was a significant change in corneal topography at all positions with OK lens wear except at 2.4mm on the nasal cornea ($F=0.774$, $p=0.314$). The general trend at all locations, except at 2.8mm on the nasal cornea, was a reduction of corneal power or flattening of the cornea with OK lens wear which became less prominent with time. At 2.8mm on the nasal cornea there was an increase in corneal power or steepening of the cornea. The statistics and p values for this analysis are listed in Appendix C7.

Moreover, there was no significant difference in change in corneal topography from baseline with 6mm (Phase 1) or 5mm (Phase 2) OZD OK lenses ($F=0.860$, $p=0.703$) (Figure 6.10).

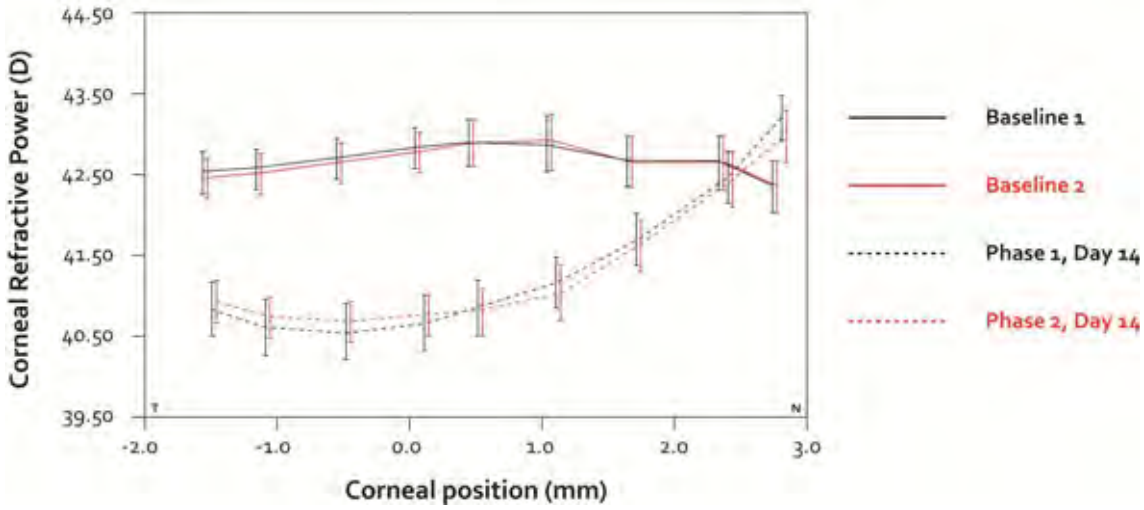


Figure 6.10 Corneal refractive power (D; mean) along the horizontal meridian at baseline 1 and 2 and after 14 days of OK lens wear with 6mm (Phase 1) and 5mm (Phase 2) OZD. Error bars represent the standard error of the mean and have been offset for clarity. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

The TZD after 2 weeks of OK lens wear with a 6mm and 5mm OZD is presented in Table 6.5. TZD sizes for 3 subjects wearing lenses during Phase 2 could not be determined as one patient developed central corneal steepening (central island), another had a treatment area which was significantly temporally decentered and the last subject did not develop a proper bullseye treatment and hence a TZD could not be measured. Changing the OZD rendered the OK fit of these 3 subjects clinically unacceptable. Therefore TZDs after OK lenses with a 6mm OZD (Phase 1) and a 5mm OZD (Phase 2) are listed in Table 6.5 for 14 subjects only.

Subject	6mm OZD OK lens TZD	5mm OZD OK lens TZD	Difference*
1	5.10	5.00	-0.10
2	5.54	5.50	-0.04
3	5.89	5.18	-0.71
4	5.46	5.66	0.20
5	5.45	5.82	0.37
6	5.68	5.86	0.18
7	5.57	5.73	0.16
8	5.25	5.79	0.54
9	5.25	5.38	0.13
10	5.41	6.14	0.73
11	5.07	5.39	0.32
12	4.48	5.29	0.81
13	6.02	5.50	-0.52
14	6.11	6.40	0.29

Table 6.5 TZD (mm) with OK lenses with 6mm (Phase 1) and 5mm (Phase 2) OZD and difference in TZD (mm) between the two lenses.

**Difference = TZD of 5mm OZD OK lens (Phase 2) – TZD of 6mm OZD OK lens (Phase 1) (mm)*

There was no statistically significant difference in TZD between an OK lens with a 6mm (Phase 1) and a 5mm (Phase 2) OZD ($t_{(13)}$=-1.497, p=0.158). The average TZD for a 6mm OZD OK lens was 5.45 ± 0.42 mm while the average TZD for a 5mm OZD OK lens was 5.62 ± 0.38mm. TZD with a 5mm OZD OK lens was on average 0.17 ± 0.42 mm wider than the TZD achieved with a 6mm OZD OK lens.

6.2.3.2 TANGENT COMPARISON

6.2.3.2.1 BASELINE VARIABLES

Central refraction and corneal refractive power at the commencement of Phase 1 (baseline 1) and at the commencement of Phase 2 after washout (baseline 2), in the eye wearing lenses comparing tangents are shown in Table 6.16.

	Refraction			Central corneal refractive power
	M	J_{180}	J_{45}	
Baseline 1	-2.27 ± 1.09	-0.01 ± 0.17	0.08 ± 0.24	43.20 ± 1.22
Baseline 2	-2.16 ± 1.10	0.03 ± 0.17	0.11 ± 0.18	43.20 ± 1.25

Table 6.6 Central refraction (D; mean ± SD) and central corneal refractive power (D; mean ± SD) at baseline 1 and baseline 2.

There were no significant differences in refraction components at baseline 1 or 2 ($F_{(1,16)M}$=2.097, p=0.167; $F_{(1,16)J180}$=1.238, p=0.282; $F_{(1,16)J45}$=0.501, p=0.489). Furthermore, there was no significant difference in central corneal refractive power at baseline 1 or 2 ($t_{(16)}$=0.001, p=0.999).

6.2.3.2.2 PERIPHERAL REFRACTION

M was myopic at all positions along the horizontal meridian at both baseline 1 and 2 (Table 6.7). At baseline 1, M was relatively more hyperopic compared to centre at 30° and 35° in the temporal VF ($F_{(1,16)T30}$=9.903, p=0.008; $F_{(1,16)T35}$=8.908, p=0.009) and at 30° and 35° in the nasal VF $F_{(1,16)N30}$=8.568, p=0.010; $F_{(1,16)N35}$=9.965, p=0.006). Similarly, relative peripheral hyperopia was measured at baseline 2 at 30° and 35° in the temporal VF ($F_{(1,16)T30}$=9.743, p=0.007; $F_{(1,16)T35}$=11.423, p=0.004) and at 35° in the

nasal VF ($F_{(1,16)N35}$=5.228, p=0.036). There was no difference in M along the horizontal meridian between baseline 1 and 2 (F=0.924, p=0.598).

J_{180} was significantly more negative compared to the centre at all positions (p<0.05) except at 10° in the temporal VF at both baseline 1 and 2 ($F_{(1,16)BL1}$=0.018, p=0.895; $F_{(1,16)BL2}$=0.000, p=0.985). Furthermore, there were no differences detected in J_{180} profiles at baseline 1 or 2 (F=3.207, p=0.058).

No significant variation in J_{45} compared to the centre across the horizontal meridian was detected at baseline 1 ($F_{(1.491,25.795)}$=2.118, p=0.148) or baseline 2 ($F_{(0.767,10.052)}$=1.221, p=0.304). Additionally, there was no difference detected in J_{45} profiles between baseline 1 or 2 (F=1.333, p=0.348).

The RPR profiles for M, J_{180} and J_{45} at baseline 1 and 2 are shown in Figure 6.11 a, b and c respectively.

	-35°	-30°	-20°	-10°	C	10°	20°	30°	35°
Baseline 1	-1.45 ± 1.28	-1.57 ± 1.25	-1.97 ± 1.23	-2.28 ± 0.93	-2.27 ± 1.09	-2.17 ± 1.10	-2.11 ± 1.13	-1.68 ± 1.24	-1.46 ± 1.31
Baseline 2	-1.40 ± 1.22	-1.49 ± 1.28	-1.97 ± 1.22	-2.15 ± 1.01	-2.16 ± 1.10	-2.05 ± 1.12	-2.09 ± 1.16	-1.75 ± 1.30	-1.52 ± 1.38

Table 6.7 Objective M (D; mean ± SD) at baseline 1 and 2 along the horizontal meridian. Negative eccentricities denote the temporal VF, positive eccentricities denote the nasal VF and C denotes the centre.

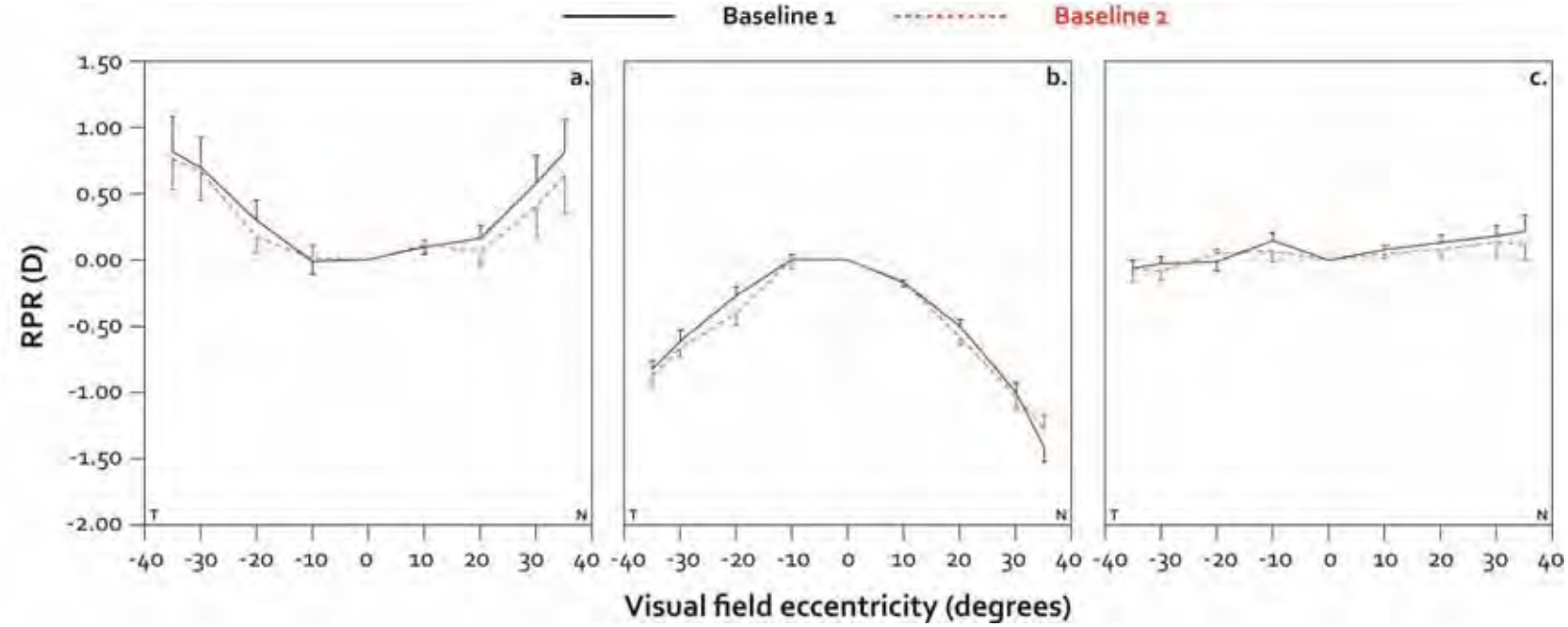


Figure 6.11 RPR profiles (D; mean) for a) M b) J_{180} and c) J_{45} at baseline 1 and 2. Error bars represent the standard error of the mean. Negative eccentricities denote the temporal VF while positive eccentricity represents the nasal VF.

In phase 1 of the study, OK lenses with a ¼ tangent caused significant change in peripheral refraction across the horizontal meridian ($F=3.624$, $p<0.001$). There was a general myopic shift in M at 35° in the temporal VF and at 30° and 35° in the nasal VF. At all other positions, there was a hyperopic shift in M with OK. This shift became greater with longer periods of OK lens wear. The statistics and p values for this analysis are listed in Appendix C5.

There was no significant difference in M profile after 2 weeks of OK lens wear with a ¼ tangent (Phase 1) or a ½ tangent (Phase 2) ($F=0.924$; $p=0.598$) (Figure 6.12).

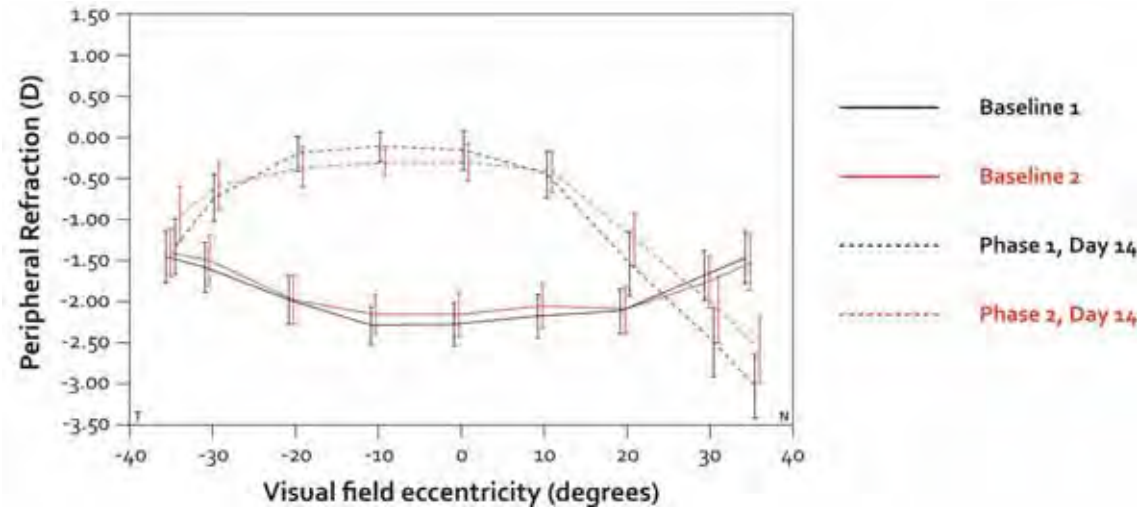


Figure 6.12 Raw M profiles (D; mean) along the horizontal meridian at baseline 1 and 2 and after 14 days of OK lens wear with a ¼ tangent (Phase 1) and a ½ tangent (Phase 2). Error bars represent the standard error of the mean and have been offset for clarity. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

Moreover, there was no significant difference in relative peripheral M profile detected after wearing an OK with ¼ tangent (Phase 1) or a ½ tangent (Phase 2) ($F=0.991$, $p=0.485$) (Figure 6.13).

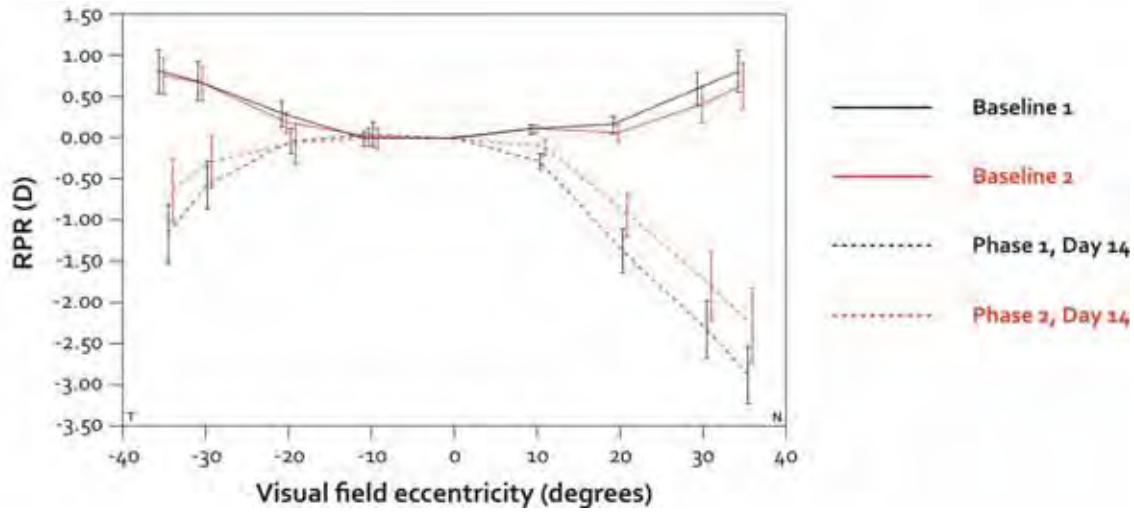


Figure 6.13 Relative peripheral M profiles (D; mean) along the horizontal meridian at baseline 1 and 2 and after 14 days of OK lens wear with ¼ tangent (Phase 1) and ½ tangent (Phase 2). Error bars represent the standard error of the mean and have been offset for clarity. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

In phase 1 of the study, J_{180} significantly changed after wearing a ¼ tangent OK lens for 14 days ($F=2.587$, $p<0.001$). There was no significant change of J_{180} from baseline with OK lens wear at either centre or 10° in the temporal VF ($F=1.583$, $p=0.191$; $F=1.406$, $p=0.243$). At all other positions, there was a general negative increase in J_{180} with OK which became greater with longer lens wear. The statistics and p values for this analysis are shown in full in Appendix C7.

Additionally, the change in J_{180} profile from baseline was similar between a ¼ tangent OK lens (Phase 1) and a ½ tangent OK lens (Phase 2) ($F=0.932$, $p=0.585$) (Figure 6.14).

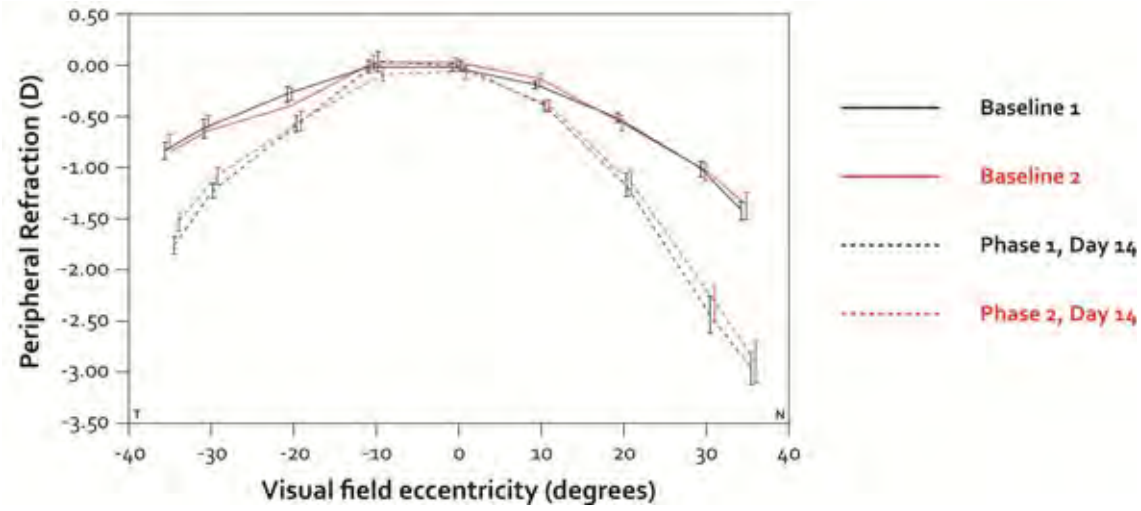


Figure 6.14 Raw J_{180} peripheral refraction profiles (D; mean) along the horizontal meridian at baseline 1 and 2 and after 14 days of OK lens wear with a ¼ tangent (Phase 1) and a ½ tangent (Phase 2). Error bars represent the standard error of the mean and have been offset for clarity. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

J_{45} did not change with OK lens wear (F=1.448, p=0.057) (Figure 6.15) and there was no significant difference in profile between an OK lens with a ¼ and a ½ tangent (F=0.912, p=0.619).

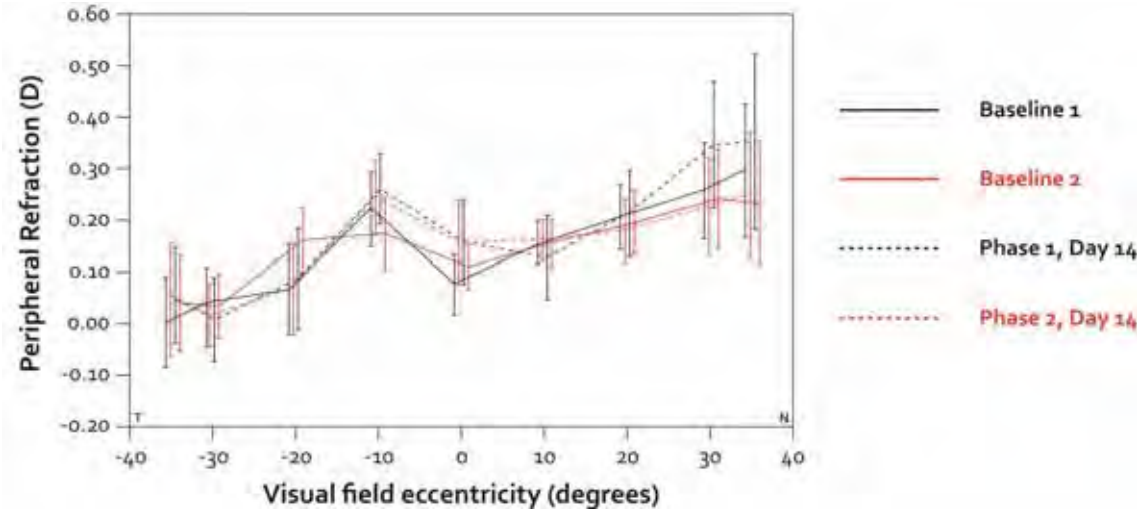


Figure 6.15 Raw J_{45} peripheral refraction profiles (D; mean) along the horizontal meridian at baseline 1 and 2 and after 14 days of OK lens wear with a ¼ tangent (Phase 1) and a ½ tangent (Phase 2). Error bars represent the standard error of the mean and have been offset for clarity. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

6.2.3.2.3 CORNEAL TOPOGRAPHY

At baseline 1, compared to centre (0.5mm nasal), no significant difference in corneal refractive power was detected at 0.5mm on the temporal cornea, 0.1mm and 1.1mm on the nasal cornea ($F_{T0.5}$=2.990, p=0.103; $F_{N0.1}$=0.382; p=0.545; $F_{N1.1}$= 0.031. p=0.863). All other positions along the horizontal corneal chord were flatter (indicated by reduced corneal refractive power) ($p<0.05$) compared to the centre (Figure 6.16). Additionally, there was no difference detected in corneal topography between baseline 1 and baseline 2 (F=0.212, p=0.775) (Figure 6.16).

OK lenses with a ¼ tangent (Phase 1) caused significant corneal topography changes (F=3.212, $p<0.001$) at all positions along the cornea measured except at 2.4mm on the nasal cornea (F=0.193, p=0.941). All positions, except at 2.8mm on the nasal cornea, experienced a reduction in corneal refractive power or flattening of the cornea which became greater with time. At 2.8mm on the nasal cornea, there was an increase in corneal refractive power or a steepening of the cornea. The statistics and p values for this analysis are listed in Appendix C7.

Additionally, OK lenses with a ¼ tangent and a ½ tangent caused similar changes in corneal topography (F=0.860, p=0.703) (Figure 6.16).

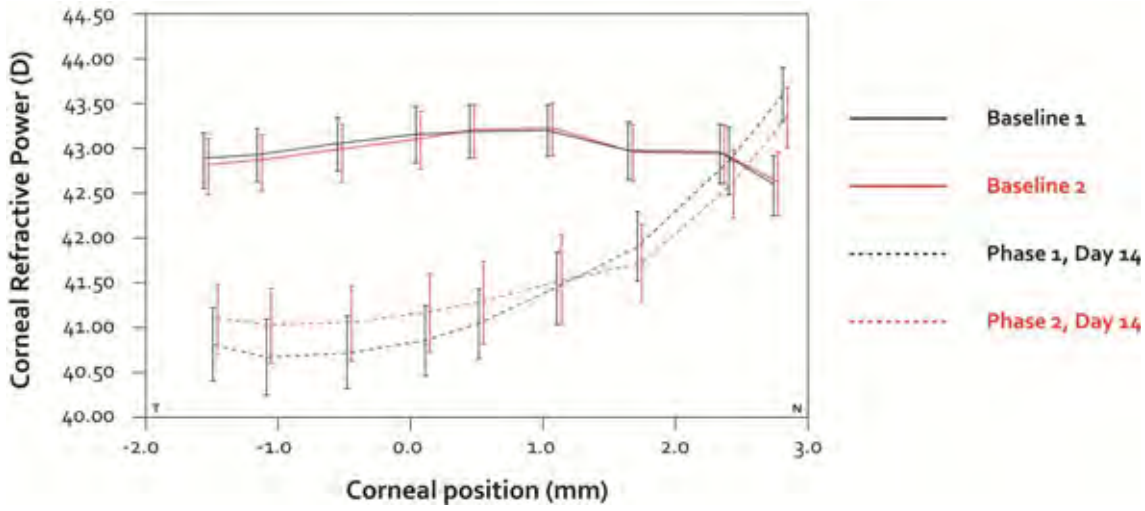


Figure 6.16 Corneal refractive power (D; mean) along the horizontal meridian at baseline 1 and 2 and after 14 days of OK lens wear with a ¼ tangent (Phase 1) and a ½ tangent (Phase 2). Error bars represent the standard error of the mean and have been offset for clarity. Negative eccentricities denote the temporal VF and positive eccentricities denote the nasal VF.

6.2.4 DISCUSSION

Characteristic peripheral refraction profiles were found in myopic eyes at both baseline 1 and 2 consistent with reports in myopic children as described in Section 5.1 and myopic adults as described in Section 5.2. Furthermore, changes in peripheral refraction and corneal topography with OK lenses during Phase 1 (standard BE OK lenses) are also consistent with changes in refraction and topography in myopic children and adults wearing OK lenses as reported in Section 5.1 and 5.2 respectively, and to published reports on myopic adults wearing OK lenses (Charman et al., 2006, Queirós et al., 2010).

It was hypothesised that decreasing the OZD would cause a smaller area of central flattening (smaller TZD) and thus induce hyperopic shifts in M at positions across the horizontal meridian closer to the visual axis. This would allow a greater area of the peripheral VF to experience myopic defocus. However, no significant difference in peripheral refraction profile or corneal topography was found after 14 days of wearing an OK lens with a standard 6mm OZD compared to an OZD of 5mm. Although

statistically insignificant, decreasing the OZD surprisingly caused a mean increase in TZD rather than the expected decrease in diameter. Pilot work by Ruston and Mountford (2004) found that increasing the OZD lead to an increase in TZD. However two different lens designs were used in that study. A BE lens (Capricornia, Brisbane) was fitted into one eye (OZD of 6mm) and an experimental lens in the contralateral eye (OZD 7.3mm).

The periphery of the BE OK lens used in this study was steepened by modifying the point of contact of the peripheral tangent (Figure 6.4). No significant change in corneal topography or peripheral refraction was found between a standard BE OK lens with a ¼ tangent and a modified steepened OK lens with a ½ tangent. It was expected that changing the tangent from a ¼ to a ½ would create greater mid peripheral corneal steepening which could be reflected by a greater peripheral myopic M shift. A possible reason for peripheral tangent modification resulting in no difference in peripheral refraction profile may be because changes in corneal topography and hence peripheral refraction occurred outside the peripheral refraction measurement zone. Peripheral refraction measurements taken at 35° in the temporal and nasal VF correspond approximately to a 4.3mm horizontal chord (1.5mm on the temporal cornea to 2.8mm on the nasal cornea, Appendix A). If we consider the typical TZD to be 5mm (Sridharan and Swarbrick, 2003) and corneal steepening to occur adjacent to the point of no change in corneal power or edge of the TZD, then it is possible that increased para-central corneal steepening and hence increased myopic shift in peripheral M may not have been detected. Only 17 subjects were recruited for this study resulting in a study statistical power of 0.42. Another 22 subjects are required to reach a power of 0.8 which may also explain the non-significant results found.

The motivation for investigation of the effects of lens parameter modification on corneal topography and peripheral refraction derived from the hypothesis that inducing myopic defocus onto the peripheral retina may slow down or stop the progression of myopia (Charman and Radhakrishnan, 2010, Smith, 2011, Wallman and Winawer, 2004). OK lenses inadvertently achieve this effect and this study

endeavoured to determine what lens parameters could be modified to possibly alter the amount of refractive and corneal topographic changes induced with a standard commercially available OK lens design. The changes in lens parameters that were investigated were relatively subtle however substantial change in lens parameters could not be made as this is likely to compromise the fit and hence the central myopia correction achieved with OK lenses. For example, if the OZD of an OK lens did indeed change the TZD, the TZD should not be made too small as it is likely to affect the optical quality of the central myopic correction particularly at night with pupil dilation. Furthermore, changing the OZD also rendered the OK fit in 3 subjects clinically unacceptable demonstrating how easily the cornea-lens fitting relationship can be compromised with OK lens parameter manipulation.

There are two proposed theories on the mechanisms of corneal flattening with OK lens wear. The moulding theory derived from early work by Jessen (1962) who reported corneal flattening with PMMA lenses that were fitted flatter than the anterior corneal curvature. Over time, improvements in unaided VA were apparent and it was proposed that eyelid pressure caused the cornea to mould to match the back surface of the lens. Jessen fitted lenses flatter by the dioptric amount of the myopic refractive error and this approach was termed the Jessen factor technique.

The hydraulic theory of OK was developed by Tabb (cited by Coon, 1982) who proposed that corneal flattening apparent with steep fitting lenses (Nolan, 1972) was due to fluid forces in the post-lens tear film. This theory was adopted into the development of the BE OK lens design (Mountford, 2004b) which was used in studies described in this thesis. Mountford (2004b) proposed that OK lenses generate a compressive or positive hydraulic force on the central cornea surrounded by a peripheral annulus of negative or suctioning force and the corneal epithelium changes in shape to equalise these forces. If hydraulic forces are responsible for changes in anterior corneal curvature, this may explain why no changes in corneal topography and peripheral refraction were found with manipulation of different lens parameters, as these hydraulic forces may not have been significantly altered by the lens parameter manipulations used.

A typical OK lens design is described in Figure 6.17. The back optic zone of an OK lens is defined by its radius of curvature and diameter. The back optic zone radius (BOZR) cannot be manipulated if OK lenses achieve corneal flattening through a moulding effect. According to the moulding theory, changing the BOZR will influence the amount of corneal flattening induced and hence myopia reduction achieved with OK lenses. The OZD was found in this study to have a minimal effect on changes in corneal topography and peripheral refraction. The asphericity of the back optic zone curve is another parameter that could be manipulated. It is unknown whether there may be differences in induced corneal topography changes with an aspheric back surface and if the degree of asphericity may also have an impact on corneal topography. The width and depth of the reverse curve could also be manipulated. The depth of the reverse curve will affect the sagittal height of the OK lens which may induce a greater moulding effect with OK lenses or induce greater positive hydraulic forces, thus influencing the response by the corneal epithelium and hence refractive correction effects of OK.

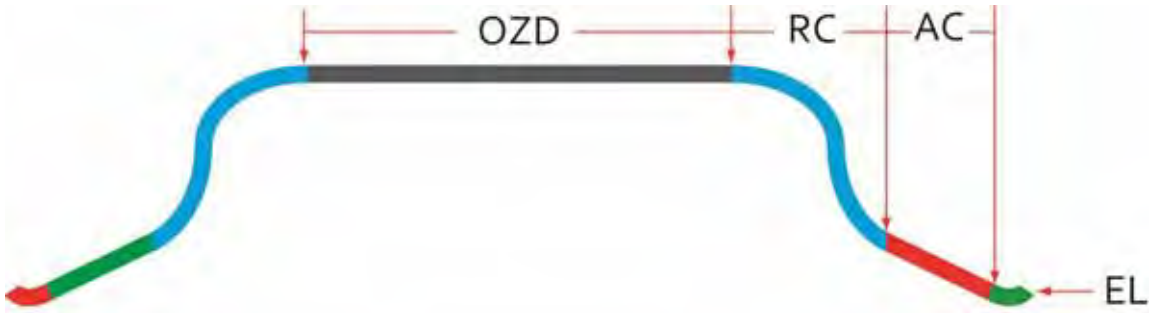


Figure 6.17 Cross-sectional view of a typical OK lens. A standard OK lens design comprises a back optic zone defined by the OZD and BOZR, reverse curve (RC), alignment curve (AC) and an edge lift (EL).

The OZD and peripheral tangent of OK lenses were modified to determine the impact of manipulating these lens parameters on corneal topography and peripheral refraction. No significant change in either corneal topography or peripheral refraction was found with reducing the OZD from 6mm to 5mm or steepening the peripheral

(alignment) OK curve by altering the tangent from ¼ to ½. There are only a few parameters on the OK lens which can be modified without having a significant impact on the refractive effects of OK and investigations of the effects of manipulation of these lens parameters are indicated. Furthermore, new methods or modifications need to be developed to measure peripheral refraction along a chord greater than 4.3mm as corneal topography changes induced by OK tend to occur along a larger chord.

6.3 CONCLUSION

The studies conducted in this chapter attempted to gain a better understanding of the relationship between corneal topography change and corresponding peripheral refraction change as well as exploring the possibility of targeted peripheral refraction modifications through changes in OK lens parameters.

Significant relationships between corneal refractive power change and peripheral M change were found primarily at locations out to 30° and 35° in the temporal VF, and at 35° in the nasal VF. Additionally manipulations of OZD and peripheral tangent in OK lenses were found to cause little difference in peripheral refraction and corneal topography change. This tends to agree with the hydraulic theory of the mechanism behind OK. The amount of OK lens parameter modification that can be implemented is restricted as central refraction correction needs to be maintained. Significant change in lens parameters will render OK fits unpredictable which will affect the refractive outcome. It may be that the changes implemented in this study were too subtle for a significant effect on corneal topography or peripheral refraction to be detected.

Assumptions used in this study need to be revisited and further investigation with larger sample sizes is required to strengthen the negative results found. This will verify if peripheral refraction can be modified in a predictable manner with OK.

CHAPTER 7

PERIPHERAL REFRACTION AND SCLS

Modification of peripheral refraction can be achieved with OK in myopic children and adults as described in Chapter 5 and 6 respectively. However results from Chapter 6 revealed that changing the OZD of a BE OK lens from 6mm to 5mm, or changing the peripheral tangent from a ¼ to a ½, yielded no significant difference in resultant peripheral refraction profiles. Furthermore, difficulty potentially arises with restrictions on which lens parameters can be modified and the amount of parameter change that can be induced without affecting the refractive effects from OK. SCLs may be another option which could provide greater flexibility and predictability in the amount of peripheral defocus change induced onto the peripheral retina of myopic individuals.

SCLs are one of the main modalities of myopia correction allowing unrestricted field of view. The range of SCL powers commercially available is extensive making SCLs readily available to individuals over a wide range of refractive errors.

Like OK, SCLs have been reported to decrease the amount of relative peripheral hyperopia in myopes (Shen et al., 2010) indicating a potential anti-myopiogenic factor intrinsic to SCLs. However, there has been minimal research investigating the effects of SCL wear on peripheral refraction. Furthermore, the effects of over and under-correction of myopia with SCLs on peripheral refraction are unknown. Reports have indicated that compared to full correction, under-correction of central myopia appears to encourage myopia progression (Adler and Millodot, 2006, Chung et al., 2002). It therefore seems appropriate to investigate the differences in peripheral defocus with different levels of SCL correction in myopes.

The study described in the first part of this chapter explores the effects of full SCL correction on peripheral refraction. Differences in peripheral refractive error profiles with under and over-correction of central myopia were subsequently analysed in an attempt to explain differences in myopia progression with different levels of

correction. The second part of this chapter then continued to examine the effects of multifocal SCL correction on peripheral refraction to determine if effects were similar to or more predictable than OK.

7.1 PERIPHERAL REFRACTION WITH DIFFERENT LEVELS OF SCL CORRECTION

Many commercially available SCLs have an extensive range of powers available creating flexibility in myopia correction. Full, under and over-correction of myopia are possible with SCLs.

It has been proposed that under-correction of myopia may reduce myopia progression through potential reduction in accommodation at near. Furthermore animal studies have demonstrated that myopic defocus hinders axial elongation (Irving et al., 1992, Smith and Hung, 1999, Wallman et al., 1995, Wildsoet and Wallman, 1995). However, the status of peripheral refraction with under-correction of myopia is unknown.

Full correction of myopia with specific brands of SCLs has been shown to reduce hyperopic field curvature (Shen et al., 2010) and produce less peripheral hyperopia compared to SV spectacle lens wear (Lazon de la Jara et al., 2010).

The current study set out to explore the effects of SCL under-correction on peripheral refraction profile in myopic individuals in addition to investigating field curvature in fully corrected myopes with SCLs. To further understand the effects of myopia correction on peripheral defocus, over-correction of myopia was also examined in this study. It was hypothesised that the different levels of correction of central myopia with SCLs would not change the shape of the peripheral refraction profile but simply shift the profile in a hyperopic direction from baseline (no correction). The most prominent hyperopic shift in peripheral refraction profile would be with over-correction, followed by full then under-correction of central myopia.

7.1.1 MATERIALS AND METHODS

7.1.1.1 STUDY DESIGN

Peripheral refraction measurements were taken along the horizontal meridian on the naked eye. Myopic subjects were then fitted with SCLs in the right eye with full, under (+0.75DS) and over (-0.75DS) correction of their manifest central refraction. Peripheral refraction measurements were then taken with each level of SCL correction. The left eye acted as a control with peripheral refraction measured on the naked left eye while each level of correction was worn on the right eye.

7.1.1.2 SUBJECTS

Thirty-four subjects from the University of New South Wales community were enrolled (age range 18 to 29 years; 14 M, 20 F). Approval from the institutional Human Research Ethics Advisory panel (Approval number HREA 10058) was obtained before study commencement. All subjects gave their informed written consent to participate in the study after being informed about the nature and possible consequences of study participation. Subjects were screened prior to enrolment and found to be in good ocular health and free from ocular disease. Inclusion criteria required that subjects were non-RGP CL wearers and SCL wearers were instructed to cease lens wear at least 24 hours prior to measurements. Inclusion criteria required that central refraction was between -0.75DS and -6.00DS with ≤-0.75DC and anisometropia of less than 1.50DS.

Subjects were split into two groups depending on their central M refraction. Central M between -0.75DS and -2.00DS inclusive was categorised as low myopia and subjects with central M between -2.25DS and -6.00DS inclusive were categorised as moderate myopes.

7.1.1.3 LENSES

Subjects were fitted with Proclear® Sphere SCLs (Coopervision; New York, USA) made from omafilcon A (62% water content). Proclear® Sphere SCLs have a diameter of 14.2mm and base curve of 8.6mm.

7.1.1.4 LENS FITTING PROTOCOL

Lens powers were chosen to fully correct vertex adjusted subjective central refractive error. SCL powers with under-correction and over-correction by 0.75DS were also selected. The lens centration, corneal coverage, movement and tightness were assessed to confirm clinically acceptable lens fits on each subject before any measurements were taken. Measurements were taken at least 5 minutes after lens insertion to allow the lens to settle on the cornea.

7.1.1.5 MEASUREMENT TECHNIQUES

7.1.1.5.1 CENTRAL AND PERIPHERAL REFRACTION

Although subjective refraction was used to select lens powers, it has been shown to be comparable to objective measurements with the Shin-Nippon NVision-K 5001 autorefractor (Davies et al., 2003). Central objective refraction was measured with the Shin-Nippon NVision-K 5001 autorefractor as described in Section 2.2.2.1.

Five peripheral refraction measurements at 10°, 20°, 30° and 35° in the nasal and temporal VF were taken and averaged as described in Section 2.2.3.1.

7.1.1.6 DATA ANALYSIS

Paired t-tests were performed on central refraction to confirm that the experimental and control eyes were matched in both low and moderate myopes.

Repeated-measures ANOVA was performed to describe the horizontal peripheral refraction profile.

Doubly MANOVA analysis allowed comparison of peripheral refraction profiles between no correction and with different levels of SCL correction in both low and moderate myopes.

7.1.2 RESULTS

7.1.2.1 BASELINE VARIABLES

There was no statistically significant difference at baseline between the experimental and control eyes in terms of central refractive error in either low myopes ($t_{(16)M}$=-0.506, p=0.619; $T(16)_{J180}$=0.295, p=0.772; $T(16)_{J45}$=-0.661, p=0.518) or moderate myopes ($t_{(16)M}$=-0.362, p=0.722; $t_{(16)J180}$=-1.9997, p=0.063; $t_{(16)J45}$=-0.219, p=0.829).

Mean objective central refraction at baseline in the right eye is shown in Table 7.1.

Mean objective central refraction	M	J_{180}	J_{45}
Low myope	-1.41 ± 0.60	-0.01 ± 0.22	0.01 ± 0.12
Moderate myope	-3.25 ± 0.80	0.06 ± 0.23	0.04 ± 0.15

Table 7.1 Objective central refraction (D; mean ± SD)

In low myopes, M was found to be significantly more hyperopic compared to centre at 30° and 35° in the temporal VF. In moderate myopes, M was found to be significantly more hyperopic compared to centre at 30° and 35° in the temporal VF and at 10°, 30° and 35° in the nasal VF. No significant overall difference in relative M profile was found between low or moderate myopes (F=1.716, p=0.095). The statistics and p values for this analysis are shown in full in Appendix C8. Relative M profiles for low and moderate myopes are shown in Figure 7.1a.

At baseline, J_{180} negatively increased with eccentricity at all positions in both low and moderate myopes and no significant difference in J_{180} profile was found between the two groups (F=1.090, p=0.402). The statistics and p values for this analysis are shown in full in Appendix C8. Relative J_{180} profiles for low and moderate myopes are illustrated in Figure 7.1b.

In both low and moderate myopes, J_{45} was significantly more negative compared to centre at 30° and 35° in the temporal VF and more positive compared to centre at 20°, 30° and 35° in the nasal VF. Additionally, no significant difference was found in J_{45} profiles between low or moderate myopes (F=0.424, p=0.711). The statistics and p values for this analysis are shown in full in Appendix C8. Relative J_{45} profiles for low and moderate myopes are illustrated in Figure 7.1c.

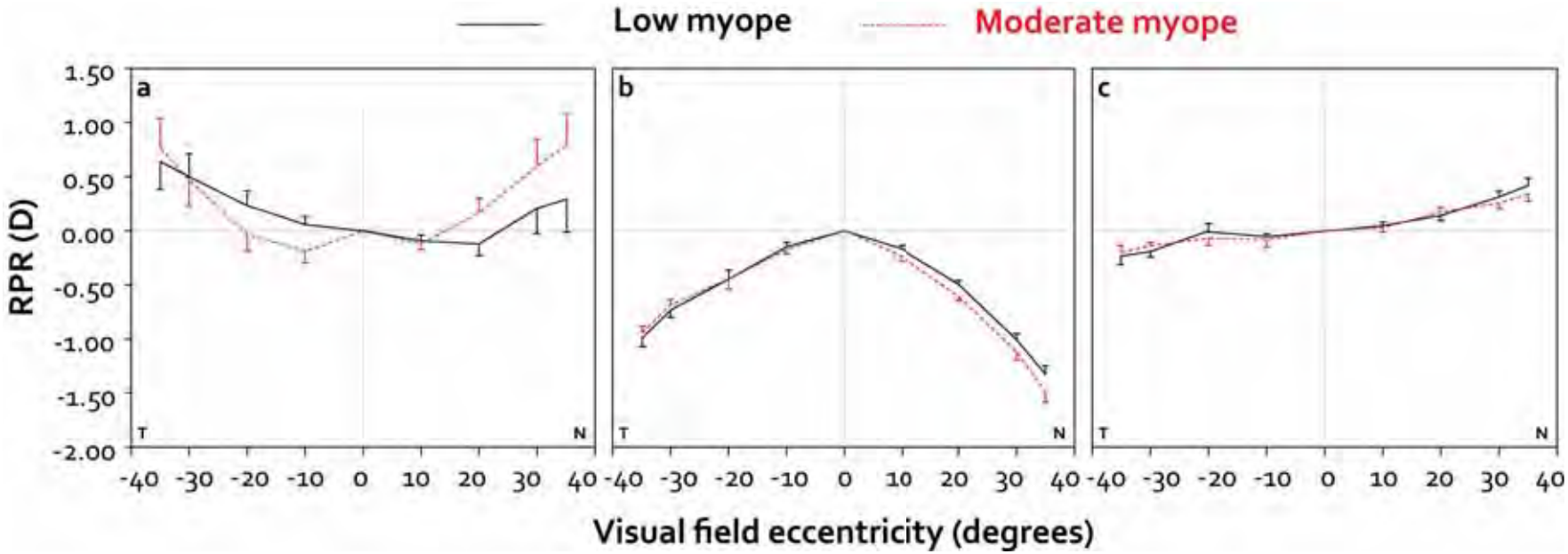


Figure 7.1 Baseline RPR profiles (D; mean) for a) M, b) J_{180} and c) J_{45} in low and moderate myopes. Error bars represent standard error of the mean. Negative eccentricities represent temporal VF while positive eccentricities represent nasal VF.

7.1.2.2 PERIPHERAL REFRACTION

Full correction of central M with SCLs caused a significant hyperopic shift in M at all locations along the horizontal meridian in low myopes ($p<0.001$) as shown in Figure 7.2a and Table 7.2.

Analysis of relative data revealed differences in peripheral refraction profiles in low myopes ($F=5.090$, $p=0.013$) with greater relative peripheral hyperopia evident with full correction compared to no correction at 35°, 30° and 20° in the temporal VF ($F_{T35}=4.664$, $p=0.046$; $F_{T30}=6.732$, $p=0.020$; $F_{T20}=5.396$, $p=0.034$) and 30° and 35° in the nasal VF ($F_{N30}=11.803$, $p=0.003$; $F_{N35}=5.776$, $p=0.029$) (Figure 7.2b).

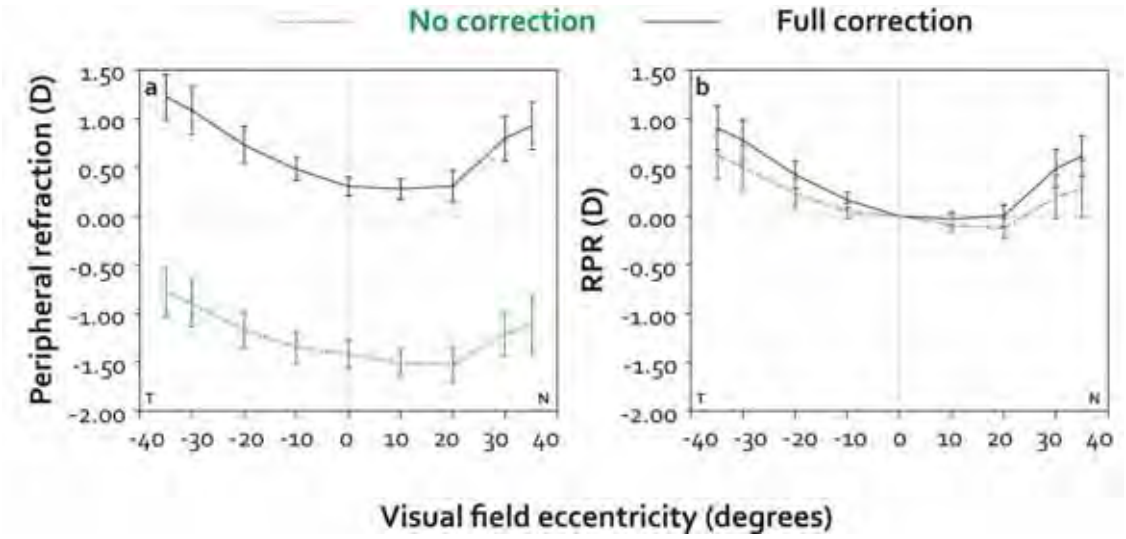


Figure 7.2 a) Raw and b) relative peripheral M (D; mean) with and without full correction. Error bars represent standard error of the mean. Negative eccentricities represent temporal VF while positive eccentricities represent nasal VF.

Significant differences in peripheral refraction were demonstrated between under and full correction at all locations ($p<0.001$) (Table 7.2). Significant differences between full and over-correction were evident only at 10° in the temporal VF ($p=0.010$), centre ($p=0.006$) and 10° and 20° in the nasal VF ($p<0.001$; $p=0.016$) (Figure 7.3a). There were

no significant differences in RPR profile between full, under or over-correction of myopia with SCLs (F=0.883, p=0.591) as demonstrated in Figure 7.3b.

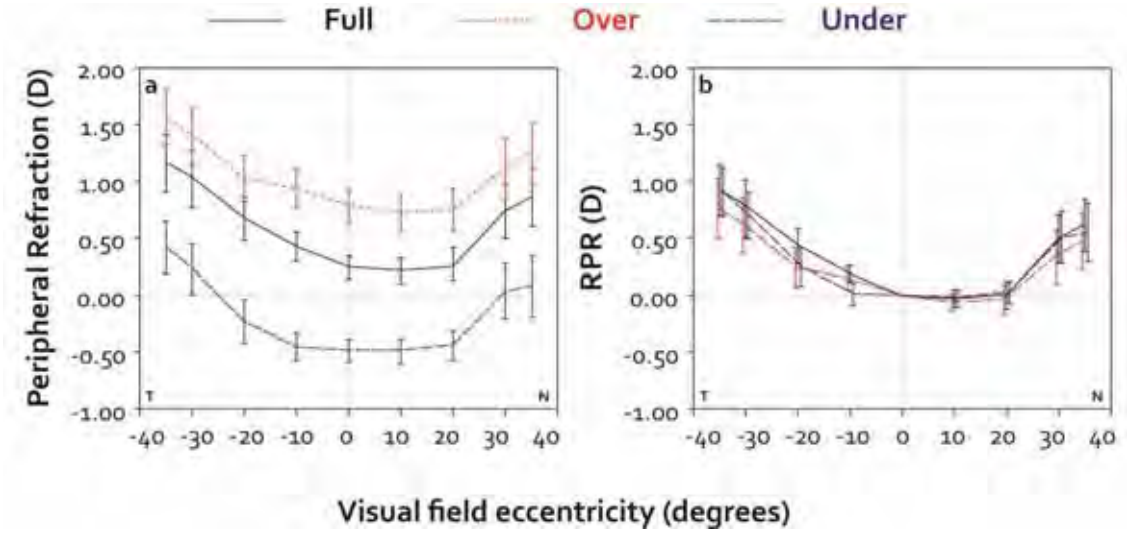


Figure 7.3 a) Raw and b) relative peripheral M profiles (D; mean) of full, over and under-correction of central refractive error in low myopes. Error bars represent standard error of the mean and have been offset for clarity. Negative eccentricities represent temporal VF while positive eccentricities represent nasal VF.

M	-35°	-30°	-20°	-10°	C	20°	25°	30°	35°
No correction	-0.77 ± 1.02	-0.90 ± 0.88	-1.17 ± 0.67	-1.35 ± 0.61	-1.41 ± 0.60	-1.50 ± 0.61	-1.53 ± 0.68	-1.20 ± 0.93	-1.12 ± 1.18
Under-correction	0.43 ± 0.95	0.24 ± 0.90	-0.22 ± 0.78	-0.44 ± 0.51	-0.47 ± 0.41	-0.48 ± 0.43	-0.43 ± 0.55	0.05 ± 1.00	0.09 ± 1.09
Full-correction	1.21 ± 1.01	1.08 ± 1.04	0.73 ± 0.79	0.48 ± 0.52	0.30 ± 0.41	0.28 ± 0.47	0.31 ± 0.67	0.79 ± 1.00	0.92 ± 1.06
Over-correction	1.55 ± 1.11	1.41 ± 1.00	1.03 ± 0.84	0.95 ± 0.67	0.78 ± 0.61	0.73 ± 0.67	0.76 ± 0.80	1.12 ± 1.08	1.26 ± 1.08

Table 7.2 Raw M (D; mean ± SD) across the horizontal meridian with no, under, full and over-correction of central refractive error with SCLs in low myopes. Negative eccentricities denote the temporal VF, positive eccentricities denote the nasal VF and C denotes the centre.

Similar to low myopes, full correction of central M significantly changed raw peripheral refraction at all locations along the horizontal meridian in moderate myopes ($p<0.001$) as demonstrated in Figure 7.4a and Table 7.3. Greater relative peripheral hyperopia was found with full correction SCLs at all positions in the temporal VF ($F_{T35}=17.467$, $p=0.001$; $F_{T30}=25.012$, $p<0.001$; $F_{T20}=9.961$, $p=0.006$; $F_{T10}=9.734$, $p=0.007$) and at 10°, 30° and 35° in the nasal VF ($F_{N10}=4.597$, $p=0.048$; $F_{N30}=11.620$, $p=0.004$; $F_{N35}=10.383$, $p=0.005$) (Figure 7.4b).

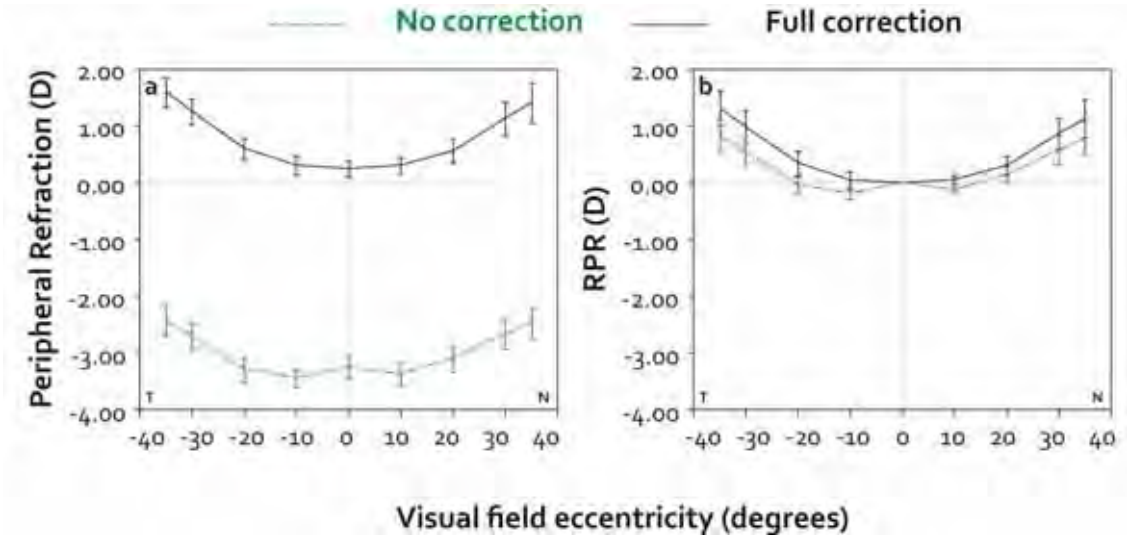


Figure 7.4 a) Raw and b) relative peripheral M (D; mean) with and without full correction in moderate myopes. Error bars represent standard error of the mean. Negative eccentricities represent temporal VF while positive eccentricities represent nasal VF.

Different levels of myopia correction (under, full and over-correction) significantly changed raw peripheral refraction at all locations along the horizontal meridian ($p<0.001$) in moderate myopes as illustrated in Figure 7.5a and Table 7.3. However, there were no differences in RPR profiles between the three levels of correction ($F=1.323$, $p=0.513$) (Figure 7.5b).

M	-35°	-30°	-20°	-10°	C	20°	25°	30°	35°
No correction	-2.41 ± 1.06	-2.69 ± 0.98	-3.27 ± 0.89	-3.43 ± 0.66	-3.25 ± 0.80	-3.36 ± 0.85	-3.08 ± 0.90	-2.66 ± 1.07	-2.46 ± 1.15
Under-correction	0.81 ± 1.10	0.56 ± 0.90	-0.22 ± 0.63	-0.49 ± 0.56	-0.37 ± 0.51	-0.37 ± 0.49	-0.10 ± 0.74	0.56 ± 1.17	0.79 ± 1.49
Full-correction	1.57 ± 1.09	1.24 ± 0.98	0.60 ± 0.74	0.29 ± 0.67	0.24 ± 0.55	0.30 ± 0.60	0.56 ± 0.85	1.12 ± 1.18	1.39 ± 1.43
Over-correction	2.13 ± 1.17	1.91 ± 0.88	1.30 ± 0.60	0.83 ± 0.55	0.86 ± 0.56	0.98 ± 0.50	1.29 ± 0.71	1.88 ± 1.01	2.35 ± 1.35

Table 7.3 Raw M (D; mean ± SD) across the horizontal meridian with no, under, full and over-correction of central refractive error with SCLs in moderate myopes. Negative eccentricities denote the temporal VF, positive eccentricities denote the nasal VF and C denotes the centre.

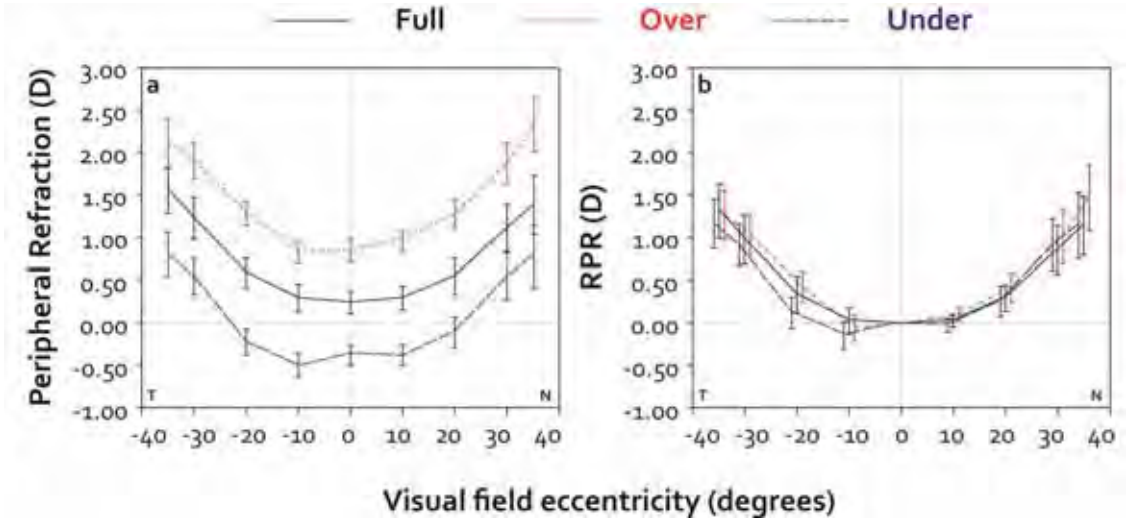


Figure 7.5 a) Raw and b) relative peripheral M profiles (D; mean) with full, over and under-correction of central refractive error in moderate myopes. Error bars represent standard error of the mean and have been offset for clarity. Negative eccentricities represent temporal VF while positive eccentricities represent nasal VF.

Compared to no correction, J_{180} changed with full correction in low myopes (F=4.220, p=0.027) with a significant positive increase in J_{180} at 35° in the temporal (F_{T35}=9.214, p=0.008) and nasal VF (F_{N35}= 10.797, p=0.005). However, there were no significant differences in raw J_{180} profiles with full, under and over-correction of central myopia (F=1.602, p=0.096) (Figure 7.6a).

Similarly, there was a significant change in J_{180} profile with full correction SCLs in moderate myopes (F=3.554, p=0.044). A positive increase was found at 35° and 30° in the temporal VF (F_{T35}=10.575, p=0.005; F_{T30}=14.794, p=0.001) and at 20°, 30° and 35° in the nasal VF (F_{N20}=6.156, p=0.025; F_{N30}=10.085, p=0.006; F_{N35}= 15.747, p=0.001). No significant differences between raw J_{180} profiles with different levels of SCL correction were found (F=0.938, p=0.540) as illustrated in Figure 7.6b.

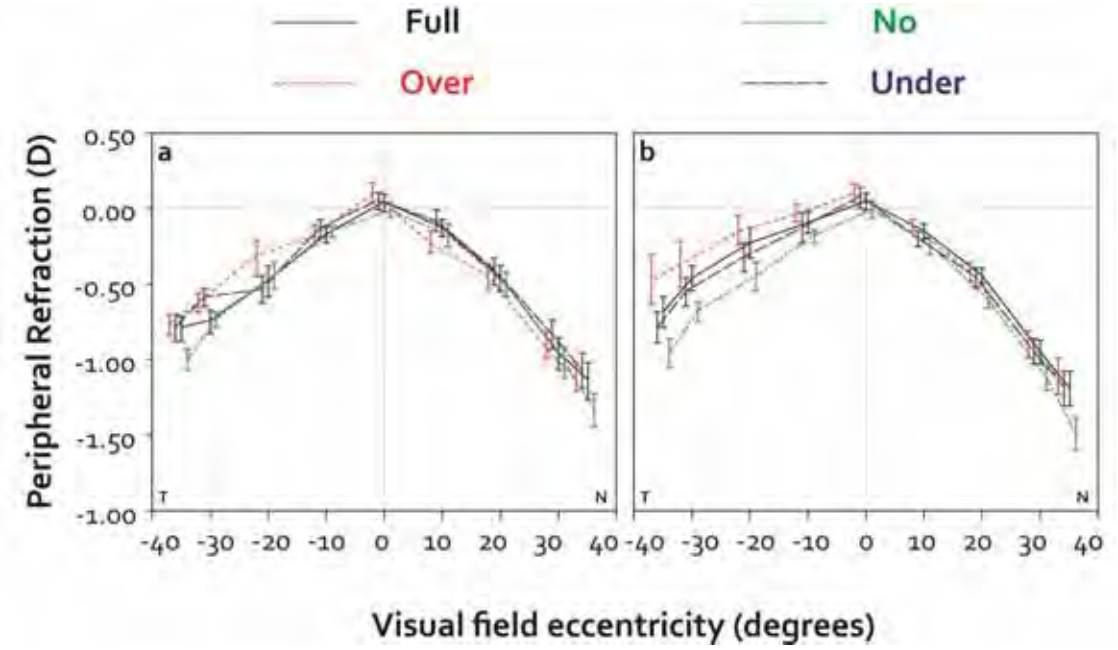


Figure 7.6 Raw J_{180} peripheral refraction profiles (D; mean) across the horizontal meridian in a) low and b) moderate myopes with no, full, over and under-correction of central refraction. Error bars represent standard error of the mean and have been offset for clarity. Negative eccentricities represent temporal VF while positive eccentricities represent nasal VF.

In low myopes, there was no effect of full correction SCLs on J_{45} (F=0.517, p=0.827). There were differences in J_{45} profiles with different levels of correction at 35° in the temporal VF (F=11.945, p<0.001) and at 20° in the nasal VF (F=3.725, p=0.035). Compared to full correction, at 35° in the temporal VF, over-correction caused a negative increase in J_{45} while causing a positive increase at 20° in the nasal VF (Figure 7.7a).

In contrast to low myopes, full correction of moderate myopia with SCLs caused significant changes in J_{45} profile (F=4.651, p=0.021) with a positive increase in J_{45} at 35° in the temporal VF. There were no differences in J_{45} found between full, under or over-correction (F=0.926, p=0.554) as demonstrated in Figure 7.7b.

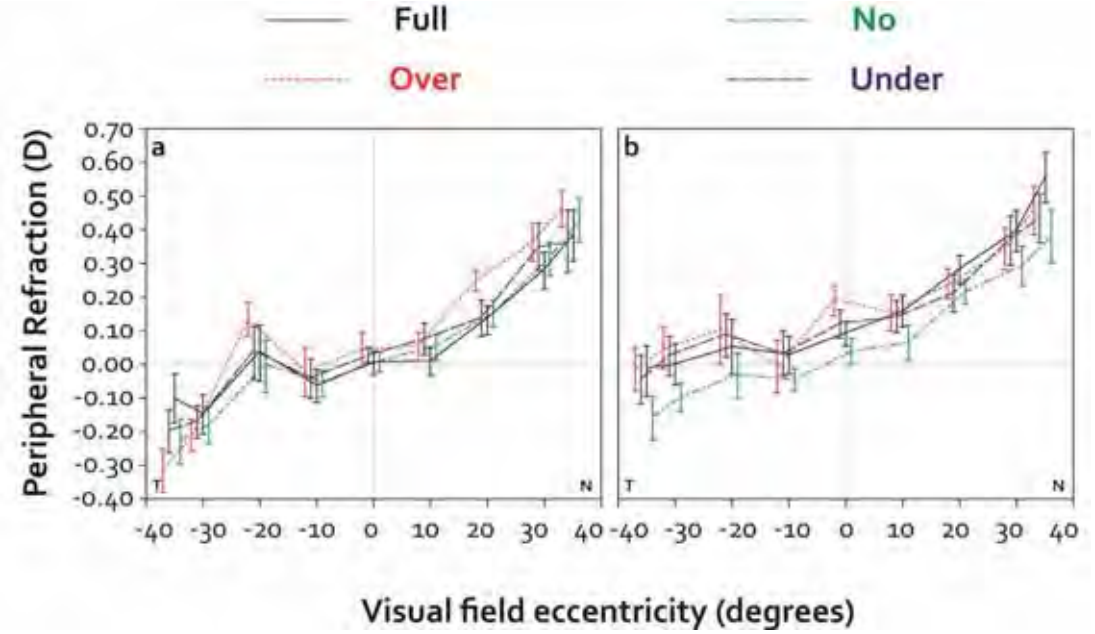


Figure 7.7 Raw J_{45} peripheral refraction profiles (D; mean) across the horizontal meridian in a) low and b) moderate myopes with no, full, over and under-correction of central refraction. Error bars represent standard error of the mean and have been offset for clarity. Negative eccentricities represent temporal VF while positive eccentricities represent nasal VF.

7.1.2.3 CONTROL

No significant differences in peripheral M profiles in the control left eye were revealed with no, full, under or over-correction of central myopia with SCLs in the experimental right eye, for either both low ($F=1.041$, $p=0.411$) or moderate myopes ($F=0.923$, $p=0.508$). Similar results were found for J_{180} in low ($F=0.890$, $p=0.536$) and moderate myopes $F=1.918$, $p=0.054$) as well as for J_{45} in low ($F=1.262$, $p=0.263$) and moderate myopes ($F=1.314$, $p=0.356$).

7.1.3 DISCUSSION

SCLs are one of the most widely used modes of myopia correction and are frequently worn by progressing myopic children. With the extensive range of powers available, and the development of new materials and lens designs, SCLs have become a popular form of myopia correction in the Australian population (Efron et al., 2010). SCLs have the advantage of unrestricted peripheral vision and freedom from spectacle wear but have been found to carry the risk of possible inflammation and infection (Forister et al., 2009).

SCLs have been reported to potentially change the state of relative peripheral defocus. Reduced relative peripheral hyperopia has been reported with SCL wear (Shen et al., 2010). With growing evidence of the potential influence of peripheral defocus on the development of refractive error, this study set out to determine the effects of full, under and over correction of central myopia using SCLs on the state of peripheral refraction.

Agreeing with results reported in Chapter 5 and 6, at baseline, myopes were found to have relative hyperopia in the periphery. J_{180} negatively increased with eccentricity and J_{45} was found to positively increase with positive eccentricity (Atchison et al., 2006, Atchison et al., 2005b, Calver et al., 2007, Seidemann et al., 2002). Objective central refraction with full correction tended to be hyperopic for both low and moderate myopes (+0.30 ± 0.10D; +0.24 ± 0.55D). This is likely to be due to the autorefractor tending to give slightly more hyperopic refraction values compared to subjective refraction (Davies et al., 2003) and similar discrepancies have been reported with the former model, the Shin-Nippon SRW-5000 autorefractor (Chat and Edwards, 2001).

Full correction of central myopia with SCLs caused a hyperopic shift in baseline M at all positions along the horizontal meridian. Furthermore full correction of central myopia with these commercially available SCLs resulted in an increase in relative peripheral hyperopia in both low and moderate myopes. These results conflict with reports by Shen et al (2010) who found a decrease in peripheral hyperopia with both

soft and rigid CL wear. However our results may be specific to the SCL design used in this study.

There are only a few reports on myopia progression with full correction SCLs. First reports were documented in the early 1970s (Barnett and Rengstorff, 1977, Grosvenor, 1975, Harris et al., 1975) with increased myopia progression found to be associated with SCL wear. However, a general steepening of the cornea evident during myopia progression was believed to be responsible for the refraction change. In contrast to a recent 6-month study by Lazon de la Jara et al (2010), Andreo (1990), who investigated myopia progression in teenage children, found no difference in progression rates between daily SCL wear and spectacle lens wear during a one-year period. Horner et al (1999) conducted a three-year randomised clinical trial and similarly found no difference in myopia progression in a group of 11 to 14 year old adolescents wearing SCLs or wearing spectacle lenses. A more recent study by Walline et al (2008) involving 247 SCL and 237 spectacle wearers (age range 8-11 years) confirmed that SCLs do not significantly affect corneal curvature or axial length increase compared to myopic children wearing spectacle lenses.

In 2003, Fulk et al (2003) discovered higher myopia progression rates in children who switched from spectacles to SCLs compared to children who remained in spectacles. An average rate of -0.74D and -0.76D of myopia progression in one year was found in those who changed from SV and bifocal spectacles to SCLs respectively. SV and bifocal wearers who remained in spectacles had myopia progression of -0.23D and -0.26D respectively. More recently, Marsh-Tootle et al (2009) reported that children who switched from spectacles to SCLs experienced a statistically significant but clinically insignificant increase in myopia progression. Children who remained in spectacles experienced myopia progression of -0.25 ± 0.39D over a two-year period while those who converted to SCL wear experienced myopia progression of -0.52 ± 0.46D in two years. These higher myopia progression rates reported with SCL wear are consistent with our results of increased relative peripheral hyperopia with full correction SCLs. At baseline with no correction, peripheral M was found to be myopic at all locations. With full correction SCLs, M at all positions along the horizontal

meridian became hyperopic. According to current theories (Charman and Radhakrishnan, 2010, Smith, 2011, Wallman and Winawer, 2004) this could potentially encourage myopia progression.

Studies have demonstrated hyperopic increase in peripheral refraction with full correction SV spectacle lenses in both Chinese children (Lin et al., 2010) and young adults (Tabernero et al., 2009). The peripheral hyperopic shift tended to increase with increasing central myopia (Lin et al., 2010). However, it has been reported that spectacle lens wear intervention has no significant effect on the progression of myopia (Ong et al., 1999). This is inconsistent with the suggestion that increased peripheral hyperopia encourages myopia progression.

Under-correction of central myopia by 0.75D was found to cause a hyperopic shift in M but not to the extent of full correction. M values between ±20° inclusive remained myopic. The rationale behind under-correction of myopia is the potential reduction in accommodation at near. Animal studies (Irving et al., 1992, Smith and Hung, 1999, Wallman et al., 1995, Wildsoet and Wallman, 1995) have also shown that images focused in front of the retina retard axial elongation and hence myopia progression in numerous animal models. However, under-correction of myopia by +0.75DS with spectacle lenses for two years in myopic children aged 9-14 years was found to increase rather than inhibit myopia progression (Chung et al., 2002). It was proposed that an inability of the eye to appropriately detect the direction of optical defocus stimulated axial elongation. Additionally, under-correction by +0.50DS was found to increase myopia progression by 0.17D compared with full correction over an 18-month period (Adler and Millodot, 2006). It may be that the peripheral retina is still experiencing hyperopic defocus, as demonstrated in our study, and this may underlie the increased myopia progression.

Over-correction resulted in a hyperopic shift in M across the horizontal meridian however to a greater extent than full correction. It was expected that under or over-correction of myopia with SCLs would simply shift the peripheral refraction profile in a myopic or hyperopic direction compared to full correction as demonstrated in Figure 7.3a and 7.5a in low and moderate myopes respectively. However, the shift between

full and over-correction was slightly less than full and under-correction in both low and moderate myopes. This is probably due to accommodation with over-correction resulting in a slightly more myopic refraction measurement. The effects of accommodation on measurements were not monitored in this study.

Contrary to Shen et al (2010), a reduction in J_{180} was found with SCL wear in this study. Corneal aberrations are compensated by internal optics and Shen et al (2010) proposed that the increased astigmatism that they measured may be due to CL wear upsetting this optical balance. Although statistically significant, the difference in J_{180} detected in the current study at peripheral locations between no correction and full correction SCL wear was minimal (<0.25D). Similarly, differences in J_{45} found between full and over correction were clinically insignificant (<0.25D). Animal studies (Kee et al., 2004, McLean and Wallman, 2003, Schmid and Wildsoet, 1997) have suggested that imposed astigmatism has little influence on refractive error development although it seems that emmetropisation occurs towards the more myopic meridian rather than the circle of least confusion (Kee et al., 2004, Schmid and Wildsoet, 1997). The extent of influence of peripheral astigmatism on emmetropisation is still unclear.

Measurements were taken in young adult subjects who were assumed to be non-progressing myopes. Young adults who have an established myopic refractive error are most likely to have developed youth-onset myopia, which has been found to slow or stop progressing during young adulthood (Goss et al., 1985, Grosvenor and Goss, 1999). As myopia progresses, full correction of central refractive error with SCLs will tend towards under-correction over time in progressing myopic children. Therefore confirmation of results on progressive myopic children is required.

The results from the current study illustrate the effects of different levels of SCL correction on peripheral refraction. Conflicting reports on myopia progression with different states of peripheral defocus resulting from different levels of myopia correction illustrate the need for studies which monitor changes in peripheral refraction with myopia progression.

7.2 PERIPHERAL REFRACTION WITH MULTIFOCAL SCLS

Corrected myopes typically experience relative hyperopia in the peripheral retina and there is debate on whether the relatively hyperopic defocus is simply a possible reflection of the prolate (or less oblate) ocular shape commonly seen in myopes (Atchison et al., 2006, Schmid, 2003b, Seidemann et al., 2002) rather than being a myopiogenic factor (Smith, 2011, Wallman and Winawer, 2004). Children who became myopic have been found to have significantly higher amounts of relative peripheral hyperopia before the onset of central myopia in addition to longer axial lengths compared to children who remained emmetropic (Mutti et al., 2007). It has been argued that the increasing relative hyperopia is due to the apparent increasing prolate eye shape evident before the onset of myopia and that this defocus may be driving myopia progression in these children.

It has been proposed that correcting this relative hyperopia or inducing myopia onto the peripheral retina of myopic individuals could potentially slow down or stop the progression of myopia (Charman, 2006, Charman and Radhakrishnan, 2010, Mutti et al., 2000b, Smith, 2011, Wallman and Winawer, 2004). As demonstrated in Chapter 5 and 6 and other studies (Charman et al., 2006, Queirós et al., 2010), this can be achieved with OK lenses. Multifocal SCLs are another modality which can potentially induce myopic defocus onto the peripheral retina in a more predictable manner compared to OK. Multifocal SCLs can be manufactured with numerous peripheral powers at specified distances from central correction.

With emerging evidence of reduced myopia progression with multifocal CL wear (Aller and Wildsoet, 2008, Holden et al., 2010, Anstice and Phillips, 2011), the study described in Section 7.1 was further extended with the aim of describing changes in peripheral defocus with one brand of commercially available multifocal SCLs. It was hypothesised that the plus peripheral add in the multifocal SCLs would induce a myopic shift in the periphery resulting in relative peripheral myopia.

7.2.1 MATERIALS AND METHODS

The same overall study design, measurement techniques and subjects were used as described in Section 7.1. Additionally, multifocal SCLs with distance correction in the centre and a +2.00D add periphery were used.

7.2.1.1 LENSES

Subjects were fitted with Proclear® Multifocal SCLs (Coopervision; New York, USA) made from omafilcon A (62% water content). Proclear® Multifocal SCLs have a diameter of 14.4mm and base curve of 8.7mm. The Proclear® Multifocal SCL design comprises a distance centre surrounded by an aspheric annulus with a progressive increase towards a +2.00DS add toward the periphery. The central spherical zone is 2.3mm in diameter and the annular near zone is 5mm in diameter.

7.2.1.2 DATA ANALYSIS

Repeated-measures ANOVA was performed to describe the horizontal peripheral refraction profile with multifocal SCL wear.

Additionally, doubly MANOVA analysis allowed comparison of peripheral refraction profiles between no, full SV and multifocal correction.

7.2.2 RESULTS

7.2.2.1 BASELINE VARIABLES

Central and peripheral refraction at baseline are shown in Section 7.1.2.1. Baseline RPR profiles are shown in Figure 7.8.

7.2.2.2 PERIPHERAL REFRACTION

In low myopes, multifocal correction significantly changed raw peripheral refraction ($F=6.242$, $p=0.008$) at all positions along the horizontal meridian ($p<0.001$) as illustrated in Figure 7.8a and Table 7.4. Profile shape in the temporal VF was similar with and without multifocal correction (Figure 7.8b). However, there was a significant myopic shift in RPR at all locations in the nasal VF ($F_{N10}=9.217$, $p=0.008$; $F_{N20}=29.491$, $p<0.001$; $F_{N30}=45.328$, $p<0.001$; $F_{N35}=18.799$, $p=0.001$) with multifocal correction (Figure 7.8b).

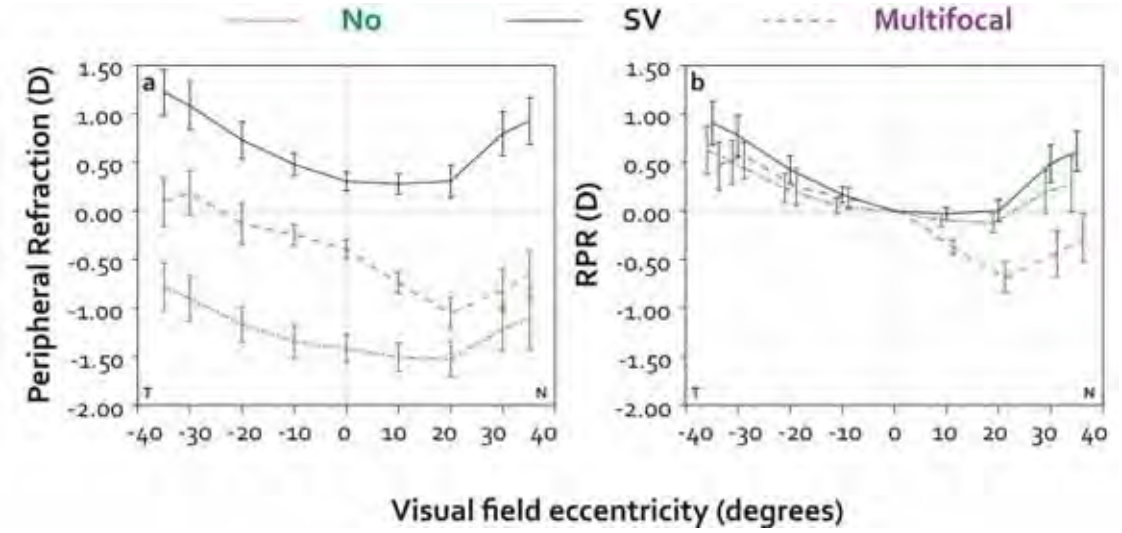


Figure 7.8 a) Raw and b) relative peripheral M profiles (D; mean) with no correction and with full SV and multifocal correction in low myopes. Error bars represent standard error of the mean and have been offset for clarity. Negative eccentricities represent temporal VF while positive eccentricities represent nasal VF.

The average differences in raw peripheral M across the horizontal meridian between full SV and multifocal SCL correction in low myopes are shown in Table 7.4.

M	-35°	-30°	-20°	-10°	C	20°	25°	30°	35°
SV correction	1.98 ± 0.72	1.98 ± 0.88	1.90 ± 0.83	1.83 ± 0.74	1.71 ± 0.70	1.77 ± 0.63	1.83 ± 0.62	2.00 ± 0.64	2.03 ± 0.71
Multifocal correction	0.88 ± 0.92	1.11 ± 0.92	1.07 ± 0.75	1.13 ± 0.61	1.04 ± 0.63	0.77 ± 0.65	0.50 ± 0.61	0.41 ± 0.49	0.49 ± 0.57
Mean Difference*	-1.10 ± 0.70	-0.87 ± 0.70	-0.84 ± 0.78	-0.70 ± 0.38	-0.67 ± 0.36	-1.00 ± 0.33	-1.34 ± 0.38	-1.59 ± 0.40	-1.55 ± 0.59
p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table 7.4 Change in raw M (D; mean ± SD) from baseline with SV and multifocal SCL correction and differences in M change between SV and multifocal SCLs across the horizontal meridian in low myopes. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

**Mean difference = Change in M with multifocal SCL correction– Change in M with SV SCL correction (D ± SD).*

In moderate myopes, a significant difference in raw M was detected between full and multifocal SCL correction ($F=28.920$, $p<0.001$) at all locations ($p<0.001$) (Figure 7.9a and Table 7.5). Moreover, differences in relative peripheral profile between full SV and multifocal correction were found ($F=16.880$, $p<0.001$) at 35° in the temporal VF ($F=8.039$, $p=0.012$) and all locations in the nasal VF ($F_{N10}=0.909$, $p=0.003$; $F_{N20}=54.100$, $p<0.001$; $F_{N30}=71.018$, $p<0.001$; $F_{N35}=50.385$, $p<0.001$) as illustrated in Figure 7.9b.

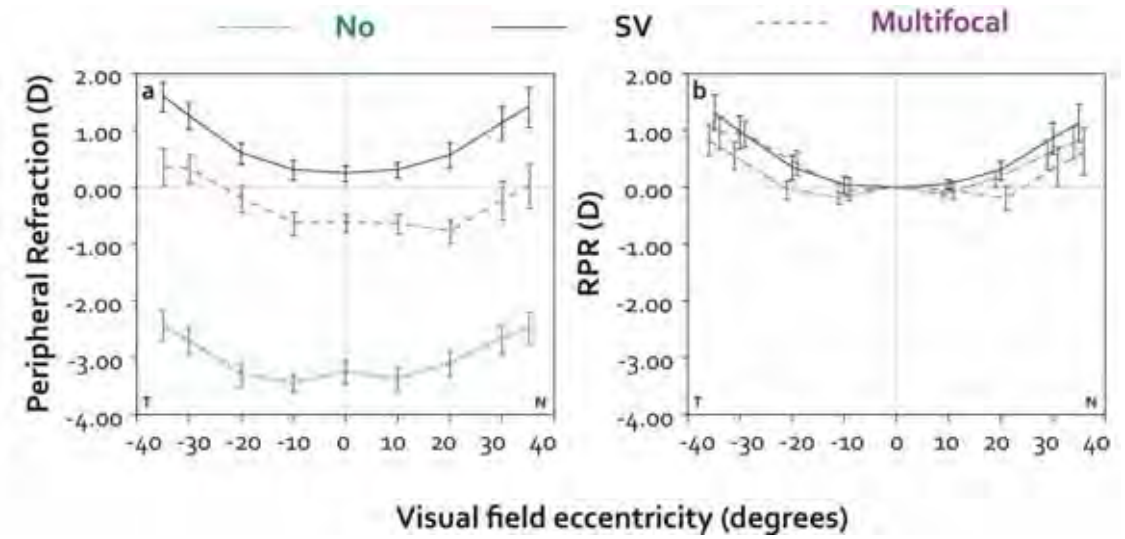


Figure 7.9 a) Raw and b) relative peripheral M profiles (D; mean) with no correction and with full SV and multifocal correction in moderate myopes. Error bars represent standard error of the mean and have been offset for clarity. Negative eccentricities represent temporal VF while positive eccentricities represent nasal VF.

The average differences in raw peripheral M across the horizontal meridian between full SV and multifocal SCL correction for moderate myopes are shown in Table 7.5.

M	-35°	-30°	-20°	-10°	C	20°	25°	30°	35°
SV correction	3.98 ± 0.72	3.92 ± 0.82	3.87 ± 0.96	3.72 ± 0.77	3.49 ± 0.67	3.66 ± 0.85	3.64 ± 0.90	3.77 ± 0.81	3.85 ± 0.88
Multifocal correction	2.77 ± 1.02	3.02 ± 0.78	3.08 ± 1.15	2.79 ± 0.76	2.62 ± 0.74	2.72 ± 1.09	2.31 ± 0.96	2.42 ± 1.01	2.47 ± 1.13
Mean Difference*	-1.21 ± 0.65	-0.91 ± 0.63	-0.79 ± 1.17	-0.93 ± 0.81	-0.87 ± 0.83	-0.95 ± 0.76	-1.33 ± 0.73	-1.35 ± 0.83	-1.38 ± 0.70
p value	<0.001	0.002	0.038	0.001	0.001	0.008	<0.001	<0.001	<0.001

Table 7.5 Change in raw M (D; mean ± SD) from baseline with SV and multifocal SCL correction and differences in M change between SV and multifocal SCLs across the horizontal meridian in moderate myopes. Negative eccentricities denote the temporal VF while positive eccentricities denote the nasal VF.

**Mean difference = Change in M with multifocal SCL correction– Change in M with SV SCL correction (D ± SD).*

Multifocal SCL correction in low myopes significantly changed raw J_{180} ($F=8.925$, $p=0.003$) with greater amounts of astigmatism evident at 10°, 20° and 30° in the nasal VF ($F_{N10}=42.563$, $p<0.001$; $F_{N20}=97.256$, $p<0.001$; $F_{N30}=17.709$, $p=0.001$) (Figure 7.10a). Furthermore, significant differences in J_{180} was found between full SV and multifocal correction in moderate myopes at 35° in the temporal VF ($F_{T35}=6.843$, $p=0.019$) and at 10°, 20°, 30° and 35° in the nasal VF ($F_{N10}=31.996$, $p<0.001$; $F_{N20}=53.403$, $p<0.001$; $F_{N30}=10.218$, $p=0.006$; $F_{N35}=8.244$, $p=0.011$). There was a negative increase in J_{180} with multifocal lens wear compared to SV (Figure 7.10b).

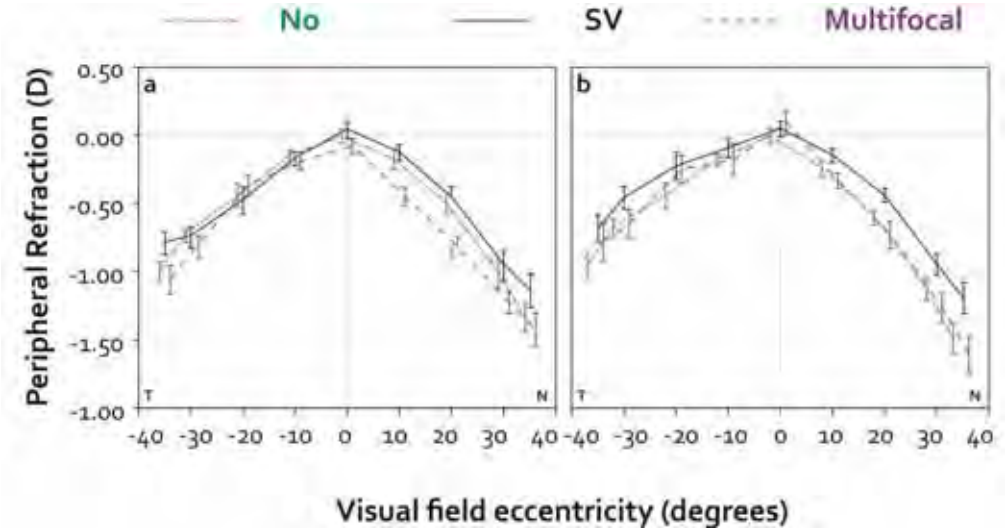


Figure 7.10 Raw J_{180} peripheral refraction profiles (D; mean) with no correction and with full SV and multifocal correction in a) low and b) moderate myopes. Error bars represent standard error of the mean and have been offset for clarity. Negative eccentricities represent temporal VF while positive eccentricities represent nasal VF.

In moderate myopes, there was a significant difference in raw J_{45} profile with no correction and with multifocal correction ($F=3.919$, $p=0.034$). A negative increase at 10°, 20° and 30° in the nasal VF ($F_{N10}=9.307$, $p=0.008$; $F_{N20}=5.509$, $p=0.032$; $F_{N30}=9.541$, $p=0.007$) was measured (Figure 7.10b). There was a difference also found between full SV and multifocal correction ($F=6.312$, $p=0.008$) at 30° in the temporal VF ($F=4.827$, $p=0.043$) and all positions in the nasal VF ($F_{N10}=11.181$, $p=0.004$, $F_{N20}=10.899$, $p=0.005$; $F_{N30}=19.639$, $p<0.001$; $F_{N35}=23.747$, $p<0.001$) (Figure 7.11b).

There was no significant difference in J_{45} profile between no correction and multifocal SCL correction (F_{LM}=2.755, p=0.084; F_{MM}=3.010, p=0.068) or between full SV and multifocal SCL correction (F_{LM}=1.797, p=0.211; F_{MM}=2.858, p=0.077) in low myopes or moderate myopes (Figure 7.11).

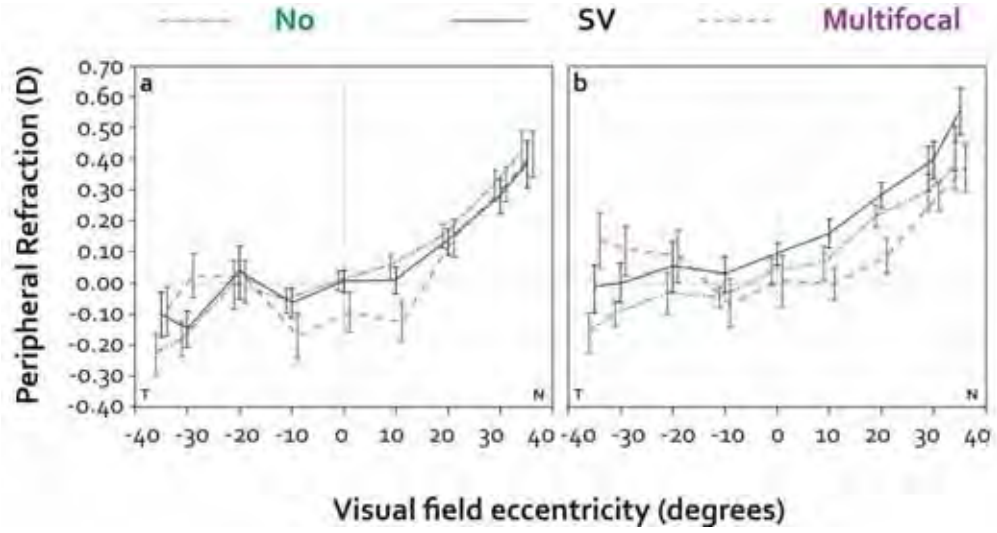


Figure 7.11 Raw J_{45} peripheral refraction profiles (D; mean) with no correction and with full SV and multifocal correction in a) low and b) moderate myopes. Error bars represent standard error of the mean and have been offset for clarity. Negative eccentricities represent temporal VF while positive eccentricities represent nasal VF.

7.2.2.3 CONTROL

There was no significant difference in M profiles in the left eye with no, full or multifocal correction in either low myopes (F=1.123, p=0.415) or moderate myopes (F=0.555, p=0.757). Similarly, there was no significant difference in either J_{180} or J_{45} with no, full SV and multifocal correction in low (F_{J180}=1.318, p=0.264; F_{J45}=0.408, P=0.871) or moderate myopes (F_{J180}=1.257, p=0.290; F_{J45}=0.529, P=0.784).

7.2.3 DISCUSSION

Human (Hoogerheide et al., 1971, Mutti et al., 2007) and animal studies (Liu and Wildsoet, 2011, Smith et al., 2009b, Smith et al., 2005, Smith et al., 2007) investigating the state of peripheral retinal defocus have lead to the proposal that correcting or inducing myopia onto the peripheral retina of myopic individuals could possibly slow down or stop the progression of myopia (Charman, 2006, Charman and Radhakrishnan, 2010, Mutti et al., 2000b, Smith, 2011, Wallman and Winawer, 2004). As demonstrated in Chapter 5, this optical manipulation is achieved with OK in both adults (Charman et al., 2006, Queirós et al., 2010) and children. Multifocal SCLs may also achieve this phenomenon (Holden et al., 2010, Anstice and Phillips, 2011). In this study, the peripheral optical effect of one brand of commercially available multifocal SCLs was measured in low and moderate myopic individuals.

Proclear® Multifocal SCLs with distance centre and a +2.00D near add in the periphery allow the correction of manifest central myopic refraction while theoretically inducing myopic defocus onto the peripheral retina to aid in near vision. Although there have been reports of reduced myopia progression with bifocal or multifocal CLs with a peripheral myopic defocus (Aller and Wildsoet, 2008, Holden et al., 2010, Anstice and Phillips, 2011), the exact mechanism behind the reduced rate of progression is unknown. Furthermore, the status of peripheral defocus induced by these lenses has not been disclosed in detail.

The Proclear® Multifocal SCLs used in the current study were found to create a myopic shift in peripheral refraction compared to SV SCLs as demonstrated in Tables 7.4 and 7.5 for low and moderate myopes respectively. The amount of myopic shift increased with eccentricity in both the nasal and temporal VF and this gradual change towards the periphery is likely to be a result from the design of the multifocal SCLs. Beyond the central 2.3mm distance correction zone, there is a gradual progression towards a +2.00DS peripheral near add.

Simple ray tracing (Appendix A) has determined that peripheral refraction measurements with the Shin-Nippon NVision-K 5001 autorefractor at 35° in the

temporal and nasal VF correspond to measurements centred around 1.5 and 2.8mm in the temporal and nasal cornea respectively. The nasal measurements would display greater amounts of myopic defocus as the autorefractor is able to take measurements more peripherally in the nasal cornea and this was reflected in our results (Tables 7.4 and 7.5). Furthermore, the myopic shift evident in the peripheral retina was not by a full +2.00DS and this is likely to be due to the 2.3mm measurement ring of the autorefractor. The autorefractor measures refraction averaged over a 2.3mm diameter area rather than at individual points along the cornea or CL and therefore a measurement at a particular position may not be a true reflection of the refractive status at that point, but rather an average over a region of the cornea or CL. Due to the progressive multifocal design of the Proclear® Multifocal, the autorefractor may not be able to detect the full myopic shift induced by the lens as the measurement would be an average of the multiple powers within the 2.3mm measurement ring.

Furthermore, as both the central zone in Proclear ® Multifocal SCLs and the Shin-Nippon NVision-K 5001 autorefractor measurement ring are 2.3mm in diameter, any slight misalignments or decentration of the CL will then result in an undercorrection reading, which was evident in both low and moderate myopes (Figure 7.8a and b respectively). A limitation of this study was that centration of the lens was not critically analysed.

There are two commercially available multifocal SCLs designed to induce myopic defocus in the peripheral retina, the AMCL and the MiSight® lens. Holden et al (2010) investigated the effect of their custom AMCL on a group of 65 Chinese children aged between 7 and 14 years. Compared to 50 subjects wearing spectacles, a reduced myopia progression of -0.26 ± 0.25D compared to -0.60 ± 0.29D, and axial length elongation of 0.08 ± 0.11mm compared to 0.25 ± 0.12mm, was reported over a 6-month period. However, the exact design of this silicone hydrogel SCL is restricted under patent laws. Furthermore, the exact amount of myopic defocus induced onto the peripheral retina of these children subjects has not yet been published.

Anstice and Phillips (2011) have also demonstrated reduced myopia progression in children wearing the Dual-Focus lens compared to SV SCLs, of -0.44 ± 0.33D

compared to -0.69 ± 0.38D and axial length elongation of 0.11 ± 0.09mm compared to 0.22 ± 0.09mm over the first 10 month period of their cross-over study. During the second 10 month period subsequent to the cross-over, the eye now assigned to wear the Dual-Focus lens had myopia progression and axial elongation of -0.17 ± 0.35D and 0.03 ± 0.10mm compared to -0.38 ± 0.38D and 0.14 ± 0.09mm in the eye now assigned to SV SCL wear. The Dual-Focus lens is concentric in design with a central distance correction zone and concentric treatment (+2.00DS) and correction zones to provide clear distance vision while simultaneously inducing myopic defocus onto the retina. However, the exact change in peripheral refraction with these CLs is yet to be published.

A limitation of this study was that accommodation was not monitored with these multifocal lenses in our pre-presbyopic subject group and the effects of the near peripheral add on accommodation and hence refraction measurements are unknown. To minimise the effect of accommodation on measurements, the testing conditions were arranged such that the fixation target was non-accommodative (Section 2.2.2.1.1) and the autorefractor used was open-field in design which minimises the problem of proximal accommodation (Section 2.2.3.1). Nevertheless, it would be interesting to repeat this study under conditions of cycloplegia.

The current hypothesis is that inducing myopia onto the peripheral retina or correcting the relative hyperopia typically seen in myopes could possibly slow down or stop the progression of myopia (Charman and Radhakrishnan, 2010, Smith, 2011, Wallman and Winawer, 2004). Peripheral refraction is variable and the amount of myopic defocus required to correct the relative peripheral hyperopia will also vary. Thus commercially available multifocal SCLs which have a +2.00D myopic shift in the periphery may not be appropriate for all individuals. Therefore caution must be used when prescribing commercially available multifocal SCLs which claim to reduce myopia progression. Furthermore, as the subjects recruited in this study were adult myopes, confirmation of peripheral defocus change with these lenses is required on progressing myopic children.

7.3 CONCLUSION

Full correction of central myopia with Proclear® Sphere SCLs caused peripheral refraction to change towards hyperopia in both low and moderate myopes. When analysing the refraction profile along the horizontal meridian, there were greater amounts of relative hyperopia with full SCL correction compared to no correction. Furthermore, under and over-correction of central myopia with SCLs also caused significant change in peripheral refraction in a similar way as full correction, with peripheral refraction shifted to become hyperopic. The least peripheral hyperopic shift was measured with under-correction and the most with over-correction. Moreover, the shape of the peripheral refraction profile was similar between all three levels of correction. This suggests that any level of correction with spherical SCLs within the ranges investigated in this study could encourage myopia progression through induced peripheral hyperopic defocus.

Proclear® Multifocal SCLs were found to induce myopic defocus in the periphery. The change was gradual with greater myopic shift measured with greater eccentricity. This study confirmed that commercially available multifocal SCLs can effectively induce myopia into the retinal periphery of myopic adults. However, as peripheral refraction is highly variable, a +2.00 myopic shift may not be appropriate for all individuals. Therefore caution must be taken when prescribing and claiming reduced myopia progression with multifocal CLs. Furthermore, confirmation of these refraction changes is required in progressing myopic children.

CHAPTER 8

OVERALL SUMMARY AND CONCLUSIONS

8.1 SUMMARY

8.1.1 PERIPHERAL REFRACTION IN DIFFERENT REFRACTIVE GROUPS

The studies reported in this thesis have presented typical peripheral refraction profiles in different refractive groups. Results from Chapters 3, 4, 5, 6 and 7 have consistently shown that myopic adults demonstrate relative hyperopia in the peripheral retina. Furthermore, relative peripheral hyperopia was measured in progressing myopic Asian children as reported in Chapter 5. Emmetropes have been found to have peripheral refraction which is similar in degree to central refractive error (reported in Chapter 3 and 4) while hyperopes have been found to have similar refractive profiles to emmetropes although slightly more myopic in the periphery (Chapter 4).

The significance of peripheral refraction measurements is that they can possibly be used to infer ocular shape. If the image shell is assumed to be spherical, an individual experiencing relatively hyperopic defocus in the periphery is thought to possess a more prolate ocular shape. If the defocus in the periphery is similar to that at the centre, the image shell is considered to coincide with the retina reflecting a more spherical ocular shape. Relatively myopic defocus experienced in the peripheral retina suggests a more oblate eye shape.

The high prevalence of myopia in Asia (Fan et al., 2004, He et al., 2009, Lin et al., 2004, Saw et al., 1996, Zhao et al., 2000) motivated the investigation to compare peripheral refraction in young adults of East Asian and Caucasian ethnicity. Although no difference in peripheral refraction profile was found in emmetropes and low myopes between East Asian and Caucasian subjects, interestingly a significant

difference in peripheral refraction profile was detected in moderately myopic East Asian and Caucasian young adults. East Asian moderate myopes showed greater relative peripheral hyperopia compared to Caucasians of a similar central refractive error. This suggested that East Asians possess a more prolate ocular shape as inferred from peripheral refraction. Thus it was postulated that the difference in ocular shape, as suggested by differences in peripheral refraction profiles, could possibly explain the difference in myopia prevalence rates between ethnicities (Ip et al., 2008, Kleinstein et al., 2003). Relative peripheral hyperopia, implying a more prolate ocular shape, has been reported in children up to 2 years before the onset of myopia (Mutti et al., 2007). Stone and Flitcroft (2004) also suggested a protective effect of oblate eye shape from myopia development. Asian eyes possessing more prolate ocular shapes, as inferred from peripheral refraction, could be at higher risk of development of myopia than individuals with less prolate or oblate ocular shapes.

8.1.2 PERIPHERAL REFRACTION AND OCULAR SHAPE

Ocular shape has been associated with peripheral refraction on the basis of ray tracing (Atchison and Smith, 2000) indicating that M relatively accurately describes ocular shape. However eye modelling studies (Dunne, 1995, Logan et al., 1995) have indicated that this may be an oversimplification and not an accurate portrayal of ocular shape. Furthermore, no studies to date have compared ocular shape derived from peripheral refraction measurements to direct measurements of ocular shape.

The study described in Chapter 4 attempted to better understand information on ocular shape derived from peripheral refraction measurements at 25° in the temporal and nasal VF along the horizontal meridian. Comparison of direct and indirect measures of axial length in the nasal retina demonstrated comparable axial length measurements while axial length calculated from peripheral refraction tended to under-estimate axial length in the temporal retina compared to direct measurements. Although not entirely comparable, the results from this study suggested that ocular shape derived from peripheral refraction may not be an over-simplification. Other

less used techniques such as MRIs and CT scans are expensive and difficult to access and thus peripheral refraction measurements provide a cost effective and simple alternative. Assumptions and equations used in the calculation of axial length from peripheral refraction data need to be revisited, and incorporating corneal topographic data into calculations would have strengthened results from this study.

8.1.3 OK AND PERIPHERAL REFRACTION

It has recently been proposed that an individual's peripheral vision has a large influence on the development of central refractive error (Charman and Radhakrishnan 2010, Smith, 2011, Wallman and Winawer, 2004). An eye that is prolate in shape experiences relative hyperopia in the periphery and the eye may grow in axial length in order to bring this peripheral hyperopia into focus despite the development of central axial myopia (Charman and Radhakrishnan, 2010). Wallman and Winawer (2004) suggested that the eye will continue to elongate until the myopic central retina balances the hyperopic periphery. Correcting central refractive error may cause a renewed imbalance and stimulate central myopia to progress until a balance is reached. However, manipulating the state of peripheral vision could have an impact on myopia development and progression (Charman and Radhakrishnan, 2010, Smith, 2011, Wallman and Winawer, 2004).

Correcting central myopia with common optical devices such as SCLs and SV spectacles shifts the image shell back and induces hyperopia onto the peripheral retina. If the theory described above is true, this would potentially encourage the development of axial myopia. OK lenses are another form of central myopia correction which inadvertently keeps the focus at the peripheral retina relatively unchanged, thus resulting a myopic defocus in the periphery (Charman, 2006, Queirós et al., 2010). This causes the peripheral image shell, which was previously relatively hyperopic, to become relatively myopic. The studies described in Chapter 5 demonstrated that these changes in peripheral refraction profiles were apparent in both myopic children and adults during OK lens wear.

Further investigation of peripheral refraction and corneal topography changes with OK found that, in line with reports of changes in refraction and corneal topography along the visual axis with OK lens wear, changes in both peripheral refraction and para-central refractive power were most prominent over the first day of OK lens wear (Chapter 5). Stability in both peripheral refraction and corneal refractive power changes was apparent after about 7 days of OK lens wear.

8.1.4 OK AND THE POTENTIAL FOR MYOPIA CONTROL

In accordance with current theories of myopia control, correction of peripheral hyperopia evident in corrected myopes, or inducing myopic defocus onto the peripheral retina, could potentially slow down or prevent axial elongation. Furthermore, emmetropic children who present with a more prolate ocular shape may be at risk of developing myopia, and inducing myopic defocus onto the peripheral retina may prevent central myopia development.

Peripheral refraction is highly variable between individuals as shown in the studies described in this thesis (Chapters 3, 4, 5, 6 and 7). In order to be able to induce appropriate changes of focus onto the peripheral retina in accordance with the hypothesised theory of possible myopia control through correction of peripheral refractive error or by inducing a peripheral myopic defocus, peripheral refraction manipulation should ideally be customised. Studies presented in Chapter 6 endeavoured to investigate this possibility with OK lenses.

Relationships between changes in para-central corneal refractive power and corresponding peripheral refraction were initially investigated (Chapter 6). Better understanding of how OK lenses change peripheral refraction through changes in corneal topography was required. Only half the locations studied (0.5mm and 0.1mm on the temporal cornea and 0.5 and 1.1mm on the nasal cornea) on the horizontal corneal chord of interest were found to show significant relationships between the amount of corneal refractive power change and the amount of peripheral refraction change. Changes in optical properties of the cornea after OK such as radius of

curvature and refractive index were postulated as possible reasons for the low correlations found. Furthermore, the autorefractor averages refraction measurements over a 2.3mm diameter zone and hence measurements may not reflect the refractive value at the point of interest at which corneal refractive power was determined.

The thesis then investigated if changes in OK lens parameters could induce predictable changes in corneal topography and peripheral refraction. There are only a few OK lens design parameters that can be manipulated while maintaining the central refractive effect of OK lenses. Significant changes in many lens parameters are likely to have an effect on the overall fit of the OK lens which will consequently compromise desired topography changes and hence the central myopia correction induced by OK lenses.

The OZD was reduced from 6mm in a standard BE OK lens to 5mm. It was hypothesised that reducing the OZD would reduce the TZD which in turn would result in a larger portion of the peripheral retina experiencing a myopic defocus. Changing OZD was found to cause no significant change in peripheral refraction. Additionally the effect of the peripheral tangent was investigated. Changing the tangent from ¼ to ½ would steepen the periphery of the lens and this was expected to increase the amount of para-central corneal steepening. This was hypothesised to increase the myopic defocus evident in the peripheral retina with OK lens wear. However changing the tangent did not cause significant changes in peripheral refraction. We conclude that the modification of OK lens parameters may have been too subtle to cause significant changes in peripheral refraction.

8.1.5 PERIPHERAL REFRACTION AND SCLS

SCLs can be manufactured with specific powers in the periphery of the lens, targeted to induce desired defocus onto the peripheral retina. Effects of different designs of SCLs on peripheral refraction were investigated to determine if SCLs could change peripheral refraction in a more predictable manner than OK lenses.

Initially, the effect of different levels of central myopia correction with SCLs was investigated. Although there have been reports of the effects of full correction SCLs on peripheral refraction, it was unknown how under or over-correction of myopia affected the status of peripheral defocus. It was found that under (+0.75DS), full and over-correction (-0.75DS) of central myopia with SCLs resulted in subjects experiencing hyperopic defocus in the peripheral retina. This may explain why increased myopia progression has been reported with under-correction with spectacles (Chung et al., 2002, Adler and Millodot, 2006) contrary to animal models (Irving et al., 1992, Smith and Hung, 1999, Wallman et al., 1995, Wildsoet and Wallman, 1995) which have demonstrated inhibition of axial elongation and myopia progression with central myopic defocus. Inability of the human myopic eye to detect the direction of optical defocus had previously been proposed to stimulate axial elongation (Chung et al., 2002).

Chapter 7 also reported an investigation of the effect of multifocal SCLs on peripheral refraction. Currently there are two commercially available multifocal SCLs designed to induce a myopic defocus onto the peripheral retina. There have only been preliminary reports on reduced rates of myopia progression and axial length elongation with these SCLs, and only limited information on the status of peripheral defocus in children fitted with these SCLs has been published. Hence the study described in Chapter 7 endeavoured to describe the changes in peripheral refraction in young myopic adults wearing a specific brand of multifocal SCL.

Compared to SV SCL correction, multifocal SCL correction induced less peripheral hyperopia in both low and moderately myopic young adults. The results from this study indicate multifocal SCLs are an alternative means to correct the peripheral hyperopia typically induced by traditional optical devices and may potentially have an anti-myopiogenic effect.

8.1.6 LIMITATIONS

The main limitation of the studies reported in this thesis is the profile of recruited subjects. The theory of potential myopia control through peripheral refraction manipulation is based on a developing eye and most of the subjects recruited for studies reported in this thesis were non-progressing, young adult myopes. Only one study included progressing myopic children. Most of these young adult subjects were from a university population which may not be an accurate reflection of the general population. Ideally these studies should be repeated on progressing myopic children for confirmation of conclusions drawn from this research.

Another limitation was low subject numbers. Studies investigating the effects of OK lenses on peripheral refraction and corneal topography were investigated in only 16 children and 19 adult myopes. Moreover, the effects of different OK lens parameters on peripheral refraction were investigated in only 17 young adult subjects. These studies did not have enough statistical power and larger sample sizes are required to achieve adequate power. This will determine if the insignificant effects found were simply due to low subject numbers or because there is no significant effect. However, the novel nature of the studies described in this thesis and questions about what is considered as a clinically significant difference in peripheral refraction created difficulty in determining appropriate sample size and study power. Furthermore, we were limited to one design of OK lenses for the studies described in Chapter 5 and 6 and only one brand of SCL was used for the studies described in Chapter 7. The results found may be specific to the design of these CLs.

The assumptions used in some of the calculations for the studies described in the thesis also limit the interpretation of our results. Parameters of an average eye were used to calculate corneal refractive power (Chapter 5 and 6; Appendix B) and to determine the location along the horizontal corneal chord at which peripheral refraction measurements were taken (Chapter 5 and 6; Appendix A). Additionally average eye parameters were used to calculate peripheral axial length from peripheral refraction data (Chapter 4). Although myopic eyes would be similar to those of

emmetropes and hyperopes, due to the simple calculations used, longer axial length deemed myopic eyes to be of less power.

Furthermore, improvements in instrumentation could have potentially given a different interpretation of results particularly in the study investigating ocular shape described by peripheral refraction (Chapter 4). Corneal topography maps of the eye could have allowed inclusion of anterior corneal curvature data such as apical corneal radius, for a more accurate calculation of peripheral axial length.

When describing peripheral refraction changes after modification of the corneal surface induced by OK lens wear, it cannot be assumed that peripheral refraction measurements are taken at the same position as the baseline measurements on the retina. Peripheral refraction measurements are taken obliquely through the eye and due to changes in corneal curvature, thickness and refractive index with OK lens wear, it is possible that oblique infrared rays (from the autorefractor) entering the eye would refract in a different manner to baseline when no OK lenses were worn. Peripheral ray tracing would have given a more accurate idea of the retinal locations where peripheral refractions were measured before and after OK lens wear. However, peripheral ray tracing is complex and beyond the scope of this thesis.

8.1.7 FUTURE RESEARCH DIRECTIONS

The main aim of the research described in this thesis was to investigate the possibility of customised peripheral defocus manipulation in myopic individuals using OK. As previously mentioned, there are limited parameters that can be modified as significant changes in OK lens parameters are likely to affect the fit of the OK lens which in turn may compromise the central refractive outcomes. Clear unaided central vision is a fundamental goal in OK. The lens design changes described in Chapter 7 may have been too subtle for significant differences in corneal topography and peripheral refraction to be measured.

Further research into the effects of other lens parameters is warranted as it will provide information not only on the effects of lens parameters on peripheral refraction, but also on the fundamental mechanisms of OK. If indeed the hydraulic theory of OK is true (Coon, 1982, Mountford, 2004b), we may find that subtle changes in any lens parameters will not create a significant change in corneal topography and hence peripheral refraction. If the moulding theory does apply (Jessen, 1962), other lens parameters such as asphericity of the back optic zone, and reverse curve width and height, may induce corresponding changes in corneal topography that significantly alter peripheral refraction. Moreover, if the anti-myopic effect of OK is due to peripheral refraction changes, it will be important to monitor and investigate the relationships between changes in peripheral refraction and axial length in children fitted with OK lenses.

Mutti et al (2007) reported that myopic children have relative hyperopia up to 2 years before the onset of central myopia. It would be interesting to see if emmetropic children who have a more prolate ocular shape could be protected from myopia development if myopic defocus is induced onto the peripheral retina. This will provide important evidence to determine whether the current theory that peripheral refraction manipulation may slow down or prevent further progression of myopia can be applied to myopic children.

Although this theory has gained much support, fundamental questions still remain. It is currently unknown exactly how much myopic defocus is required to be induced onto the peripheral retina to have an effect on central refractive error development. Therefore future investigation into the effects of different levels of peripheral myopic defocus on central refractive error progression is required. Additionally, it is unknown how long these peripheral defocus manipulations need to be induced. Although reduced myopia progression has been reported with optical devices which manipulate peripheral refraction such as OK and multifocal spectacle and SCLs, it is also unknown if there will be a rebound effect after the cessation of treatment and an accrual of effect with continuing wear of these optical devices.

REFERENCES

ADAMS, D. W. & MCBRIEN, N. A. 1992. Prevalence of myopia and myopic progression in a population of clinical microscopists. *Optom Vis Sci,* 69**,** 467-73.

ADLER, D. & MILLODOT, M. 2006. The possible effect of undercorrection on myopic progression in children. *Clin Exp Optom,* 89**,** 315-21.

AGGARWALA, K. R., KRUGER, E. S., MATHEWS, S. & KRUGER, P. B. 1995a. Spectral bandwidth and ocular accommodation. *J Opt Soc Am A Opt Image Sci Vis,* 12**,** 450-5.

AGGARWALA, K. R., NOWBOTSING, S. & KRUGER, P. B. 1995b. Accommodation to monochromatic and white-light targets. *Invest Ophthalmol Vis Sci,* 36**,** 2695-705.

AHNELT, P. K. 1998. The photoreceptor mosaic. *Eye,* 12**,** 531-40.

ALHARBI, A. & SWARBRICK, H. A. 2003. The effects of overnight orthokeratology lens wear on corneal thickness. *Invest Ophthalmol Vis Sci,* 44**,** 2518-23.

ALLER, T. A. & WILDSOET, C. F. 2008. Bifocal soft contact lenses as a possible myopia control treatment: a case report involving identical twins. *Clin Exp Optom,* 91**,** 394-9.

ALSBIRK, P. H. 1978. Corneal thickness. I. Age variation, sex difference and oculometric correlations. *Acta Ophthalmol (Copenh),* 56**,** 95-104.

ANDREO, L. K. 1990. Long-term effects of hydrophilic contact lenses on myopia. *Ann Ophthalmol,* 22**,** 224-7, 229.

ANSTICE, N. S. & PHILLIPS, J. R. 2011. Effects of Dual-Focus soft contact lens wear on axial myopia progression in children. *Ophthalmology,* 118**,** 1152-61.

ARTAL, P. 2000. Understanding aberrations by using double-pass techniques. *J Refract Surg,* 16**,** S560-2.

ARTAL, P., DERRINGTON, A. M. & COLOMBO, E. 1995a. Refraction, aliasing, and the absence of motion reversals in peripheral vision. *Vision Res,* 35**,** 939-47.

ARTAL, P., MARCOS, S., NAVARRO, R. & WILLIAMS, D. R. 1995b. Odd aberrations and double-pass measurements of retinal image quality. *J Opt Soc Am A Opt Image Sci Vis,* 12**,** 195-201.

ASHBY, R., OHLENDORF A. & SCHAEFFEL F. 2009. The effect of ambient illuminance on the development of deprivation of myopia in chicks. *Invest Ophthalmol Vis Sci* 50**,** 5348-54.

ATCHISON, D. A. 2003. Comparison of peripheral refractions determined by different instruments. *Optom Vis Sci,* 80**,** 655-60.

ATCHISON, D. A. 2009. Objective refraction. *In:* ROSENFIELD, M., LOGAN, N. & EDWARDS, K. (eds.) *Optometry: Science, Techniques and Clinical Management.* 2 ed. London: Butterworth Heinemann, 187-208

ATCHISON, D. A. & CHARMAN, W. N. 2011. Can partial coherence interferometry be used to determine retinal shape? *Optom Vis Sci,* 88**,** E601-7.

ATCHISON, D. A., JONES, C. E., SCHMID, K. L., PRITCHARD, N., POPE, J. M., STRUGNELL, W. E. & RILEY, R. A. 2004. Eye shape in emmetropia and myopia. *Invest Ophthalmol Vis Sci,* 45**,** 3380-6.

ATCHISON, D. A. & MARKWELL, E. L. 2008. Aberrations of emmetropic subjects at different ages. *Vision Res,* 48**,** 2224-31.

ATCHISON, D. A., MARKWELL, E. L., KASTHURIRANGAN, S., POPE, J. M., SMITH, G. & SWANN, P. G. 2008. Age-related changes in optical and biometric characteristics of emmetropic eyes. *J Vis,* 8**,** 1-20.

ATCHISON, D. A., PRITCHARD, N. & SCHMID, K. L. 2006. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res,* 46**,** 1450-8.

ATCHISON, D. A., PRITCHARD, N., SCHMID, K. L., SCOTT, D. H., JONES, C. E. & POPE, J. M. 2005a. Shape of the retinal surface in emmetropia and myopia. *Invest Ophthalmol Vis Sci,* 46**,** 2698-707.

ATCHISON, D. A., PRITCHARD, N., WHITE, S. D. & GRIFFITHS, A. M. 2005b. Influence of age on peripheral refraction. *Vision Res,* 45**,** 715-20.

ATCHISON, D. A., SCOTT, D. H. & CHARMAN, W. N. 2003. Hartmann-Shack technique and refraction across the horizontal visual field. *J Opt Soc Am A Opt Image Sci Vis,* 20**,** 965-73.

ATCHISON, D. A., SCOTT, D. H. & CHARMAN, W. N. 2007. Measuring ocular aberrations in the peripheral visual field using Hartmann-Shack aberrometry. *J Opt Soc Am A Opt Image Sci Vis,* 24**,** 2963-73.

ATCHISON, D. A. & SMITH, G. 2000. Monochromatic aberrations. *In:* ATCHISON, D. A. & SMITH, G. *Optics of the Human Eye*, Oxford: Butterworth-Heinemann, 137-59

ATTEBO, K., IVERS, R. Q. & MITCHELL, P. 1999. Refractive errors in an older population: the Blue Mountains Eye Study. *Ophthalmology*, 106, 1066-72.

AZZOPARDI, P. & COWEY, A. 1993. Preferential representation of the fovea in the primary visual cortex. *Nature*, 361, 719-21.

BAGHERI, A., FARAHI, A. & GUYTON, D. L. 2003. Astigmatism induced by simultaneous recession of both horizontal rectus muscles. *J AAPOS*, 7, 42-6.

BAKER, T. Y., 1943. Ray tracing through non-spherical surfaces. *Proc Phys Soc*, 55,361-4.

BARNES, D. A., DUNNE, M. C. & CLEMENT, R. A. 1987. A schematic eye model for the effects of translation and rotation of ocular components on peripheral astigmatism. *Ophthalmic Physiol Opt*, 7, 153-8.

BARNETT, W. A. & RENGSTORFF, R. H. 1977. Adaptation to hydrogel contact lenses: variations in myopia and corneal curvature measurements. *J Am Optom Assoc*, 48, 363-6.

BARTLETT, J. D., NIEMANN, D., HOUDE, B., ALLRED, T., EDMONDSON, M. J. & CROCKETT, R.S. 2003. A tolerability study of pirenzipine ophthalmic gel in myopic chidren. *J Ocul Pharmacol Ther*, 19, 271-9.

BELIN, M. W. & KHACHIKIAN, S. S. 2009. An introduction to understanding elevation-based topography: how elevation data are displayed - a review. *Clin Exp Ophthalmol*, 37, 14-29.

BELIN, M. W. & RATLIFF, C. D. 1996. Evaluating data acquisition and smoothing functions of currently available videokeratoscopes. *J Cataract Refract Surg*, 22, 421-426.

BENNETT, A. G., 1966. The calibration of keratometry. *Optician*, 151, 317-22.

BERDEAUX, G., ALIO, J. L., MARTINEZ, J. M., MAGAZ, S. & BADIA, X. 2002. Socioeconomic aspects of laser in situ keratomileusis, eyeglasses, and contact lenses in mild to moderate myopia. *J Cataract Refract Surg*, 28, 1914-23.

BERNTSEN, D. A., MUTTI, D. O. & ZADNIK, K. 2008. Validation of aberrometry-based relative peripheral refraction measurements. *Ophthalmic Physiol Opt*, 28, 83-90.

BERNTSEN, D. A., MUTTI, D. O. & ZADNIK, K. 2010. Study of Theories about Myopia Progression (STAMP) design and baseline data. *Optom Vis Sci,* 87**,** 823-32.

BERNTSEN, D. A., SINNOTT, L. T., MUTTI, D. O. & ZADNIK, K. 2011. Accommodative lag and juvenile-onset myopia progression in children wearing refractive correction. *Vision Res*, 51**,** 1039-46.

BERSON, D. M. 2003. Strange vision: ganglion cells as circadian photoreceptors. *Trends Neurosci,* 26**,** 314-20.

BLAND, J. M. & ALTMAN, D. G. 1999. Measuring agreement in method comparison studies. *Stat Methods Med Res,* 8**,** 135-60.

BOBIER, W. R., CAMPBELL, M. C. & HINCH, M. 1992. The influence of chromatic aberration on the static accommodative response. *Vision Res,* 32**,** 823-32.

BOUR, L. J. 1981. The influence of the spatial distribution of a target on the dynamic response and fluctuations of the accommodation of the human eye. *Vision Res,* 21**,** 1287-96.

BRENNAN, N. A., SMITH, G., MACDONALD, J. A. & BRUCE, A. S. 1989. Theoretical principles of optical pachometry. *Ophthalmic Physiol Opt,* 9**,** 247-54.

BUDAK, K., KHATER, T. T., FRIEDMAN, N. J., HOLLADAY, J. T. & KOCH, D. D. 1999. Evaluation of relationships among refractive and topographic parameters. *J Cataract Refract Surg,* 25**,** 814-20.

CAIRNS, G. & MCGHEE, C. N. 2005. Orbscan computerized topography: attributes, applications, and limitations. *J Cataract Refract Surg,* 31**,** 205-20.

CAIRNS, G., MCGHEE, C. N., COLLINS, M. J., OWENS, H. & GAMBLE, G. D. 2002. Accuracy of Orbscan II slit-scanning elevation topography. *J Cataract Refract Surg,* 28**,** 2181-7.

CALVER, R., RADHAKRISHNAN, H., OSUOBENI, E. & O'LEARY, D. J. 2007. Peripheral refraction for distance and near vision in emmetropes and myopes. *Ophthalmic Physiol Opt,* 27**,** 584-93.

CARKEET, A., SAW, S. M., GAZZARD, G., TANG, W. & TAN, D. T. 2004. Repeatability of IOLMaster biometry in children. *Optom Vis Sci,* 81**,** 829-34.

CARNEY, L. G., MAINSTONE, J. C. & HENDERSON, B. A. 1997. Corneal topography and myopia. A cross-sectional study. *Invest Ophthalmol Vis Sci,* 38**,** 311-20.

CHAN-LING, T. & PYE, D. C. 1994. Pachometry: clinical and scientific applications. *In:* RUBEN, M. AND GUILLON, M. (eds.) *Contact Lens Practice*, London: Chapman & Hall, 407-435

CHAN, B., CHO, P. & CHEUNG, S. W. 2006. Repeatability and agreement of two A-scan ultrasonic biometers and IOLMaster in non-orthokeratology subjects and post-orthokeratology children. *Clin Exp Optom,* 89**,** 160-8.

CHAN, B., CHO, P. & MOUNTFORD, J. 2010. Relationship between corneal topographical changes and subjective myopic reduction in overnight orthokeratology: a retrospective study. *Clin Exp Optom,* 93**,** 237-42.

CHARMAN, W. N. 2005. Aberrations and myopia. *Ophthalmic Physiol Opt,* 25**,** 285-301.

CHARMAN, W. N. 2006. The Charles F. Prentice Award Lecture 2005: optics of the human eye: progress and problems. *Optom Vis Sci,* 83**,** 335-45.

CHARMAN, W. N. & ATCHISON, D. A. 2009. Decentred optical axes and aberrations along principal visual field meridians. *Vision Res,* 49**,** 1869-76.

CHARMAN, W. N. & JENNINGS, J. A. 2006. Longitudinal changes in peripheral refraction with age. *Ophthalmic Physiol Opt,* 26**,** 447-55.

CHARMAN, W. N., MOUNTFORD, J., ATCHISON, D. A. & MARKWELL, E. L. 2006. Peripheral refraction in orthokeratology patients. *Optom Vis Sci,* 83**,** 641-8.

CHARMAN, W. N. & RADHAKRISHNAN, H. 2010. Peripheral refraction and the development of refractive error: a review. *Ophthalmic Physiol Opt,* 30**,** 321-38.

CHARMAN, W. N. & TUCKER, J. 1978. Accommodation and color. *J Opt Soc Am,* 68**,** 459-71.

CHAT, S. W. & EDWARDS, M. H. 2001. Clinical evaluation of the Shin-Nippon SRW-5000 autorefractor in children. *Ophthalmic Physiol Opt,* 21**,** 87-100.

CHEN, D. & LAM, A. K. 2009. Reliability and repeatability of the Pentacam on corneal curvatures. *Clin Exp Optom,* 92**,** 110-8.

CHEN, X., SANKARIDURG, P., DONOVAN, L., LIN, Z., LI, L., MARTINEZ, A., HOLDEN, B. A. & GE, J. 2010. Characteristics of peripheral refractive errors of myopic and non-myopic Chinese eyes. *Vision Res,* 50**,** 31-5.

CHENG, H. M. 1991. Magnetic resonance imaging of the human eye in vivo. *Optom Vis Sci,* 68**,** 976-80.

CHENG, H. M., SINGH, O. S., KWONG, K. K., XIONG, J., WOODS, B. T. & BRADY, T. J. 1992. Shape of the myopic eye as seen with high-resolution magnetic resonance imaging. *Optom Vis Sci,* 69**,** 698-701.

CHO, P., CHEUNG, S. W. & EDWARDS, M. 2005. The longitudinal orthokeratology research in children (LORIC) in Hong Kong: a pilot study on refractive changes and myopic control. *Curr Eye Res,* 30**,** 71-80.

CHO, P., LAM, A. K., MOUNTFORD, J. & NG, L. 2002. The performance of four different corneal topographers on normal human corneas and its impact on orthokeratology lens fitting. *Optom Vis Sci,* 79**,** 175-83.

CHOI, M., WEISS, S., SCHAEFFEL, F., SEIDEMANN, A., HOWLAND, H. C., WILHELM, B. & WILHELM, H. 2000. Laboratory, clinical, and kindergarten test of a new eccentric infrared Photorefractor (PowerRefractor). *Optom Vis Sci,* 77**,** 537-548.

CHUA, W. H., BALAKRISHNAN, V., CHAN, Y. H., TONG, L., LING, Y., QUAH, B. L. & TAN, D. 2006. Atropine for the treatment of childhood myopia. *Ophthalmology,* 113**,** 2285-91.

CHUNG, K., MOHIDIN, N. & O'LEARY, D. J. 2002. Undercorrection of myopia enhances rather than inhibits myopia progression. *Vision Res,* 42**,** 2555-9.

CIUFFREDA, K. J. 1991. The Glenn A. Fry invited lecture. Accommodation to gratings and more naturalistic stimuli. *Optom Vis Sci,* 68**,** 243-60.

CIUFFREDA, K. J., ROSENFIELD, M., ROSEN, J., AZIMI, A. & ONG, E. 1990. Accommodative responses to naturalistic stimuli. *Ophthalmic Physiol Opt,* 10**,** 168-74.

CIUFFREDA, K. J. & RUMPF, D. 1985. Contrast and accommodation in amblyopia. *Vision Res,* 25**,** 1445-57.

COLLINS, C. C., CARLSON, M. R., SCOTT, A. B. & JAMPOLSKY, A. 1981. Extraocular muscle forces in normal human subjects. *Invest Ophthalmol Vis Sci,* 20**,** 652-64.

COLLINS, M. J., WILDSOET, C. F. & ATCHISON, D. A. 1995. Monochromatic aberrations and myopia. *Vision Res,* 35**,** 1157-63.

COON, L. J. 1982. Orthokeratology: part I historical perspective. *J Am Optom Assoc,* 53**,** 187-95.

CURCIO, C. A. & ALLEN, K. A. 1990. Topography of ganglion cells in human retina. *J Comp Neurol,* 300**,** 5-25.

CURCIO, C. A., SLOAN, K. R., KALINA, R. E. & HENDRICKSON, A. E. 1990. Human photoreceptor topography. *J Comp Neurol,* 292**,** 497-523.

DAVE, T. 2004. Corneal topography and its measurements. *In:* MOUNTFORD, J., RUSTON, D. & DAVE, T.(ed.) *Orthokeratology: Principles and Practice.* London: Butterworth Heinemann, 17-47

DAVIES, L. N., MALLEN, E. A., WOLFFSOHN, J. S. & GILMARTIN, B. 2003. Clinical evaluation of the Shin-Nippon NVision-K 5001/Grand Seiko WR-5100K autorefractor. *Optom Vis Sci,* 80**,** 320-4.

DELLER, J. F., O'CONNOR, A. D. & SORSBY, A. 1947. X-ray measurement of the diameters of the living eye. *Proc R Soc Med,* 134**,** 456-67.

DIETHER, S. & SCHAEFFEL, F. 1997. Local changes in eye growth induced by imposed local refractive error despite active accommodation. *Vision Res,* 37**,** 659-68.

DIRANI, M., TONG, L., GAZZARD, G., ZHANG, X., CHIA, A., YOUNG, T. L., ROSE, K. A., MITCHELL, P. R. & SAW, S. M. 2009. Outdoor activity and myopia in Singapore teenage children. *Br J Ophthalmol*, 93, 997-1000

DONOVAN, L., MARTINEZ, A., SANKARIDURG, P., HO, A., HARTWIG, A., CHEN, X. & HOLDEN, A. B. 2007. Comparison of peripheral refractions determined by infrared autorefraction, Hartmann-Shack aberrometry and streak retinoscopy. *American Academy of Optometry.* Tampa, USA (Poster).

DORJE, F., WESS, J., LAMBRECHT, G., TACKE, R., MUTSCHLER, E. & BRANN, M.R. 1991. Antagonist binding properties of five cloned human muscarinic receptor subtypes. *J Pharmacol Exp Ther,* 256**,** 727-33.

DOUTHWAITE, W. A., HOUGH, T., EDWARDS, K. & NOTAY, H. 1999. The EyeSys videokeratoscopic assessment of apical radius and p-value in the normal human cornea. *Ophthalmic Physiol Opt*, 19**,** 467-74.

DREXLER, W., BAUMGARTNER, A., FINDL, O., HITZENBERGER, C. K. & FERCHER, A. F. 1997. Biometric investigation of changes in the anterior eye segment during accommodation. *Vision Res,* 37**,** 2789-800.

DREXLER, W., FINDL, O., SCHMETTERER, L., HITZENBERGER, C. K. & FERCHER, A. F. 1998. Eye elongation during accommodation in humans: differences between emmetropes and myopes. *Invest Ophthalmol Vis Sci,* 39**,** 2140-7.

DU TOIT, R., VEGA, J. A., FONN, D. & SIMPSON, T. 2003. Diurnal variation of corneal sensitivity and thickness. *Cornea,* 22**,** 205-9.

DUNCAN, R. O. & BOYNTON, G. M. 2003. Cortical magnification within human primary visual cortex correlates with acuity thresholds. *Neuron,* 38**,** 659-71.

DUNNE, M. C. 1995. A computing scheme for determination of retinal contour from peripheral refraction, keratometry and A-scan ultrasonography. *Ophthalmic Physiol Opt,* 15**,** 133-43.

DUNNE, M. C. & BARNES, D. A. 1990. Modelling oblique astigmatism in eyes with known peripheral refraction and optical dimensions. *Ophthalmic Physiol Opt,* 10**,** 46-8.

DUNNE, M. C., MISSON, G. P., WHITE, E. K. & BARNES, D. A. 1993. Peripheral astigmatic asymmetry and angle alpha. *Ophthalmic Physiol Opt,* 13**,** 303-5.

EDWARDS, M. H. 1998. Myopia: definitions, classifications and economic implications. *In:* ROSENFIELD, M., GILMARTIN, B. (eds.) *Myopia and Nearwork.* Boston: Butterworth-Heinemann, 1-11

EDWARDS, M. H. 1999. The development of myopia in Hong Kong children between the ages of 7 and 12 years: a five-year longitudinal study. *Ophthalmic Physiol Opt,* 19**,** 286-94.

EDWARDS, M. H. & LAM, C. S. 2004. The epidemiology of myopia in Hong Kong. *Ann Acad Med Singapore,* 33**,** 34-8.

EDWARDS, M. H., LI, R. W., LAM, C. S., LEW, J. K. & YU, B. S. 2002. The Hong Kong progressive lens myopia control study: study design and main findings. *Invest Ophthalmol Vis Sci,* 43**,** 2852-8.

EFRON, N., MORGAN, P. B. & WOODS, C. A. 2010. Trends in Australian contact lens prescribing during the first decade of the 21st Century (2000-2009). *Clin Exp Optom,* 93**,** 243-52.

EGHBALI, F., YEUNG, K. K. & MALONEY, R. K. 1995. Topographic determination of corneal asphericity and its lack of effect on the refractive outcome of radial keratotomy. *Am J Ophthalmol,* 119**,** 275-80.

EHLERS, N. & HANSEN, F. K. 1971. On the optical measurement of corneal thickness. *Acta Ophthalmol (Copenh),* 49**,** 65-81.

EHLERS, N. & HJORTDAL, J. 2004. Corneal thickness: measurement and implications. *Exp Eye Res,* 78**,** 543-8.

EHSAEI, A., MALLEN, E. A., CHISHOLM, C. M. & PACEY, I. E. 2011. Cross-sectional sample of peripheral refraction in four meridians in myopes and emmetropes. *Invest Ophthalmol Vis Sci,* 52**,** 7574-85.

FAN, D. S., LAM, D. S., LAM, R. F., LAU, J. T., CHONG, K. S., CHEUNG, E. Y., LAI, R. Y. & CHEW, S. J. 2004. Prevalence, incidence, and progression of myopia of school children in Hong Kong. *Invest Ophthalmol Vis Sci,* 45**,** 1071-5.

FEDTKE, C., EHRMANN, K. & HOLDEN, B. A. 2009. A review of peripheral refraction techniques. *Optom Vis Sci,* 86**,** 429-46.

FENG, Y., VARIKOOTY, J. & SIMPSON, T. L. 2001. Diurnal variation of corneal and corneal epithelial thickness measured using optical coherence tomography. *Cornea,* 20**,** 480-3.

FERREE, C. E. & RAND, G. 1933. Interpretation of refractive conditions in the peripheral field of vision. *Arch Ophthalmol,* 9**,** 925-38.

FERREE, C. E., RAND, G. & HARDY, C. 1931. Refraction for the peripheral field of vision. *Arch Ophthalmol,* 5**,** 717-31.

FERREE, C. E., RAND, G. & HARDY, C. 1932. Refractive asymmetry in the temporal and nasal halves of the visual field. *Am J Ophthalmol,* 15**,** 513-22.

FORISTER, J. F., FORISTER, E. F., YEUNG, K. K., YE, P., CHUNG, M. Y., TSUI, A. & WEISSMAN, B. A. 2009. Prevalence of contact lens-related complications: UCLA contact lens study. *Eye Contact Lens,* 35**,** 176-80.

FRAZIER, M. & JAANUS, S. D. 2008. Cycloplegics. *In:* BARTLETT, J. D. & JAANUS, S. D. (eds.) *Clinical Ocular Pharmacology.* 5 ed. Oxford: Butterworth-Heinemann, 128-38.

FRENCH, C. N. & JENNINGS, J. A. M. 1974. Errors in subjective refraction: an exploratory study. *The Optician,* 14(16)**,** 797-806.

FULK, G. W., CYERT, L. A. & PARKER, D. A. 2002. Seasonal variation in myopia progression and ocular elongation. *Optom Vis Sci,* 79**,** 46-51.

FULK, G. W., CYERT, L. A. & PARKER, D. E. 2000. A randomized trial of the effect of single-vision vs. bifocal lenses on myopia progression in children with esophoria. *Optom Vis Sci,* 77**,** 395-401.

FULK, G. W., CYERT, L. A., PARKER, D. E. & WEST, R. W. 2003. The effect of changing from glasses to soft contact lenses on myopia progression in adolescents. *Ophthalmic Physiol Opt,* 23**,** 71-7.

GANESAN, P. & WILDSOET, C. F. 2010. Pharmaceutical intervention for myopia control. *Expert Rev of Ophthalmol.* 5**,** 759-87.

GARNER, L. F. & YAP, M. K. 1997. Changes in ocular dimensions and refraction with accommodation. *Ophthalmic Physiol Opt,* 17**,** 12-7.

GORDON, A., BOGGESS, E. A. & MOLINARI, J. F. 1990. Variability of ultrasonic pachometry. *Optom Vis Sci,* 67**,** 162-5.

GOSS, D. A. 1991. Clinical accommodation and heterophoria findings preceding juvenile onset of myopia. *Optom Vis Sci,* 68**,** 110-6.

GOSS, D. A., ERICKSON, P. & COX, V. D. 1985. Prevalence and pattern of adult myopia progression in a general optometric practice population. *Am J Optom Physiol Opt,* 62**,** 470-7.

GOSS, D. A. & GROSVENOR, T. 1996. Reliability of refraction-a literature review. *J Am Optom Assoc,* 67**,** 619-30.

GOTO, T., KLYCE, S. D., ZHENG, X., MAEDA, N., KURODA, T. & IDE, C. 2001. Gender- and age-related differences in corneal topography. *Cornea,* 20**,** 270-6.

GRODUM, K., HEIJL, A. & BENGTSSON, B. 2001. Refractive error and glaucoma. *Acta Ophthalmol Scand,* 79**,** 560-6.

GROSSNIKLAUS, H. E. & GREEN, W. R. 1992. Pathologic findings in pathologic myopia. *Retina,* 12**,** 127-33.

GROSVENOR, T. 1975. Changes in corneal curvature and subjective refraction of soft contact lens wearers. *Am J Optom Physiol Opt,* 52**,** 405-13.

GROSVENOR, T. 1987. A review and a suggested classification system for myopia on the basis of age-related prevalence and age of onset. *Am J Optom Physiol Opt,* 64**,** 545-54.

GROSVENOR, T. 2007. Subjective refraction. *In:* GROSVENOR, T. (ed) *Primary Care Optometry.* 5th ed. St Louis. MO: Butterworth-Heinemann/Elsevier**,** 209-23.

GROSVENOR, T. & GOSS, D. A. 1998. Role of the cornea in emmetropia and myopia. *Optom Vis Sci,* 75**,** 132-45.

GROSVENOR, T. & GOSS, D. A. 1999. Epidemiology of myopia. *In:* GROSVENOR, T. & GOSS, D. A. (eds) *Clinical Management of Myopia***,** Boston: Butterworth Heinemann**,** 3-48.

GROSVENOR, T. & SCOTT, R. 1991. Comparison of refractive components in youth-onset and early adult-onset myopia. *Optom Vis Sci,* 68**,** 204-9.

GUGGENHEIM, J. A., KIROV, G. & HODSON, S. A. 2000. The heritability of high myopia: a reanalysis of Goldschmidt's data. *J Med Genet,* 37**,** 227-31.

GUILLON, M., LYDON, D. P. & WILSON, C. 1986. Corneal topography: a clinical model. *Ophthalmic Physiol Opt,* 6**,** 47-56.

GUSTAFSSON, J., TERENIUS, E., BUCHHEISTER, J. & UNSBO, P. 2001. Peripheral astigmatism in emmetropic eyes. *Ophthalmic Physiol Opt,* 21**,** 393-400.

GUSTAFSSON, J. & UNSBO, P. 2003. Eccentric correction for off-axis vision in central visual field loss. *Optom Vis Sci,* 80**,** 535-41.

GWIAZDA, J., BAUER, J., THORN, F. & HELD, R. 1995. A dynamic relationship between myopia and blur-driven accommodation in school-aged children. *Vision Res,* 35**,** 1299-304.

GWIAZDA, J., CHANDLER, M.S.P.H., COTTER, S. A., EVERETT, D. F., HYMAN, L., KAMINSKI, B. M., ET AL. 2011. Progressive addition lenses versus single vision lenses for slowing progression in myopia in children with high accommodative lag and near esophoria. *Invest Ophthalmol Vis Sci*, 52**,** 2749-57.

GWIAZDA, J., GRICE, K. & THORN, F. 1999. Response AC/A ratios are elevated in myopic children. *Ophthalmic Physiol Opt,* 19**,** 173-9.

GWIAZDA, J., HYMAN, L., HUSSEIN, M., EVERETT, D., NORTON, T. T., KURTZ, D., LESKE, M. C., MANNY, R., MARSH-TOOTLE, W. & SCHEIMAN, M. 2003. A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. *Invest Ophthalmol Vis Sci,* 44**,** 1492-500.

GWIAZDA, J., THORN, F., BAUER, J. & HELD, R. 1993. Myopic children show insufficient accommodative response to blur. *Invest Ophthalmol Vis Sci,* 34**,** 690-4.

GWIAZDA, J., THORN, F. & HELD, R. 2005. Accommodation, accommodative convergence, and response AC/A ratios before and at the onset of myopia in children. *Optom Vis Sci,* 82**,** 273-8.

HAINSWORTH, D. P., BIERLY, J. R., SCHMEISSER, E. T. & BAKER, R. S. 1999. Corneal topographic changes after extraocular muscle surgery. *J AAPOS,* 3**,** 80-6.

HAMMOND, C. J., SNIEDER, H., GILBERT, C. E. & SPECTOR, T. D. 2001. Genes and environment in refractive error: the twin eye study. *Invest Ophthalmol Vis Sci,* 42**,** 1232-6.

HANDA, T., MUKUNO, K., NIIDA, T., UOZATO, H., TANAKA, S. & SHIMIZU, K. 2002. Diurnal variation of human corneal curvature in young adults. *J Refract Surg,* 18**,** 58-62.

HAQUE, S., FONN, D., SIMPSON, T. & JONES, L. 2004. Corneal and epithelial thickness changes after 4 weeks of overnight corneal refractive therapy lens wear, measured with optical coherence tomography. *Eye Contact Lens,* 30**,** 189-93.

HARPER, C. L., BOULTON, M. E., BENNETT, D., MARCYNIUK, B., JARVIS-EVANS, J. H., TULLO, A. B. & RIDGWAY, A. E. 1996. Diurnal variations in human corneal thickness. *Br J Ophthalmol,* 80**,** 1068-72.

HARRIS, M. G., SARVER, M. D. & POLSE, K. A. 1975. Corneal curvature and refractive error changes associated with wearing hydrogel contact lenses. *Am J Optom Physiol Opt,* 52**,** 313-9.

HASEBE, S., OHTSUKI, H., NONAKA, T., NAKATSUKA, C., MIYATA, M., HAMASAKI, I. & KIMURA, S. 2008. Effect of progressive addition lenses on myopia progression in Japanese children: a prospective, randomized, double-masked, crossover trial. *Invest Ophthalmol Vis Sci,* 49**,** 2781-9.

HE, M., HUANG, W., ZHENG, Y., HUANG, L. & ELLWEIN, L. B. 2007. Refractive error and visual impairment in school children in rural southern China. *Ophthalmology,* 114**,** 374-82.

HE, M., ZENG, J., LIU, Y., XU, J., POKHAREL, G. P. & ELLWEIN, L. B. 2004. Refractive error and visual impairment in urban children in southern China. *Invest Ophthalmol Vis Sci,* 45**,** 793-9.

HE, M., ZHENG, Y. & XIANG, F. 2009. Prevalence of myopia in urban and rural children in mainland China. *Optom Vis Sci,* 86**,** 40-4.

HERSE, P. & YAO, W. 1993. Variation of corneal thickness with age in young New Zealanders. *Acta Ophthalmol (Copenh),* 71**,** 360-4.

HIRJI, N. K. & LARKE, J. R. 1978. Thickness of human cornea measured by topographic pachometry. *Am J Optom Physiol Opt,* 55**,** 97-100.

HODOS, W. & ERICHSEN, J. T. 1990. Lower-field myopia in birds: an adaptation that keeps the ground in focus. *Vision Res,* 30**,** 653-7.

HODOS, W. & KUENZEL, W. J. 1984. Retinal-image degradation produces ocular enlargement in chicks. *Invest Ophthalmol Vis Sci,* 25**,** 652-9.

HOLDEN, B. A., PAYOR, S. & MERTZ, G. W. 1979. Changes in thickness in the corneal layers. *Am J Optom Physiol Opt,* 56**,** 821.

HOLDEN, B. A., SANKARIDURG, P., LAZON DE LA JARA, P., SMITH, E. L., 3RD, CHEN, X., KWAN, J., MARTINEZ, A., HO, A. & GE, J. 2010. Reduction in the rate of progress of myopia with a contact lens designed to reduce relative peripheral hyperopia. *Invest Ophthalmol Vis Sci,* 51**,** E-Abstract 2220.

HOLDEN, B. A., POLSE, K. A., FONN, D. & MERTZ, G. W. 1982. Effects of cataract surgery on corneal function. *Invest Ophthalmol Vis Sci,* 22**,** 343-50.

HOOGERHEIDE, J., REMPT, F. & HOOGENBOOM, W. P. 1971. Acquired myopia in young pilots. *Ophthalmologica,* 163**,** 209-15.

HORNER, D. G., SONI, P. S., SALMON, T. O. & SWARTZ, T. S. 1999. Myopia progression in adolescent wearers of soft contact lenses and spectacles. *Optom Vis Sci,* 76**,** 474-9.

HORTON, J. C. & HOYT, W. F. 1991. The representation of the visual field in human striate cortex. A revision of the classic Holmes map. *Arch Ophthalmol,* 109**,** 816-24.

HOYT, C. S., STONE, R. D., FROMER, C. & BILLSON, F. A. 1981. Monocular axial myopia associated with neonatal eyelid closure in human infants. *Am J Ophthalmol,* 91**,** 197-200.

HSU, W. M., CHENG, C. Y., LIU, J. H., TSAI, S. Y. & CHOU, P. 2004. Prevalence and causes of visual impairment in an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Ophthalmology,* 111**,** 62-9.

HUANG, J., HUNG, L. F., RAMAMIRTHAM, R., BLASDEL, T. L., HUMBIRD, T. L., BOCKHORST, K. H. & SMITH, E. L., 3RD. 2009. Effects of form deprivation on peripheral refractions and ocular shape in infant rhesus monkeys (Macaca mulatta). *Invest Ophthalmol Vis Sci,* 50**,** 4033-44.

HUNG, G. K., CIUFFREDA, K. J. & ROSENFIELD, M. 1996. Proximal contribution to a linear static model of accommodation and vergence. *Ophthalmic Physiol Opt,* 16**,** 31-41.

HUNG, L. F., CRAWFORD, M. L. & SMITH, E. L., 3RD. 1995. Spectacle lenses alter eye growth and the refractive status of young monkeys. *Nat Med,* 1**,** 761-5.

HUNG, L. F., WALLMAN, J. & SMITH, E. L., 3RD. 2000. Vision-dependent changes in the choroidal thickness of macaque monkeys. *Invest Ophthalmol Vis Sci,* 41**,** 1259-69.

IP, J. M., HUYNH, S. C., KIFLEY, A., ROSE, K. A., MORGAN, I. G., VARMA, R. & MITCHELL, P. 2007. Variation of the contribution from axial length and other oculometric parameters to refraction by age and ethnicity. *Invest Ophthalmol Vis Sci,* 48**,** 4846-53.

IP, J. M., HUYNH, S. C., ROBAEI, D., KIFLEY, A., ROSE, K. A., MORGAN, I. G., WANG, J. J. & MITCHELL, P. 2008. Ethnic differences in refraction and ocular biometry in a population-based sample of 11-15-year-old Australian children. *Eye,* 22**,** 649-56.

IRVING, E. L., CALLENDER, M. G. & SIVAK, J. G. 1995. Inducing ametropias in hatchling chicks by defocus-aperture effects and cylindrical lenses. *Vision Res,* 35**,** 1165-74.

IRVING, E. L., SIVAK, J. G. & CALLENDER, M. G. 1992. Refractive plasticity of the developing chick eye. *Ophthalmic Physiol Opt,* 12**,** 448-56.

IWASE, A., ARAIE, M., TOMIDOKORO, A., YAMAMOTO, T., SHIMIZU, H. & KITAZAWA, Y. 2006. Prevalence and causes of low vision and blindness in a Japanese adult population: the Tajimi Study. *Ophthalmology,* 113**,** 1354-62.

JACKSON, D. W., PAYSSE, E. A., WILHELMUS, K. R., HUSSEIN, M. A., ROSBY, G. & COATS, D. K. 2004. The effect of off-the-visual-axis retinoscopy on objective refractive measurement. *Am J Ophthalmol,* 137**,** 1101-4.

JAVITT, J. C. & CHIANG, Y. P. 1994. The socioeconomic aspects of laser refractive surgery. *Arch Ophthalmol,* 112**,** 1526-30.

JENNINGS, J. A. & CHARMAN, W. N. 1978. Optical image quality in the peripheral retina. *Am J Optom Physiol Opt,* 55**,** 582-90.

JENNINGS, J. A. & CHARMAN, W. N. 1981a. The effects of central and peripheral refraction on critical fusion frequency. *Ophthalmic Physiol Opt,* 1**,** 91-6.

JENNINGS, J. A. & CHARMAN, W. N. 1981b. Off-axis image quality in the human eye. *Vision Res,* 21**,** 445-55.

JESSEN, G. N. 1962. Orthofocus techniques. *Contacto,* 6**,** 200-4.

JIANG, B. C. 1995. Parameters of accommodative and vergence systems and the development of late-onset myopia. *Invest Ophthalmol Vis Sci,* 36**,** 1737-42.

JOHNSON, C. A. & LEIBOWITZ, H. 1974. Practice, refractive error, and feedback as factors influencing peripheral motion thresholds. *Percept Psychophys,* 15**,** 276-80.

JOHNSON, C. A., POST, R. B., CHALUPA, L. M. & LEE, T. J. 1982. Monocular deprivation in humans: a study of identical twins. *Invest Ophthalmol Vis Sci,* 23**,** 135-8.

JONAS, J. B., SCHNEIDER, U. & NAUMANN, G. O. 1992. Count and density of human retinal photoreceptors. *Graefes Arch Clin Exp Ophthalmol,* 230**,** 505-10.

JONES, L. A., SINNOTT, L. T., MUTTI, D. O., MITCHELL, G. L., MOESCHBERGER, M. L. & ZADNIK, K. 2007. Parental history of myopia, sports and outdoor activities, and future myopia. *Invest Ophthalmol Vis Sci,* 48**,** 3524-32.

JONES, L. W. & HODES, D. T. 1991. Possible allergic reactions to cyclopentolate hydrochloride: case reports with literature review of uses and adverse reactions. *Ophthalmic Physiol Opt,* 11**,** 16-21.

JUNGHANS, B. M. & CREWTHER, S. G. 2005. Little evidence for an epidemic of myopia in Australian primary school children over the last 30 years. *BMC Ophthalmol,* 5**,** 1.

KAKITA, T., HIRAOKA, T. & OSHIKA, T. 2011. Influence of overnight orthokeratology on axial length elongation in childhood myopia. *Invest Ophthalmol Vis Sci*, 52**,** 2170-4.

KATZ, J., SCHEIN, O. D., LEVY, B., CRUISCULLO, T., SAW, S. M., RAJAN, U., CHAN, T. K., YEW KHOO, C. & CHEW, S. J. 2003. A randomized trial of rigid gas permeable contact lenses to reduce progression of children's myopia. *Am J Ophthalmol,* 136**,** 82-90.

KEE, C. S., HUNG, L. F., QIAO-GRIDER, Y., ROORDA, A. & SMITH, E. L., 3RD. 2004. Effects of optically imposed astigmatism on emmetropization in infant monkeys. *Invest Ophthalmol Vis Sci,* 45**,** 1647-59.

KEMPEN, J. H., MITCHELL, P., LEE, K. E., TIELSCH, J. M., BROMAN, A. T., TAYLOR, H. R., IKRAM, M. K., CONGDON, N. G. & O'COLMAIN, B. J. 2004. The prevalence of refractive errors among adults in the United States, Western Europe, and Australia. *Arch Ophthalmol,* 122**,** 495-505.

KHOO, C. Y., CHONG, J. & RAJAN, U. 1999. A 3-year study on the effect of RGP contact lenses on myopic children. *Singapore Med J,* 40**,** 230-7.

KIELY, P. M., CARNEY, L. G. & SMITH, G. 1982a. Diurnal variations of corneal topography and thickness. *Am J Optom Physiol Opt,* 59**,** 976-82.

KIELY, P. M., SMITH, G. & CARNEY, L. G. 1982b. The mean shape of the human cornea. *Optica Acta,* 29**,** 1027-1040.

KIRSCHKAMP, T., DUNNE, M. & BARRY, J. C. 2004. Phakometric measurement of ocular surface radii of curvature, axial separations and alignment in relaxed and accommodated human eyes. *Ophthalmic Physiol Opt,* 24**,** 65-73.

KLEINSTEIN, R. N., JONES, L. A., HULLETT, S., KWON, S., LEE, R. J., FRIEDMAN, N. E., MANNY, R. E., MUTTI, D. O., YU, J. A. & ZADNIK, K. 2003. Refractive error and ethnicity in children. *Arch Ophthalmol,* 121**,** 1141-7.

KLYCE, S. D. & WILSON, S. E. 1989. Methods of analysis of corneal topography. *Refract Corneal Surg,* 5**,** 368-71.

KRUGER, P. B., MATHEWS, S., AGGARWALA, K. R. & SANCHEZ, N. 1993. Chromatic aberration and ocular focus: Fincham revisited. *Vision Res,* 33**,** 1397-411.

KRUGER, P. B. & POLA, J. 1986. Stimuli for accommodation: blur, chromatic aberration and size. *Vision Res,* 26**,** 957-71.

KRUGER, P. B. & POLA, J. 1987. Dioptric and non-dioptric stimuli for accommodation: target size alone and with blur and chromatic aberration. *Vision Res,* 27**,** 555-67.

KURTZ, D., HYMAN, L., GWIAZDA, J. E., MANNY, R., DONG, L. M., WANG, Y. & SCHEIMAN, M. 2007. Role of parental myopia in the progression of myopia and its interaction with treatment in COMET children. *Invest Ophthalmol Vis Sci,* 48**,** 562-70.

KWITKO, S., FELDON, S. & MCDONNELL, P. J. 1992. Corneal topographic changes following strabismus surgery in Grave's disease. *Cornea,* 11**,** 36-40.

LAI, T. Y., FAN, D. S., LAI, W. W. & LAM, D. S. 2008. Peripheral and posterior pole retinal lesions in association with high myopia: a cross-sectional community-based study in Hong Kong. *Eye,* 22**,** 209-13.

LAM, A. K., CHAN, R. & PANG, P. C. 2001. The repeatability and accuracy of axial length and anterior chamber depth measurements from the IOLMaster. *Ophthalmic Physiol Opt,* 21**,** 477-83.

LAM, A. K. & DOUTHWAITE, W. A. 1998. The corneal-thickness profile in Hong Kong Chinese. *Cornea,* 17**,** 384-8.

LAM, C. S., GOLDSCHMIDT, E. & EDWARDS, M. H. 2004. Prevalence of myopia in local and international schools in Hong Kong. *Optom Vis Sci,* 81**,** 317-22.

LAM, D. S., FAN, D. S., CHAN, W. M., TAM, B. S., KWOK, A. K., LEUNG, A. T. & PARSONS, H. 2005. Prevalence and characteristics of peripheral retinal degeneration in Chinese adults with high myopia: a cross-sectional prevalence survey. *Optom Vis Sci,* 82**,** 235-8.

LAM, D. S., FAN, D. S., LAM, R. F., RAO, S. K., CHONG, K. S., LAU, J. T., LAI, R. Y. & CHEUNG, E. Y. 2008. The effect of parental history of myopia on children's eye size and growth: results of a longitudinal study. *Invest Ophthalmol Vis Sci,* 49**,** 873-6.

LANDRUM, B. T. 2009. *The Effect of Letter Size on the Accomodative Response.* Masters thesis**,** Ohio State University.

LAZON DE LA JARA, P., SANKARIDURG, P., HO, A., MARTINEZ, A., DONOVAN, L., SMITH, E. L., 3RD, CHEN, X., GE, J. & HOLDEN, B. A. 2010. A silicone hydrogel contact lens produced less myopia progression than single vision spectacles in Chinese cihldren over a 6 month period. *Invest Ophthalmol Vis Sci,* 51**,** E-Abstract 2198.

LEIBOWITZ, H. W., JOHNSON, C. A. & ISABELLE, E. 1972. Peripheral motion detection and refractive error. *Science,* 177**,** 1207-8.

LEVENE, J. R. 1965. The true inventors of the keratoscope and photo-keratoscope. *Br J Hist Sci,* 2**,** 324-342.

LIANG, J. & WILLIAMS, D. R. 1997. Aberrations and retinal image quality of the normal human eye. *J Opt Soc Am A Opt Image Sci Vis,* 14**,** 2873-83.

LIANG, Y. B., FRIEDMAN, D. S., WONG, T. Y., ZHAN, S. Y., SUN, L. P., WANG, J. J., DUAN, X. R., YANG, X. H., WANG, F. H., ZHOU, Q. & WANG, N. L. 2008. Prevalence and causes of low vision and blindness in a rural Chinese adult population: the Handan Eye Study. *Ophthalmology,* 115**,** 1965-72.

LIM, L. S., YANG, X., GAZZARD, G., LIN, X., SNG, C., SAW, S.M. & QUI, A. 2011. Variations in eye volume, surface area, and shape with refractive error in young children by magnetic resonance imaging analysis. *Invest Ophthalmol Vis Sci,* (doi: 10.1167/iovs.11-7269)

LIM, M. C., GAZZARD, G., SIM, E. L., TONG, L. & SAW, S. M. 2009. Direct costs of myopia in Singapore. *Eye,* 23**,** 1086-9.

LIM, R., MITCHELL, P. & CUMMING, R. G. 1999. Refractive associations with cataract: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci,* 40**,** 3021-6.

LIN, L. L., SHIH, Y. F., HSIAO, C. K. & CHEN, C. J. 2004. Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. *Ann Acad Med Singapore,* 33**,** 27-33.

LIN, L. L., SHIH, Y. F., TSAI, C. B., CHEN, C. J., LEE, L. A., HUNG, P. T. & HOU, P. K. 1999. Epidemiologic study of ocular refraction among schoolchildren in Taiwan in 1995. *Optom Vis Sci,* 76**,** 275-81.

LIN, Z., MARTINEZ, A., CHEN, X., LI, L., SANKARIDURG, P., HOLDEN, B. A. & GE, J. 2010. Peripheral defocus with single-vision spectacle lenses in myopic children. *Optom Vis Sci,* 87**,** 4-9.

LIU, J., HE, X., RICHDALE, K., BULLIMORE, M. & ZADNIK, K. 2008. In vivo measurements of corneal speed of sound and stiffness. *Invest Ophthalmol Vis Sci,* 49**,** E-Abstract 647.

LIU, Y. & WILDSOET, C. F. 2011. The effect of two-zone concentric bifocal spectacle lenses on refractive error development and eye growth in young chicks. *Invest Ophthalmol Vis Sci,* 52**,** 1078-86.

LLORENTE, L., BARBERO, S., CANO, D., DORRONSORO, C. & MARCOS, S. 2004. Myopic versus hyperopic eyes: axial length, corneal shape and optical aberrations. *J Vis,* 4**,** 288-98.

LOGAN, N. S., GILMARTIN, B. & DUNNE, M. C. 1995. Computation of retinal contour in anisomyopia. *Ophthalmic Physiol Opt,* 15**,** 363-6.

LOGAN, N. S., GILMARTIN, B., WILDSOET, C. F. & DUNNE, M. C. 2004. Posterior retinal contour in adult human anisomyopia. *Invest Ophthalmol Vis Sci,* 45**,** 2152-62.

LOMBARDO, M. & LOMBARDO, G. 2010. Wave aberration of human eyes and new descriptors of image optical quality and visual performance. *J Cataract Refract Surg,* 36**,** 313-31.

LOTMAR, W. & LOTMAR, T. 1974. Peripheral astigmatism in the human eye: experimental data and theoretical model predictions. *J Opt Soc Am,* 64**,** 510-3.

LOVASIK, J. V. 1986. Pharmacokinetics of topically applied cyclopentolate HCl and tropicamide. *Am J Optom Physiol Opt,* 63**,** 787-803.

LOVASIK, J. V., KERGOAT, H. & KOTHE, A. C. 1987. The influence of letter size on the focusing response of the eye. *J Am Optom Assoc,* 58**,** 631-9.

LUDLAM, W. M. & WITTENBERG, S. 1966. Measurements of the ocular dioptric elements utilizing photographic methods. *Am J Optom Arch Am Acad Optom,* 43**,** 249-267.

LUNDSTROM, L., GUSTAFSSON, J., SVENSSON, I. & UNSBO, P. 2005. Assessment of objective and subjective eccentric refraction. *Optom Vis Sci,* 82**,** 298-306.

LUNDSTROM, L., GUSTAFSSON, J. & UNSBO, P. 2007. Vision evaluation of eccentric refractive correction. *Optom Vis Sci,* 84**,** 1046-52.

LUO, H. D., GAZZARD, G., FONG, A., AUNG, T., HOH, S. T., LOON, S. C., HEALEY, P., TAN, D. T., WONG, T. Y. & SAW, S. M. 2006. Myopia, axial length, and OCT characteristics of the macula in Singaporean children. *Invest Ophthalmol Vis Sci,* 47**,** 2773-81.

MACFADDEN, L. A., GRAY, L. S., STRANG, N. C. & SEIDEL, D. 2007. The effect of eye rotation on measurements of peripheral retinal shape using the IOLMaster. *Invest Ophthalmol Vis Sci,* 48**,** E-Abstract 4002.

MALLEN, E. A. & KASHYAP, P. 2007. Technical note: measurement of retinal contour and supine axial length using the Zeiss IOLMaster. *Ophthalmic Physiol Opt,* 27**,** 404-11.

MALLEN, E. A., KASHYAP, P. & HAMPSON, K. M. 2006. Transient axial length change during the accommodation response in young adults. *Invest Ophthalmol Vis Sci,* 47**,** 1251-4.

MALLEN, E. A., WOLFFSOHN, J. S., GILMARTIN, B. & TSUJIMURA, S. 2001. Clinical evaluation of the Shin-Nippon SRW-5000 autorefractor in adults. *Ophthalmic Physiol Opt,* 21**,** 101-7.

MANDELL, R. B., POLSE, K. A. & BONANNO, J. A. 1988. Reassessment of optical pachometry. *In:* CAVANAGH, H. D. (ed.) *The Cornea: Transactions of the World Congress on the Cornea III.* New York: Raven Press Ltd, 201-5.

MARSH-TOOTLE, W. L., DONG, L. M., HYMAN, L., GWIAZDA, J., WEISE, K. K., DIAS, L. & FERNP, K. D. 2009. Myopia progression in children wearing spectacles vs. switching to contact lenses. *Optom Vis Sci,* 86**,** 741-7.

MARSH-TOOTLE, W. L. & NORTON, T. T. 1989. Refractive and structural measures of lid-suture myopia in tree shrew. *Invest Ophthalmol Vis Sci,* 30**,** 2245-57.

MARTINEZ, A. 2007. *On and Off-Axis Monochromatic Aberrations and Myopia in Young Children.* PhD thesis, The University of New South Wales.

MARTOLA, E. L. & BAUM, J. L. 1968. Central and peripheral corneal thickness. A clinical study. *Arch Ophthalmol,* 79**,** 28-30.

MATHUR, A., ATCHISON, D. A., KASTHURIRANGAN, S., DIETZ, N. A., LUONG, S., CHIN, S. P., LIN, W. L. & HOO, S. W. 2009. The influence of oblique viewing on axial and peripheral refraction for emmetropes and myopes. *Ophthalmic Physiol Opt,* 29**,** 155-61.

MCBRIEN, N. A. & ADAMS, D. W. 1997. A longitudinal investigation of adult-onset and adult-progression of myopia in an occupational group. Refractive and biometric findings. *Invest Ophthalmol Vis Sci,* 38**,** 321-33.

MCBRIEN, N. A. & MILLODOT, M. 1986. The effect of refractive error on the accommodative response gradient. *Ophthalmic Physiol Opt,* 6**,** 145-9.

MCBRIEN, N. A. & MILLODOT, M. 1987. A biometric investigation of late onset myopic eyes. *Acta Ophthalmol (Copenh),* 65**,** 461-8.

MCBRIEN, N. A., MOGHADDAM, H. O. & REEDER, A. P. 1993. Atropine reduces experimental myopia and eye enlargement via a nonaccommodative mechanism. *Invest Ophthalmol Vis Sci,* 34**,** 205-15.

MCBRIEN, N. A. & NORTON, T. T. 1992. The development of experimental myopia and ocular component dimensions in monocularly lid-sutured tree shrews (Tupaia belangeri). *Vision Res,* 32**,** 843-52.

MCFADZEAN, R., BROSNAHAN, D., HADLEY, D. & MUTLUKAN, E. 1994. Representation of the visual field in the occipital striate cortex. *Br J Ophthalmol,* 78**,** 185-90.

MCLEAN, R. C. & WALLMAN, J. 2003. Severe astigmatic blur does not interfere with spectacle lens compensation. *Invest Ophthalmol Vis Sci,* 44**,** 449-57.

MERTZ, G. W. 1980. Overnight swelling of the living human cornea. *J Am Optom Assoc,* 51**,** 211-4.

MICHON, J. J., LAU, J., CHAN, W. S. & ELLWEIN, L. B. 2002. Prevalence of visual impairment, blindness, and cataract surgery in the Hong Kong elderly. *Br J Ophthalmol,* 86**,** 133-9.

MIGLIOR, S., ALBE, E., GUARESCHI, M., MANDELLI, G., GOMARASCA, S. & ORZALESI, N. 2004. Intraobserver and interobserver reproducibility in the evaluation of ultrasonic pachymetry measurements of central corneal thickness. *Br J Ophthalmol,* 88**,** 174-7.

MILLER-MEEKS, M. J., BENNETT, S. R., KEECH, R. V. & BLODI, C. F. 1990. Myopia induced by vitreous hemorrhage. *Am J Ophthalmol,* 109**,** 199-203.

MILLER, J. M., WILDSOET, C. F., GUAN, H., LIMBO, M. & DEMER, J. L. 2004. Refractive error and eye shape by MRI. *Invest Ophthalmol Vis Sci,* 45**,** E-Abstract 2388.

MILLODOT, M. 1981. Effect of ametropia on peripheral refraction. *Am J Optom Physiol Opt,* 58**,** 691-5.

MILLODOT, M. 1984. Peripheral refraction in aphakic eyes. *Am J Optom Physiol Opt,* 61**,** 586-9.

MILLODOT, M. & LAMONT, A. 1974. Letter: Refraction of the periphery of the eye. *J Opt Soc Am,* 64**,** 110-11.

MITCHELL, P., HOURIHAN, F., SANDBACH, J. & WANG, J. J. 1999. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. *Ophthalmology,* 106**,** 2010-5.

MOLINARI, J. F. & BONDS, T. 1983. Pachometry: a comparison between touch and overlap measurement method. *Am J Optom Physiol Opt,* 60**,** 61-6.

MOLLON, J. D., REGAN, B. C. & BOWMAKER, J. K. 1998. What is the function of the cone-rich rim of the retina? *Eye,* 12**,** 548-52.

MOUNTFORD, J. 1997. An analysis of the changes in corneal shape and refractive error induced by accelerated orthokeratology. *Int Contact Lens Clinic,* 24**,** 128-144.

MOUNTFORD, J. 2004. Design variables and fitting philosophies of reverse geometry lenses. *In:* MOUNTFORD, J., RUSTON, D. & DAVE, T.(ed.) *Orthokeratology: Principles and Practice.* London: Butterworth Heinemann, 69-107.

MOUNTFORD, J. 2004a. History and general principles. *In:* MOUNTFORD, J., RUSTON, D. & DAVE, T.(ed.) *Orthokeratology: Principles and Practice.* London: Butterworth Heinemann, 269-301.

MOUNTFORD, J. 2004b. A model of forces acting in orthokeratology. *In:* MOUNTFORD, J., RUSTON, D. & DAVE, T.(ed.) *Orthokeratology: Principles and Practice.* London: Butterworth Heinemann, 1-16.

MUTTI, D. O., HAYES, J. R., MITCHELL, G. L., JONES, L. A., MOESCHBERGER, M. L., COTTER, S. A., KLEINSTEIN, R. N., MANNY, R. E., TWELKER, J. D. & ZADNIK, K. 2007. Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. *Invest Ophthalmol Vis Sci,* 48**,** 2510-9.

MUTTI, D. O., JONES, L. A., MOESCHBERGER, M. L. & ZADNIK, K. 2000a. AC/A ratio, age, and refractive error in children. *Invest Ophthalmol Vis Sci,* 41**,** 2469-78.

MUTTI, D. O., MITCHELL, G. L., HAYES, J. R., JONES, L. A., MOESCHBERGER, M. L., COTTER, S. A., KLEINSTEIN, R. N., MANNY, R. E., TWELKER, J. D. & ZADNIK, K. 2006. Accommodative lag before and after the onset of myopia. *Invest Ophthalmol Vis Sci,* 47**,** 837-46.

MUTTI, D. O., MITCHELL, G. L., MOESCHBERGER, M. L., JONES, L. A. & ZADNIK, K. 2002. Parental myopia, near work, school achievement, and children's refractive error. *Invest Ophthalmol Vis Sci,* 43**,** 3633-40.

MUTTI, D. O., SHOLTZ, R. I., FRIEDMAN, N. E. & ZADNIK, K. 2000b. Peripheral refraction and ocular shape in children. *Invest Ophthalmol Vis Sci,* 41**,** 1022-30.

MUTTI, D. O., SINNOTT, L. T., MITCHELL, G. L., JONES-JORDAN, L. A., COTTER, S. A., KLEINSTEIN, R. N., MANNY, R. E., TWELKER, J. D. & ZADNIK, K. 2011. Relative peripheral refractive error and the risk of onset of myopia progression in children. *Invest Ophthalmol Vis Sci,* 52**,** 199-205.

MUTTI, D. O., ZADNIK, K., FUSARO, R. E., FRIEDMAN, N. E., SHOLTZ, R. I. & ADAMS, A. J. 1998. Optical and structural development of the crystalline lens in childhood. *Invest Ophthalmol Vis Sci,* 39**,** 120-33.

NAPPER, G. A., BRENNAN, N. A., BARRINGTON, M., SQUIRES, M. A., VESSEY, G. A. & VINGRYS, A. J. 1995. The duration of normal visual exposure necessary to prevent form deprivation myopia in chicks. *Vision Res,* 35**,** 1337-44.

NARDI, M., RIZZO, S., PELLEGRINI, G. & LEPRI, A. 1997. Effects of strabismus surgery on corneal topography. *J Pediatr Ophthalmol Strabismus,* 34**,** 244-6.

NASTRI, G., PERUGINI, G. C., SAVASTANO, S., POLZELLA, A. & SBORDONE, G. 1984. The evolution of refraction in the fixing and the amblyopic eye. *Documenta Ophthalmologica,* 56**,** 265-274.

NATHAN, J., KIELY, P. M., CREWTHER, S. G. & CREWTHER, D. P. 1985. Disease-associated visual image degradation and spherical refractive errors in children. *Am J Optom Physiol Opt,* 62**,** 680-8.

NAVARRO, R., ARTAL, P. & WILLIAMS, D. R. 1993. Modulation transfer of the human eye as a function of retinal eccentricity. *J Opt Soc Am A,* 10**,** 201-12.

NICHOLS, J. J., MARSICH, M. M., NGUYEN, M., BARR, J. T. & BULLIMORE, M. A. 2000. Overnight orthokeratology. *Optom Vis Sci,* 77**,** 252-9.

NOLAN, J. 1972. Orthokeratology with steep lenses. *Contacto,* 16**,** 31-7.

NORTON, T. T., ESSINGER, J. A. & MCBRIEN, N. A. 1994. Lid-suture myopia in tree shrews with retinal ganglion cell blockade. *Vis Neurosci,* 11**,** 143-53.

O'LEARY, D. J. & MILLODOT, M. 1979. Eyelid closure causes myopia in humans. *Experientia,* 35**,** 1478-9.

OLSEN, T. & EHLERS, N. 1984. The thickness of the human cornea as determined by a specular method. *Acta Ophthalmol (Copenh),* 62**,** 859-71.

OLSEN, T., NIELSEN, C. B. & EHLERS, N. 1980a. On the optical measurement of corneal thickness. I. Optical principle and sources of error. *Acta Ophthalmol (Copenh),* 58**,** 760-6.

OLSEN, T., NIELSEN, C. B. & EHLERS, N. 1980b. On the optical measurement of corneal thickness. II. The measuring conditions and sources of error. *Acta Ophthalmol (Copenh),* 58**,** 975-84.

OLSON, C. L. 1974. Comparative robustness of six tests in multivariate analysis of variance. *J Am Statist Assoc,* 69**,** 894-908.

ONG, E., GRICE, K., HELD, R., THORN, F. & GWIAZDA, J. 1999. Effects of spectacle intervention on the progression of myopia in children. *Optom Vis Sci,* 76**,** 363-9.

OWENS, D. A. & LEIBOWITZ, H. W. 1975. The fixation point as a stimulus for accommodation. *Vision Res,* 15**,** 1161-3.

OWENS, H., GARNER, L. F., CRAIG, J. P. & GAMBLE, G. 2004. Posterior corneal changes with orthokeratology. *Optom Vis Sci,* 81**,** 421-6.

PERRIGIN, J., PERRIGIN, D., QUINTERO, S. & GROSVENOR, T. 1990. Silicone-acrylate contact lenses for myopia control: 3-year results. *Optom Vis Sci,* 67**,** 764-9.

PHILLIPS, J. 2005. Monovision slows juvenile myopia progression unilaterally. *Br J Ophthalmol,* 89**,** 1196-1200.

QUEIRÓS, A., GONZALEZ-MEIJOME, J. M., JORGE, J., VILLA-COLLAR, C. & GUTIERREZ, A. R. 2010. Peripheral refraction in myopic patients after orthokeratology. *Optom Vis Sci,* 87**,** 323-9.

QUEIRÓS, A., JORGE, J. & GONZALEZ-MEIJOME, J. 2009. Influence of fogging lenses and cycloplegia on peripheral refraction. *J Optom,* 2**,** 83-9.

QUEK, T. P., CHUA, C. G., CHONG, C. S., CHONG, J. H., HEY, H. W., LEE, J., LIM, Y. F. & SAW, S. M. 2004. Prevalence of refractive errors in teenage high school students in Singapore. *Ophthalmic Physiol Opt,* 24**,** 47-55.

RABBETTS, R. B. 2007a. Spherical ametropia. *In:* RABBETTS, R. B. (ed.) *Bennett & Rabbetts' Clinical Visual Optics.* 4 ed. Edinburgh: Butterworth Heinemann, 67-83.

RABBETTS, R. B. 2007b. Visual examination of the eye and ophthalmoscopy. *In:* RABBETTS, R. B. (ed.) *Bennett & Rabbetts' Clinical Visual Optics.* 4 ed. Edinburgh: Butterworth-Heinemann, 313-424.

RADHAKRISHNAN, H. & CHARMAN, W. N. 2007. Refractive changes associated with oblique viewing and reading in myopes and emmetropes. *J Vis,* 7**,** 1-15.

RADHAKRISHNAN, H. & CHARMAN, W. N. 2008. Peripheral refraction measurement: does it matter if one turns the eye or the head? *Ophthalmic Physiol Opt,* 28**,** 73-82.

RAJAVI, Z., MOHAMMAD RABEI, H., RAMEZANI, A., HEIDARI, A. & DANESHVAR, F. 2008. Refractive effect of the horizontal rectus muscle recession. *Int Ophthalmol,* 28**,** 83-8.

RAYMOND, J. E., LINDBLAD, I. M. & LEIBOWITZ, H. W. 1984. The effect of contrast on sustained detection. *Vision Res,* 24**,** 183-8.

READ, S. A. & COLLINS, M. J. 2009. Diurnal variation of corneal shape and thickness. *Optom Vis Sci,* 86**,** 170-80.

READ, S. A., COLLINS, M. J., CARNEY, L. G. & FRANKLIN, R. J. 2006. The topography of the central and peripheral cornea. *Invest Ophthalmol Vis Sci,* 47**,** 1404-15.

READ, S. A., COLLINS, M. J., CHEONG, S. H. & WOODMAN, E. C. 2010a. Sustained convergence, axial length, and corneal topography. *Optom Vis Sci,* 87**,** E45-52.

READ, S. A., COLLINS, M. J., ISKANDER, D. R. & DAVIS, B. A. 2009. Corneal topography with Scheimpflug imaging and videokeratography: comparative study of normal eyes. *J Cataract Refract Surg,* 35**,** 1072-81.

READ, S. A., COLLINS, M. J., WOODMAN, E. C. & CHEONG, S. H. 2010b. Axial length changes during accommodation in myopes and emmetropes. *Optom Vis Sci,* 87**,** 656-62.

REMINGTON, L. 2005. The retina. *In:* REMINGTON, L. (ed) *Clinical Anatomy of the Visual System,* Missouri, Butterworth Heinemann, 49-77.

REMPT, F., HOOGERHEIDE, J. & HOOGENBOOM, W. P. 1971. Peripheral retinoscopy and the skiagram. *Ophthalmologica,* 162**,** 1-10.

RONCHI, L. 1971. Absolute threshold before and after correction of oblique-ray astigmatism. *J Opt Soc Am A Opt Image Sci Vis,* 61**,** 1705-9.

ROSE, K., SMITH, W., MORGAN, I. & MITCHELL, P. 2001. The increasing prevalence of myopia: implications for Australia. *Clin Exp Ophthalmol,* 29**,** 116-20.

ROSE, K. A., MORGAN, I. G., IP, J., KIFLEY, A., HUYNH, S., SMITH, W. & MITCHELL, P. 2008a. Outdoor activity reduces the prevalence of myopia in children. *Ophthalmology,* 115**,** 1279-85.

ROSE, K. A., MORGAN, I. G., SMITH, W., BURLUTSKY, G., MITCHELL, P. & SAW, S. M. 2008b. Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney. *Arch Ophthalmol,* 126**,** 527-30.

ROSENFIELD, M. 2009. Subjective refraction. *In:* ROSENFIELD, M., LOGAN, N. (ed) *Optometry: Science, Techniques and Clinical Management.* 2 ed. Edinburgh: Butterworth Heinemann, 209-28.

ROSENFIELD, M., CIUFFREDA, K. J., ONG, E. & AZIMI, A. 1990. Proximally induced accommodation and accommodative adaptation. *Invest Ophthalmol Vis Sci,* 31**,** 1162-7.

RUSTON, D. & MOUNTFORD, J. 2004. Patient selection and preliminary examination. *In:* MOUNTFORD, J., RUSTON, D. & DAVE, T.(ed.) *Orthokeratology: Principles and Practice.* London: Butterworth Heinemann, 109-138

SALZ, J. J., AZEN, S. P., BERSTEIN, J., CAROLINE, P., VILLASENOR, R. A. & SCHANZLIN, D.J. 1983. Evaluation and comparison of sources of variability in the measurement of corneal thickness with ultrasonic and optical pachymeters. *Ophthalmic Surg,* 14**,** 750-4.

SANKARIDURG, P., DONOVAN, L., VARNAS, S., HO, A., CHEN, X., MARTINEZ, A., FISHER, S., LIN, Z., SMITH, E. L., 3RD, GE, J. & HOLDEN, B. A. 2010. Spectacle lenses designed to reduce progression of myopia: 12-month results. *Optom Vis Sci,* 87**,** 631-41.

SANTODOMINGO-RUBIDO, J., MALLEN, E. A., GILMARTIN, B. & WOLFFSOHN, J. S. 2002. A new non-contact optical device for ocular biometry. *Br J Ophthalmol,* 86**,** 458-62.

SAW, S. M. 2003. A synopsis of the prevalence rates and environmental risk factors for myopia. *Clin Exp Optom,* 86**,** 289-94.

SAW, S. M., CARKEET, A., CHIA, K. S., STONE, R. A. & TAN, D. T. 2002a. Component dependent risk factors for ocular parameters in Singapore Chinese children. *Ophthalmology,* 109**,** 2065-71.

SAW, S. M., CHIA, S. E. & CHEW, S. J. 1999. Relation between work and myopia in Singapore women. *Optom Vis Sci,* 76**,** 393-6.

SAW, S. M., CHUA, W. H., HONG, C. Y., WU, H. M., CHAN, W. Y., CHIA, K. S., STONE, R. A. & TAN, D. 2002b. Nearwork in early-onset myopia. *Invest Ophthalmol Vis Sci,* 43**,** 332-9.

SAW, S. M., GAZZARD, G., SHIH-YEN, E. C. & CHUA, W. H. 2005a. Myopia and associated pathological complications. *Ophthalmic Physiol Opt,* 25**,** 381-91.

SAW, S. M., HONG, R. Z., ZHANG, M. Z., FU, Z. F., YE, M., TAN, D. & CHEW, S. J. 2001a. Near-work activity and myopia in rural and urban schoolchildren in China. *J Pediatr Ophthalmol Strabismus,* 38**,** 149-55.

SAW, S. M., KATZ, J., SCHEIN, O. D., CHEW, S. J. & CHAN, T. K. 1996. Epidemiology of myopia. *Epidemiol Rev,* 18**,** 175-87.

SAW, S. M., NIETO, F. J., KATZ, J., SCHEIN, O. D., LEVY, B. & CHEW, S. J. 2000. Factors related to the progression of myopia in Singaporean children. *Optom Vis Sci,* 77**,** 549-54.

SAW, S. M., NIETO, F. J., KATZ, J., SCHEIN, O. D., LEVY, B. & CHEW, S. J. 2001b. Familial clustering and myopia progression in Singapore school children. *Ophthalmic Epidemiol,* 8**,** 227-36.

SAW, S. M., TONG, L., CHUA, W. H., CHIA, K. S., KOH, D., TAN, D. T. & KATZ, J. 2005b. Incidence and progression of myopia in Singaporean school children. *Invest Ophthalmol Vis Sci,* 46**,** 51-7.

SAW, S. M., WU, H. M., SEET, B., WONG, T. Y., YAP, E., CHIA, K. S., STONE, R. A. & LEE, L. 2001c. Academic achievement, close up work parameters, and myopia in Singapore military conscripts. *Br J Ophthalmol,* 85**,** 855-60.

SCHAEFFEL, F., GLASSER, A. & HOWLAND, H. C. 1988. Accommodation, refractive error and eye growth in chickens. *Vision Res,* 28**,** 639-57.

SCHAEFFEL, F., HAGEL, G., EIKERMANN, J. & COLLETT, T. 1994. Lower-field myopia and astigmatism in amphibians and chickens. *J Opt Soc Am A Opt Image Sci Vis,* 11**,** 487-95.

SCHAEFFEL, F., TROILO, D., WALLMAN, J. & HOWLAND, H. C. 1990. Developing eyes that lack accommodation grow to compensate for imposed defocus. *Vis Neurosci,* 4**,** 177-83.

SCHIPPERT, R. & SCHAEFFEL, F. 2006. Peripheral defocus does not necessarily affect central refractive development. *Vision Res,* 46**,** 3935-40.

SCHMID, G. F. 2011. Association between retinal steepness and central myopic shift in children. *Optom Vis Sci,* 88**,** 684-90.

SCHMID, G. F. 2003a. Axial and peripheral eye length measured with optical low coherence reflectometry. *J Biomed Opt,* 8**,** 655-62.

SCHMID, G. F. 2003b. Variability of retinal steepness at the posterior pole in children 7-15 years of age. *Curr Eye Res,* 27**,** 61-8.

SCHMID, K. & WILDSOET, C. F. 1997. Natural and imposed astigmatism and their relation to emmetropization in the chick. *Exp Eye Res,* 64**,** 837-47.

SEIDEMANN, A., SCHAEFFEL, F., GUIRAO, A., LOPEZ-GIL, N. & ARTAL, P. 2002. Peripheral refractive errors in myopic, emmetropic, and hyperopic young subjects. *J Opt Soc Am A Opt Image Sci Vis,* 19**,** 2363-73.

SEITZ, B., BEHRENS, A. & LAGENBUCHER, A. 1997. Corneal topography. *Curr Opinion Ophthalmol,* 8**,** 8-24.

SHAIKH, A. W., SIEGWART, J. T., JR. & NORTON, T. T. 1999. Effect of interrupted lens wear on compensation for a minus lens in tree shrews. *Optom Vis Sci,* 76**,** 308-15.

SHEN, J., CLARK, C. A., SONI, P. S. & THIBOS, L. N. 2010. Peripheral refraction with and without contact lens correction. *Optom Vis Sci,* 87**,** 642-55.

SHENG, H., BOTTJER, C. A. & BULLIMORE, M. A. 2004. Ocular component measurement using the Zeiss IOLMaster. *Optom Vis Sci,* 81**,** 27-34.

SHERIDAN, M. & DOUTHWAITE, W. A. 1989. Corneal asphericity and refractive error. *Ophthalmic Physiol Opt,* 9**,** 235-8.

SHIH, Y. F., HSIAO, C. K., CHEN, C. J., CHANG, C. W., HUNG, P. T. & LIN, L. L. 2001. An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression. *Acta Ophthalmol Scand,* 79**,** 233-6.

SIATKOWSKI, R. M., COTTER, S., MILLER, J. M., SCHER, C. A., CROCKETT, R. S. & NOVACK, G. D. 2004. Safety and efficacy of 2% pirenzipine ophthalmic gel in children with myopia: a 1-year, multicenter, double-masked, placebo-controlled parallel study. *Arch Ophthalmol,* 122**,** 1667-74.

SIEVING, P. A. & FISHMAN, G. A. 1978. Refractive errors of retinitis pigmentosa patients. *Br J Ophthalmol,* 62**,** 163-7.

SINGH, K. D., LOGAN, N. S. & GILMARTIN, B. 2006. Three-dimensional modeling of the human eye based on magnetic resonance imaging. *Invest Ophthalmol Vis Sci,* 47**,** 2272-9.

SIU, A. W. & HERSE, P. R. 1993. The effect of age on the edema response of the central and mid-peripheral cornea. *Acta Ophthalmol (Copenh),* 71**,** 57-61.

SMITH, E.L., 3RD. 2011. Prentice Award Lecture 2010: A case for peripheral optical treatment strategies for myopia. *Optom Vis Sci,* 88**,** 1029-44.

SMITH, E. L., 3RD, HARWERTH, R. S., CRAWFORD, M. L. & VON NOORDEN, G. K. 1987. Observations on the effects of form deprivation on the refractive status of the monkey. *Invest Ophthalmol Vis Sci,* 28**,** 1236-45.

SMITH, E. L., 3RD, HUANG, J., HUNG, L. F., BLASDEL, T. L., HUMBIRD, T. L. & BOCKHORST, K. H. 2009a. Hemiretinal form deprivation: evidence for local control of eye growth and refractive development in infant monkeys. *Invest Ophthalmol Vis Sci,* 50**,** 5057-69.

SMITH, E. L., 3RD. & HUNG, L. F. 1999. The role of optical defocus in regulating refractive development in infant monkeys. *Vision Res,* 39**,** 1415-35.

SMITH, E. L., 3RD, HUNG, L. F. & HUANG, J. 2009b. Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. *Vision Res,* 49**,** 2386-92.

SMITH, E. L., 3RD, HUNG, L. F., KEE, C. S. & QIAO, Y. 2002. Effects of brief periods of unrestricted vision on the development of form-deprivation myopia in monkeys. *Invest Ophthalmol Vis Sci,* 43**,** 291-9.

SMITH, E. L., 3RD, KEE, C. S., RAMAMIRTHAM, R., QIAO-GRIDER, Y. & HUNG, L. F. 2005. Peripheral vision can influence eye growth and refractive development in infant monkeys. *Invest Ophthalmol Vis Sci,* 46**,** 3965-72.

SMITH, E. L., 3RD, RAMAMIRTHAM, R., QIAO-GRIDER, Y., HUNG, L. F., HUANG, J., KEE, C. S., COATS, D. & PAYSSE, E. 2007. Effects of foveal ablation on emmetropization and form-deprivation myopia. *Invest Ophthalmol Vis Sci,* 48**,** 3914-22.

SMITH, G., MILLODOT, M. & MCBRIEN, N. A. 1988. The effect of accommodation on oblique astigmatism and field curvature of the human eye. *Clin Exp Optom,* 71**,** 119-125.

SMITHSON, H. E. 2005. Sensory, computational and cognitive components of human colour constancy. *Philos Trans R Soc Lond B Biol Sci,* 360**,** 1329-46.

SNG, C. C., LIN, X. Y., GAZZARD, G., CHANG, B., DIRANI, M., CHIA, A., SELVARAJ, P., IAN, K., DROBE, B., WONG, T. Y. & SAW, S. M. 2011. Peripheral refraction and refractive error in Singapore Chinese children. *Invest Ophthalmol Vis Sci,* 52**,** 1181-90.

SONI, P. S., NGUYEN, T. T. & BONANNO, J. A. 2003. Overnight orthokeratology: visual and corneal changes. *Eye Contact Lens,* 29**,** 137-45.

SORBARA, L., FONN, D., SIMPSON, T., LU, F. & KORT, R. 2005. Reduction of myopia from corneal refractive therapy. *Optom Vis Sci,* 82**,** 512-8.

SRIDHARAN, R. & SWARBRICK, H. 2003. Corneal response to short-term orthokeratology lens wear. *Optom Vis Sci,* 80**,** 200-6.

STILLITANO, I. G., CHALITA, M. R., SCHOR, P., MAIDANA, E., LUI, M. M., LIPENER, C. & HOFLING-LIMA, A. L. 2007. Corneal changes and wavefront analysis after orthokeratology fitting test. *Am J Ophthalmol*, 144**,** 378-86

STONE, J. 1976. The possible influence of contact lenses on myopia. *Br J Physiol Optics*, 31**,** 89-114.

STONE, R. A. & FLITCROFT, D. I. 2004. Ocular shape and myopia. *Ann Acad Med Singapore,* 33**,** 7-15.

STONE, R. A., PENDRAK, K., SUGIMOTO, R., LIN, T., GILL, A. S., CAPEHART, C. & LIU, J. 2006. Local patterns of image degradation differentially affect refraction and eye shape in chick. *Curr Eye Res,* 31**,** 91-105.

SWARBRICK, H. 2004. The e's, p's and Q's of corneal shape. *Refractive Eyecare for Ophthalmologists,* 8**,** 5-8.

SWARBRICK, H. A. 2006. Orthokeratology review and update. *Clin Exp Optom,* 89**,** 124-43.

SWARBRICK, H., ALHARBI, A., WATT, K. & LUM, E. 2010. Overnight orthokeratology lens wear slows axial eye growth in myopic children. *Invest Ophthalmol Vis Sci*, 51**,** E-Abstract 1721.

SWARBRICK, H., WONG, G. & O'LEARY, D. J. 1998. Corneal response to orthokeratology. *Optom Vis Sci,* 75**,** 791-9.

SWITKES, E., BRADLEY, A. & SCHOR, C. 1990. Readily visible changes in color contrast are insufficient to stimulate accommodation. *Vision Res,* 30**,** 1367-76.

TABERNERO, J., VAZQUEZ, D., SEIDEMANN, A., UTTENWEILER, D. & SCHAEFFEL, F. 2009. Effects of myopic spectacle correction and radial refractive gradient spectacles on peripheral refraction. *Vision Res,* 49**,** 2176-86.

TAM, E. S. & ROOTMAN, D. S. 2003. Comparison of central corneal thickness measurements by specular microscopy, ultrasound pachymetry, and ultrasound biomicroscopy. *J Cataract Refract Surg,* 29**,** 1179-84.

TAN, D. T., LAM, D. S., CHUA, W. H., SHU-PING, D. F. & CROCKETT, R. S. 2005. One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *Ophthalmol,* 112**,** 84-91.

TAN, N. W., SAW, S. M., LAM, D. S., CHENG, H. M., RAJAN, U. & CHEW, S. J. 2000. Temporal variations in myopia progression in Singaporean children within an academic year. *Optom Vis Sci,* 77**,** 465-72.

TAN, R. K. & O'LEARY, D. J. 1985. Steady-state accommodation response to different Snellen letter sizes. *Am J Optom Physiol Opt*, 62**,** 751-4.

TANG, W., COLLINS, M. J., CARNEY, L. & DAVIS, B. 2000. The accuracy and precision performance of four videokeratoscopes in measuring test surfaces. *Optom Vis Sci,* 77**,** 483-91.

TEJEDOR, J. & DE LA VILLA, P. 2003. Refractive changes induced by form deprivation in the mouse eye. *Invest Ophthalmol Vis Sci,* 44**,** 32-6.

THIBOS, L. N., WHEELER, W. & HORNER, D. 1997. Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. *Optom Vis Sci,* 74**,** 367-75.

TOMLINSON, A. 1972. A clinical study of the central and peripheral thickness and curvature of the human cornea. *Acta Ophthalmol (Copenh),* 50**,** 73-82.

TONG, L., HUANG, X. L., KOH, A. L., ZHANG, X., TAN, D. T. & CHUA, W. H. 2009. Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. *Ophthalmology,* 116**,** 572-9.

TROILO, D., GOTTLIEB, M. D. & WALLMAN, J. 1987. Visual deprivation causes myopia in chicks with optic nerve section. *Curr Eye Res,* 6**,** 993-9.

TROILO, D., NICKLA, D. L. & WILDSOET, C. F. 2000. Form deprivation myopia in mature common marmosets (Callithrix jacchus). *Invest Ophthalmol Vis Sci,* 41**,** 2043-9.

TSAI, M. Y., LIN, L. L., LEE, V., CHEN, C. J. & SHIH, Y. F. 2009. Estimation of heritability in myopic twin studies. *Jpn J Ophthalmol,* 53**,** 615-22.

TSUKIYAMA, J., MIYAMOTO, Y., HIGAKI, S., FUKUDA, M. & SHIMOMURA, Y. 2008. Changes in the anterior and posterior radii of the corneal curvature and anterior chamber depth by orthokeratology. *Eye Contact Lens,* 34**,** 17-20.

TUNNACLIFFE, A. H. & HIRST, J. G. 2003. Aberrations. *In:* TUNNACLIFFE, A. H. & HIRST, J. G. *Optics.* Kent: Association of British Dispensing Opticians, 178-213.

TWELKER, J. D., MITCHELL, G. L., MESSER, D. H., BHAKTA, R., JONES, L. A., MUTTI, D. O., COTTER, S. A., KLENSTEIN, R. N., MANNY, R. E. & ZADNIK, K. 2009. Children's ocular components and age, gender, and ethnicity. *Optom Vis Sci,* 86**,** 918-35.

VITALE, S., ELLWEIN, L., COTCH, M. F., FERRIS, F. L., 3RD & SPERDUTO, R. 2008. Prevalence of refractive error in the United States, 1999-2004. *Arch Ophthalmol,* 126**,** 1111-9.

VON BAHR, G. 1948. Measurements of the thickness of the cornea. *Acta Ophthalmol (Copenh),* 26**,** 247-66.

VON NOORDEN, G. K. & LEWIS, R. A. 1987. Ocular axial length in unilateral congenital cataracts and blepharoptosis. *Invest Ophthalmol Vis Sci,* 28**,** 750-2.

VONGPHANIT, J., MITCHELL, P. & WANG, J. J. 2002. Prevalence and progression of myopic retinopathy in an older population. *Ophthalmology,* 109**,** 704-11.

WALKER, T. W. & MUTTI, D. O. 2002. The effect of accommodation on ocular shape. *Optom Vis Sci,* 79**,** 424-30.

WALLINE, J. J., JONES, L. A., MUTTI, D. O. & ZADNIK, K. 2003. Use of a run-in period to decrease loss to follow-up in the Contact Lens and Myopia Progression (CLAMP) study. *Control Clin Trials,* 24**,** 711-8.

WALLINE, J. J., JONES, L. A., SINNOTT, L., MANNY, R. E., GAUME, A., RAH, M. J., CHITKARA, M. & LYONS, S. 2008. A randomized trial of the effect of soft contact lenses on myopia progression in children. *Invest Ophthalmol Vis Sci,* 49**,** 4702-6.

WALLINE, J. J., JONES, L. A. & SINNOTT, L. T. 2009. Corneal reshaping and myopia progression. *Br J Ophthalmol,* 93**,** 1181-5.

WALLINE, J. J., MUTTI, D. O., JONES, L. A., RAH, M. J., NICHOLS, K. K., WATSON, R. & ZADNIK, K. 2001. The contact lens and myopia progression (CLAMP) study: design and baseline data. *Optom Vis Sci,* 78**,** 223-33.

WALLMAN, J. & ADAMS, J. I. 1987. Developmental aspects of experimental myopia in chicks: susceptibility, recovery and relation to emmetropization. *Vision Res,* 27**,** 1139-63.

WALLMAN, J., GOTTLIEB, M. D., RAJARAM, V. & FUGATE-WENTZEK, L. A. 1987. Local retinal regions control local eye growth and myopia. *Science,* 237**,** 73-7.

WALLMAN, J., TURKEL, J. & TRACHTMAN, J. 1978. Extreme myopia produced by modest change in early visual experience. *Science,* 201**,** 1249-51.

WALLMAN, J., WILDSOET, C. F., XU, A., GOTTLIEB, M. D., NICKLA, D. L., MARRAN, L., KREBS, W. & CHRISTENSEN, A. M. 1995. Moving the retina: choroidal modulation of refractive state. *Vision Res,* 35**,** 37-50.

WALLMAN, J. & WINAWER, J. 2004. Homeostasis of eye growth and the question of myopia. *Neuron,* 43**,** 447-68.

WANDELL, B. A., DUMOULIN, S. O. & BREWER, A. A. 2007. Visual field maps in human cortex. *Neuron,* 56**,** 366-83.

WANG, F. R., ZHOU, X. D. & ZHOU, S. Z. 1994. [A CT study of the relation between ocular axial biometry and refraction]. *Zhonghua Yan Ke Za Zhi,* 30**,** 39-40.

WANG, J., FONN, D., SIMPSON, T. L., SORBARA, L., KORT, R. & JONES, L. 2003a. Topographical thickness of the epithelium and total cornea after overnight wear of

reverse-geometry rigid contact lenses for myopia reduction. *Invest Ophthalmol Vis Sci*, 44**,** 4742-6.

WANG, Y., ZHAO, K., JIN, Y., NIU, Y. & ZUO, T. 2003b. Changes of higher order aberration with various pupil sizes in the myopic eye. *J Refract Surg*, 19**,** S270-4.

WANG, Y. Z., THIBOS, L. N., LOPEZ, N., SALMON, T. & BRADLEY, A. 1996. Subjective refraction of the peripheral field using contrast detection acuity. *J Am Optom Assoc*, 67**,** 584-9.

WARING, G. O. 1989. Making sense of keratospeak II: Proposed conventional terminology for corneal topography. *Refract Corneal Surg*, 5**,** 362-7.

WEIZHONG, L., ZHIKUAN, Y., WEN, L., XIANG, C. & JIAN, G. 2008. A longitudinal study on the relationship between myopia development and near accommodation lag in myopic children. *Ophthalmic Physiol Opt*, 28**,** 57-61.

WHATHAM, A., ZIMMERMANN, F., MARTINEZ, A., DELGADO, S., LAZON DE LA JARA, P., SANKARIDURG, P. & HO, A. 2009. Influence of accommodation on off-axis refractive errors in myopic eyes. *J Vis*, 9**,** 14 1-13.

WILDSOET, C. F. & PETTIGREW, J. D. 1988. Experimental myopia and anomalous eye growth unaffected by optic nerve section in chickens: evidence for local control of eye growth. *Clin Vis Sci*, 3**,** 99-107.

WILDSOET, C. F. & WALLMAN, J. 1995. Choroidal and scleral mechanisms of compensation for spectacle lenses in chicks. *Vision Res*, 35**,** 1175-94.

WILDSOET, C. F. 1997. Active emmetropization-evidence for its existence and ramifications for clinical practice. *Ophthalmic Physiol Opt*, 17**,** 279-90.

WOLFE, J. M. & OWENS, D. A. 1981. Is accommodation colorblind? Focusing chromatic contours. *Perception*, 10**,** 53-62.

WONG, T. Y., FOSTER, P. J., HEE, J., NG, T. P., TIELSCH, J. M., CHEW, S. J., JOHNSON, G. J. & SEAH, S. K. 2000. Prevalence and risk factors for refractive errors in adult Chinese in Singapore. *Invest Ophthalmol Vis Sci*, 41**,** 2486-94.

WONG, T. Y., KLEIN, B. E., KLEIN, R., TOMANY, S. C. & LEE, K. E. 2001. Refractive errors and incident cataracts: the Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci*, 42**,** 1449-54.

WOODMAN, E. C., READ, S. A., COLLINS, M. J., HEGARTY, K. J., PRIDDLE, S. B., SMITH, J. M. & PERRO, J. V. 2010. Axial elongation following prolonged near work in myopes and emmetropes. *Br J Ophthalmol*, 95**,** 652-6.

WU, H. M., SEET, B., YAP, E. P., SAW, S. M., LIM, T. H. & CHIA, K. S. 2001. Does education explain ethnic differences in myopia prevalence? A population-based study of young adult males in Singapore. *Optom Vis Sci,* 78**,** 234-9.

XIE, R., ZHOU, X. T., LU, F., CHEN, M., XUE, A., CHEN, S. & QU, J. 2009. Correlation between myopia and major biometric parameters of the eye: a retrospective clinical study. *Optom Vis Sci,* 86**,** E503-8.

XU, L., WANG, Y., LI, Y., WANG, Y., CUI, T., LI, J. & JONAS, J. B. 2006. Causes of blindness and visual impairment in urban and rural areas in Beijing: the Beijing Eye Study. *Ophthalmology,* 113**,** 1134 e1-11.

YOON, J. 2009. *Modelling Outcomes from Orthokeratology.* PhD thesis, University of New South Wales.

YURA, T. 1998. The relationship between the types of axial elongation and the prevalence of lattice degeneration of the retina. *Acta Ophthalmol Scand,* 76**,** 90-5.

ZADNIK, K. 1997. The Glenn A. Fry Award Lecture (1995). Myopia development in childhood. *Optom Vis Sci,* 74**,** 603-8.

ZADNIK, K., MANNY, R. E., YU, J. A., MITCHELL, G. L., COTTER, S. A., QUIRALTE, J. C., SHIPP, M., FRIEDMAN, N. E., KLEINSTEIN, R. N., WALKER, T. W., JONES, L. A., MOESCHBERGER, M. L. & MUTTI, D. O. 2003. Ocular component data in schoolchildren as a function of age and gender. *Optom Vis Sci,* 80**,** 226-36.

ZADNIK, K., MUTTI, D. O., MITCHELL, G. L., JONES, L. A., BURR, D. & MOESCHBERGER, M. L. 2004. Normal eye growth in emmetropic schoolchildren. *Optom Vis Sci,* 81**,** 819-28.

ZADNIK, K., SATARIANO, W. A., MUTTI, D. O., SHOLTZ, R. I. & ADAMS, A. J. 1994. The effect of parental history of myopia on children's eye size. *JAMA,* 271**,** 1323-7.

ZHAO, J., PAN, X., SUI, R., MUNOZ, S. R., SPERDUTO, R. D. & ELLWEIN, L. B. 2000. Refractive error study in children: results from Shunyi District, China. *Am J Ophthalmol,* 129**,** 427-35.

APPENDIX A

Simple ray tracing to determine corneal locations at which peripheral refraction measurements are taken. Angles in the diagram have been exaggerated for clarity. Average parameter values were used in these calculations which may vary between individuals.

A1 REFRACTION MEASUREMENTS TAKEN AT PRIMARY GAZE

Pupil decentration is assumed to be 250μm

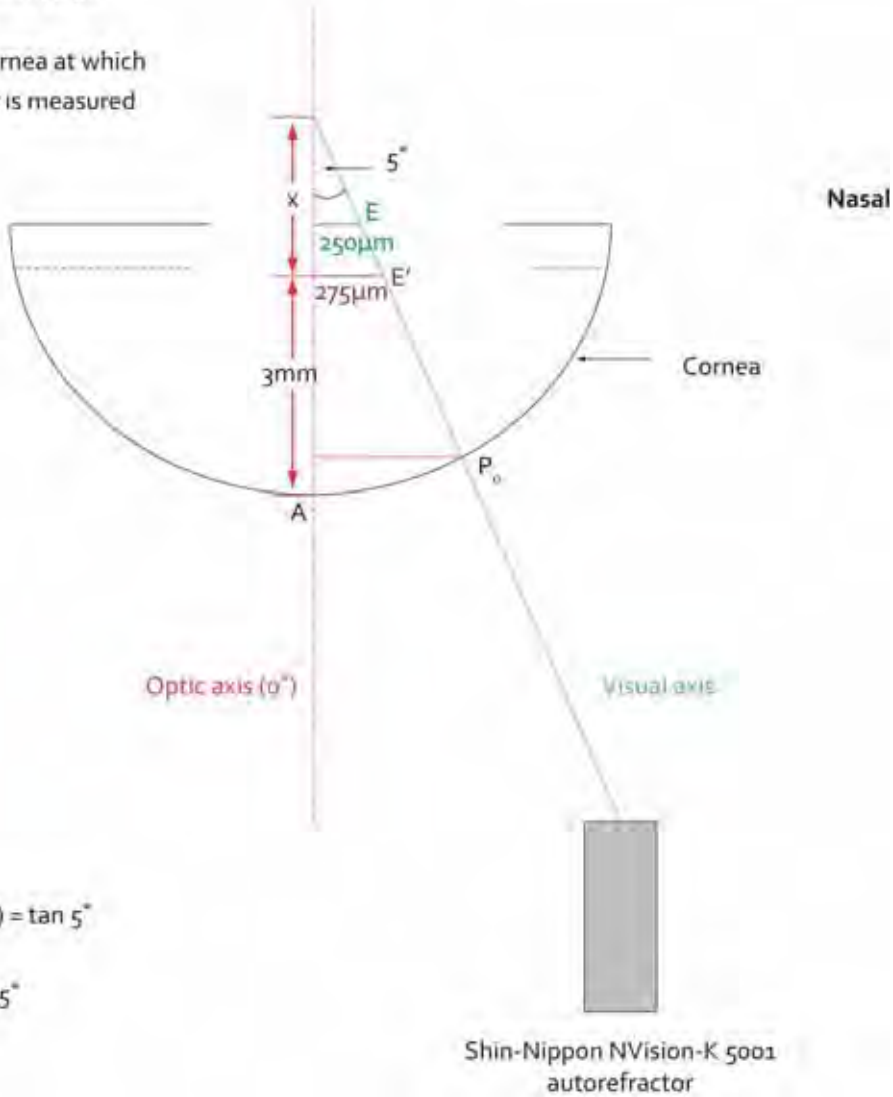
Pupil magnification by the cornea is assumed to be 1.1x

E - Centre of pupil

E' - Centre of entrance pupil

A - Corneal apex

P_o - Point on the cornea at which refractive error is measured



Calculation

$(0.275 / x) = AP_o / (x + 3) = \tan 5^\circ$

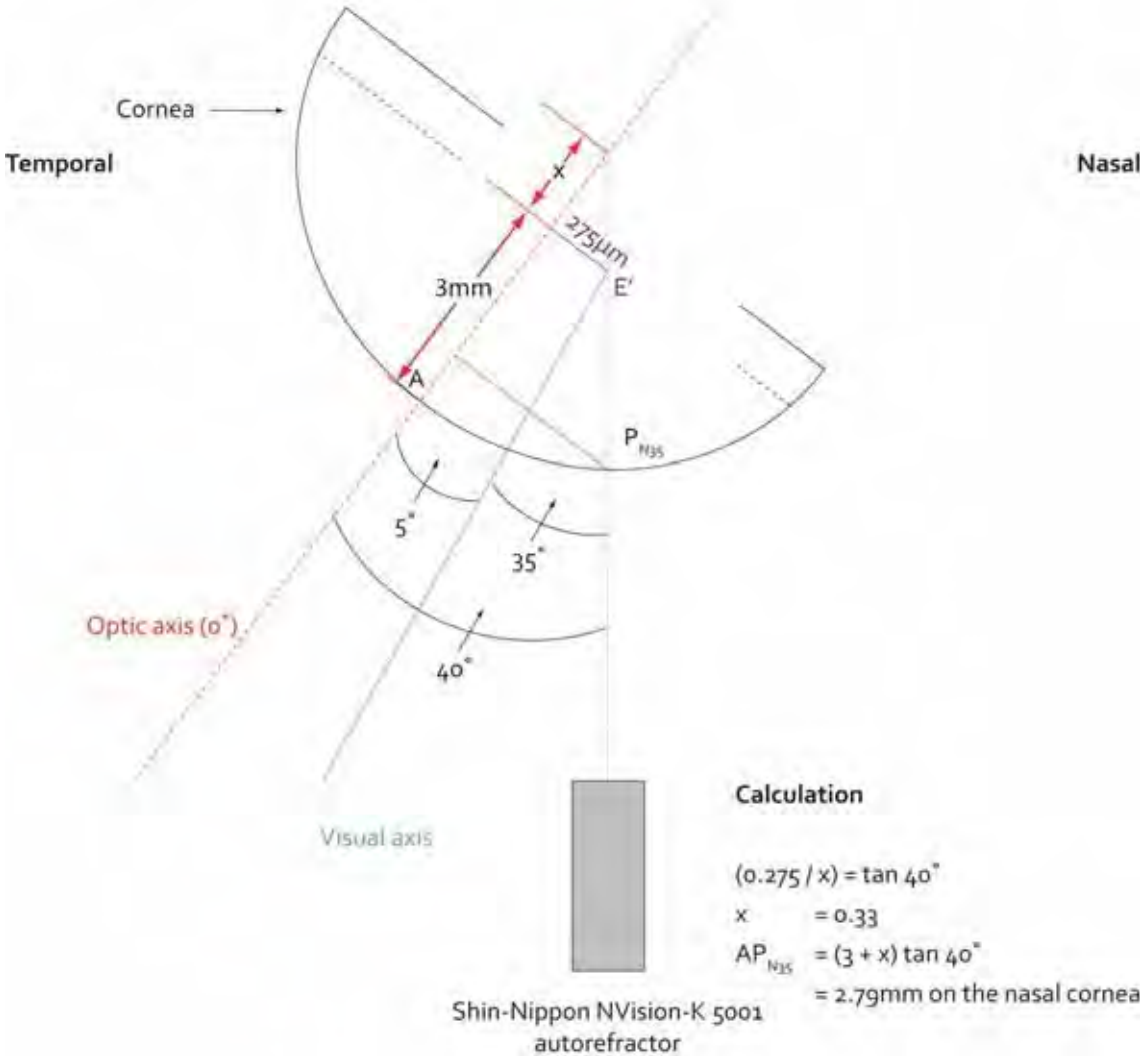
$x = 3.14mm$

$AP_o = (3.14 + 3) \tan 5^\circ$

$= 0.54mm$

A2 REFRACTION MEASUREMENTS TAKEN AT TEMPORAL GAZE

P_{N35} - Point on the cornea at which refractive error is measured when the eye has rotated temporally by 35°



Calculation

$(0.275 / x) = \tan 40°$

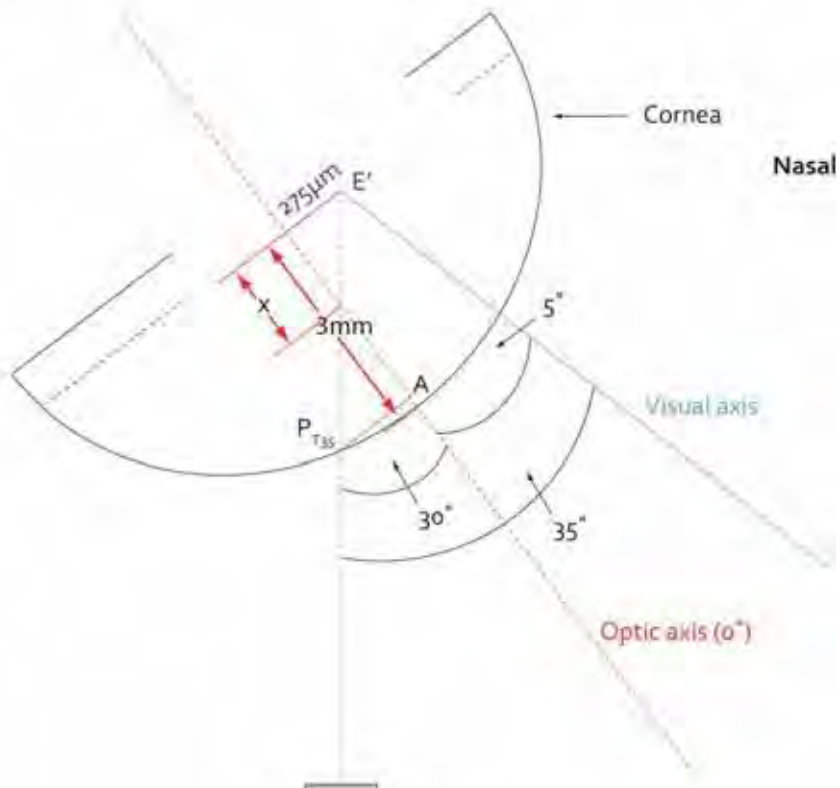
$x = 0.33$

$AP_{N35} = (3 + x) \tan 40°$

$= 2.79$mm on the nasal cornea

A3 REFRACTION MEASUREMENTS TAKEN AT NASAL GAZE

P_{T35} - Point on the cornea at which refractive error is measured when the eye has rotated nasally by 35°



Calculation

$(0.275 / x) = \tan 30°$

$x = 0.48$

$AP_{T35} = (3 - x) \tan 30°$

$= 1.46$mm on the temporal cornea

Shin-Nippon NVision-K 5001 autorefractor

APPENDIX B

Corneal refractive power was calculated from axial radius of curvature and corneal sagittal height extracted from corneal topography maps. The following equations and properties were used incorporating average parameter values which may vary between individuals. :

Calculation of corneal refractive power

$\Theta_{in} = \arcsin(|RD|/r)$

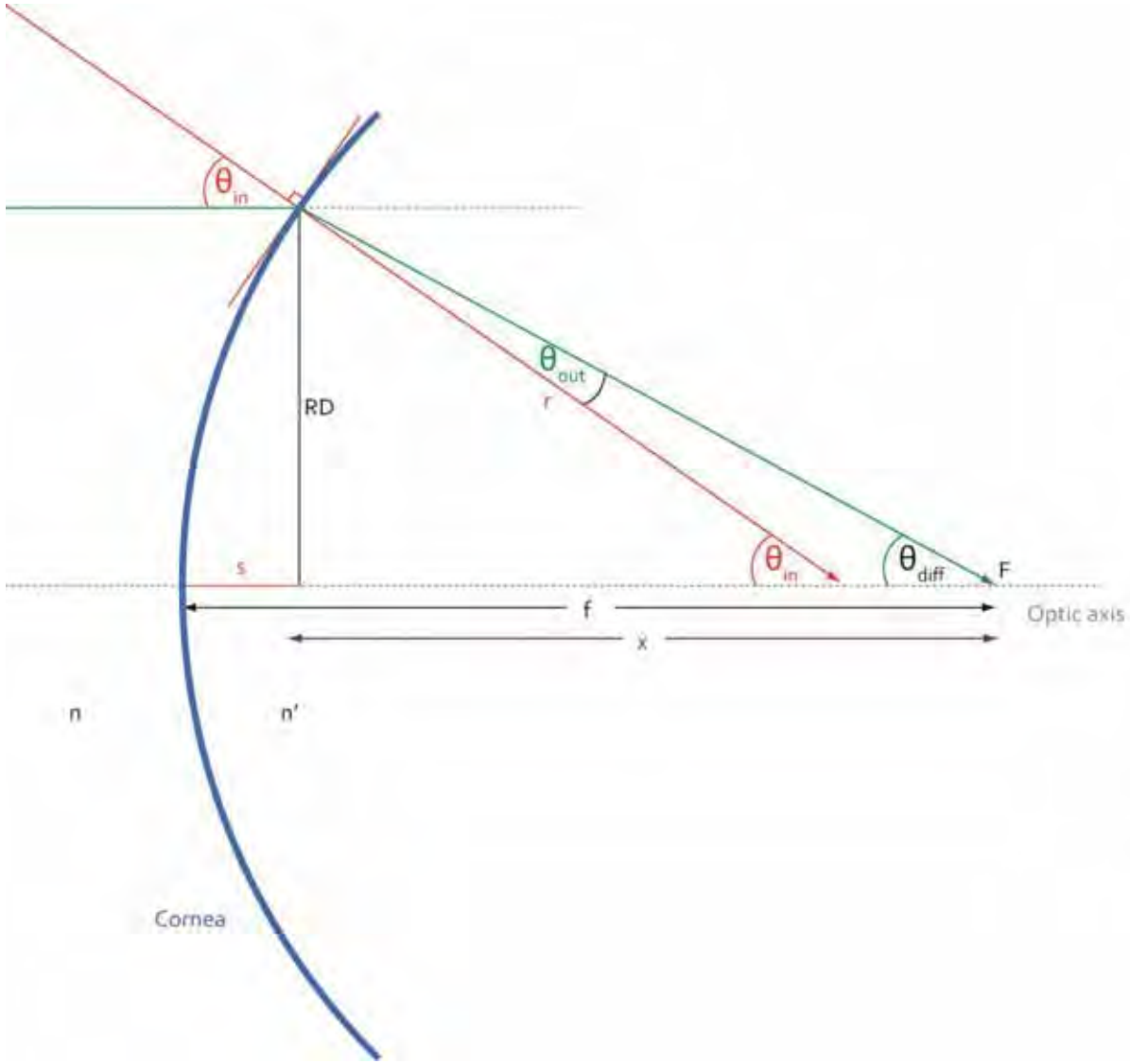
Using Snell's Law; $\Theta_{out} = \arcsin(n * \sin \Theta_{in}/n')$

$\Theta_{diff} = \Theta_{in} - \Theta_{out}$

$x = |RD| / \tan(\Theta_{diff})$

$f = x + s$;

Corneal refractive power = $1000*(n'/f)$;



n = refractive index of incident medium (air) = 1.000

n' = refractive index of refractive medium (cornea) = 1.3375

RD = radial distance (mm)

r = axial radius of curvature (mm)

s = corneal sag (mm)

f = focal length (mm)

F = focal point

θ_{in} = angle of incidence

θ_{out} = angle of refraction

θ_{diff} = difference between angle of incidence and refraction

APPENDIX C

Statistics and p values of statistical analysis performed in the studies reported in this thesis. P values less than 0.05 are marked with an asterisk.

C1 PERIPHERAL REFRACTION IN DIFFERENT REFRACTIVE GROUPS STUDY

REFRACTION ALONG THE HORIZONTAL MERIDIAN

Planned contrasts were conducted to compare M at different positions along the horizontal VF in myopes and J_{180} and J_{45} along the horizontal VF in all refractive groups.

	M	
Comparison	**F**	**Significance**
Centre *vs* temporal 5°	0.380	0.543
Centre *vs* temporal 10°	3.937	0.058
Centre *vs* temporal 20°	0.541	0.469
Centre *vs* temporal 25°	0.254	0.619
Centre *vs* temporal 30°	1.519	0.229
Centre *vs* temporal 35°	2.067	0.163
Centre *vs* nasal 5°	5.052	0.034 *
Centre *vs* nasal 10°	2.107	0.159
Centre *vs* nasal 15°	0.872	0.359
Centre *vs* nasal 20°	1.853	0.186
Centre *vs* nasal 25°	6.421	0.018 *
Centre *vs* nasal 30°	5.303	0.030 *
Centre *vs* nasal 35°	6.256	0.019 *

J180

Comparison	F	Significance
Centre *vs* temporal 5°	4.778	0.032 *
Centre *vs* temporal 10°	29.998	<0.001 *
Centre *vs* temporal 20°	80.342	<0.001 *
Centre *vs* temporal 25°	190.114	<0.001 *
Centre *vs* temporal 30°	256.516	<0.001 *
Centre *vs* temporal 35°	330.057	<0.001 *
Centre *vs* nasal 5°	4.087	0.047 *
Centre *vs* nasal 10°	54.677	<0.001 *
Centre *vs* nasal 15°	134.314	<0.001 *
Centre *vs* nasal 20°	161.123	<0.001 *
Centre *vs* nasal 25°	330.176	<0.001 *
Centre *vs* nasal 30°	310.204	<0.001 *
Centre *vs* nasal 35°	257.441	<0.001 *

J_{45}

Comparison	F	Significance
Centre *vs* temporal 5°	0.306	0.582
Centre *vs* temporal 10°	6.988	0.010 *
Centre *vs* temporal 20°	12.336	0.001 *
Centre *vs* temporal 25°	19.330	<0.001 *
Centre *vs* temporal 30°	24.082	<0.001 *
Centre *vs* temporal 35°	26.455	<0.001 *
Centre *vs* nasal 5°	4.804	0.036 *
Centre *vs* nasal 10°	39.054	<0.001 *
Centre *vs* nasal 15°	17.773	<0.001 *
Centre *vs* nasal 20°	68.774	<0.001 *
Centre *vs* nasal 25°	91.882	<0.001 *
Centre *vs* nasal 30°	70.074	<0.001 *
Centre *vs* nasal 35°	81.179	<0.001 *

C2 TIME COURSE OF EFFECTS OF OK STUDY

CHANGE IN M WITH OK

Pairwise comparisons to compare M at different positions along the horizontal VF during different days of OK treatment.

Position	Comparison	Significance
T35	Baseline *vs* Day 1	1.000
	Baseline *vs* Day 4	1.000
	Baseline *vs* Day 7	1.000
	Baseline *vs* Day 14	1.000
	Day 1 *vs* Day 4	1.000
	Day 1 *vs* Day 7	0.325
	Day 1 *vs* Day 14	0.710
	Day 4 *vs* Day 7	0.314
	Day 4 *vs* Day 14	1.000
	Day 7 *vs* Day 14	1.000
T30	Baseline *vs* Day 1	1.000
	Baseline *vs* Day 4	0.467
	Baseline *vs* Day 7	0.221
	Baseline *vs* Day 14	0.079
	Day 1 *vs* Day 4	0.311
	Day 1 *vs* Day 7	0.125
	Day 1 *vs* Day 14	0.032 *
	Day 4 *vs* Day 7	0.192
	Day 4 *vs* Day 14	0.130
	Day 7 *vs* Day 14	1.000

T20	Baseline *vs* Day 1	0.117
	Baseline *vs* Day 4	0.003 *
	Baseline *vs* Day 7	0.003 *
	Baseline *vs* Day 14	<0.001 *
	Day 1 *vs* Day 4	0.187
	Day 1 *vs* Day 7	0.023 *
	Day 1 *vs* Day 14	0.001 *
	Day 4 *vs* Day 7	0.835
	Day 4 *vs* Day 14	0.059
	Day 7 *vs* Day 14	1.000
T10	Baseline *vs* Day 1	0.007 *
	Baseline *vs* Day 4	<0.001 *
	Baseline *vs* Day 7	<0.001 *
	Baseline *vs* Day 14	<0.001 *
	Day 1 *vs* Day 4	<0.001 *
	Day 1 *vs* Day 7	<0.001 *
	Day 1 *vs* Day 14	<0.001 *
	Day 4 *vs* Day 7	0.033 *
	Day 4 *vs* Day 14	0.005 *
	Day 7 *vs* Day 14	0.763
Centre	Baseline *vs* Day 1	0.263
	Baseline *vs* Day 4	0.044 *
	Baseline *vs* Day 7	0.008 *
	Baseline *vs* Day 14	0.002 *
	Day 1 *vs* Day 4	0.002 *
	Day 1 *vs* Day 7	<0.001 *
	Day 1 *vs* Day 14	<0.001 *
	Day 4 *vs* Day 7	0.010 *
	Day 4 *vs* Day 14	0.001 *
	Day 7 *vs* Day 14	0.813
N10	Baseline *vs* Day 1	1.000
	Baseline *vs* Day 4	0.681
	Baseline *vs* Day 7	0.133
	Baseline *vs* Day 14	0.044 *
	Day 1 *vs* Day 4	0.287
	Day 1 *vs* Day 7	0.002 *
	Day 1 *vs* Day 14	0.001 *
	Day 4 *vs* Day 7	0.066
	Day 4 *vs* Day 14	0.010 *
	Day 7 *vs* Day 14	1.000

N20	Baseline *vs* Day 1	1.000
	Baseline *vs* Day 4	1.000
	Baseline *vs* Day 7	1.000
	Baseline *vs* Day 14	1.000
	Day 1 *vs* Day 4	1.000
	Day 1 *vs* Day 7	1.000
	Day 1 *vs* Day 14	1.000
	Day 4 *vs* Day 7	1.000
	Day 4 *vs* Day 14	1.000
	Day 7 *vs* Day 14	1.000
N30	Baseline *vs* Day 1	1.000
	Baseline *vs* Day 4	0.613
	Baseline *vs* Day 7	0.591
	Baseline *vs* Day 14	0.259
	Day 1 *vs* Day 4	1.000
	Day 1 *vs* Day 7	0.381
	Day 1 *vs* Day 14	0.165
	Day 4 *vs* Day 7	1.000
	Day 4 *vs* Day 14	1.000
	Day 7 *vs* Day 14	1.000
N35	Baseline *vs* Day 1	0.736
	Baseline *vs* Day 4	0.184
	Baseline *vs* Day 7	0.073
	Baseline *vs* Day 14	0.049 *
	Day 1 *vs* Day 4	1.000
	Day 1 *vs* Day 7	0.177
	Day 1 *vs* Day 14	0.002 *
	Day 4 *vs* Day 7	1.000
	Day 4 *vs* Day 14	0.689
	Day 7 *vs* Day 14	1.000

C3 TIME COURSE OF EFFECTS OF OK STUDY

CHANGE IN J_{180} WITH OK

Pairwise comparisons to compare J_{180} at different positions along the horizontal VF during different days of OK treatment.

Position	Comparison	Significance
T35	Baseline *vs* Day 1	0.037 *
	Baseline *vs* Day 4	0.001 *
	Baseline *vs* Day 7	<0.001 *
	Baseline *vs* Day 14	<0.001 *
	Day 1 *vs* Day 4	0.443
	Day 1 *vs* Day 7	0.018 *
	Day 1 *vs* Day 14	0.089
	Day 4 *vs* Day 7	0.169
	Day 4 *vs* Day 14	0.426
	Day 7 *vs* Day 14	1.000
T30	Baseline *vs* Day 1	0.259
	Baseline *vs* Day 4	0.268
	Baseline *vs* Day 7	0.034 *
	Baseline *vs* Day 14	0.023 *
	Day 1 *vs* Day 4	1.000
	Day 1 *vs* Day 7	0.130
	Day 1 *vs* Day 14	0.046 *
	Day 4 *vs* Day 7	0.338
	Day 4 *vs* Day 14	0.828
	Day 7 *vs* Day 14	1.000
T20	Baseline *vs* Day 1	1.000
	Baseline *vs* Day 4	1.000
	Baseline *vs* Day 7	1.000
	Baseline *vs* Day 14	1.000
	Day 1 *vs* Day 4	1.000
	Day 1 *vs* Day 7	0.958
	Day 1 *vs* Day 14	1.000
	Day 4 *vs* Day 7	0.334
	Day 4 *vs* Day 14	0.359
	Day 7 *vs* Day 14	1.000

T10	Baseline *vs* Day 1	1.000
	Baseline *vs* Day 4	1.000
	Baseline *vs* Day 7	1.000
	Baseline *vs* Day 14	1.000
	Day 1 *vs* Day 4	1.000
	Day 1 *vs* Day 7	1.000
	Day 1 *vs* Day 14	1.000
	Day 4 *vs* Day 7	1.000
	Day 4 *vs* Day 14	1.000
	Day 7 *vs* Day 14	1.000
Centre	Baseline *vs* Day 1	1.000
	Baseline *vs* Day 4	1.000
	Baseline *vs* Day 7	1.000
	Baseline *vs* Day 14	1.000
	Day 1 *vs* Day 4	1.000
	Day 1 *vs* Day 7	1.000
	Day 1 *vs* Day 14	1.000
	Day 4 *vs* Day 7	1.000
	Day 4 *vs* Day 14	1.000
	Day 7 *vs* Day 14	1.000
N10	Baseline *vs* Day 1	0.006 *
	Baseline *vs* Day 4	0.003 *
	Baseline *vs* Day 7	<0.001 *
	Baseline *vs* Day 14	0.004 *
	Day 1 *vs* Day 4	1.000
	Day 1 *vs* Day 7	0.626
	Day 1 *vs* Day 14	1.000
	Day 4 *vs* Day 7	1.000
	Day 4 *vs* Day 14	1.000
	Day 7 *vs* Day 14	1.000
N20	Baseline *vs* Day 1	0.004 *
	Baseline *vs* Day 4	<0.001 *
	Baseline *vs* Day 7	<0.001 *
	Baseline *vs* Day 14	<0.001 *
	Day 1 *vs* Day 4	0.096
	Day 1 *vs* Day 7	0.016 *
	Day 1 *vs* Day 14	0.001 *
	Day 4 *vs* Day 7	0.990
	Day 4 *vs* Day 14	0.002 *
	Day 7 *vs* Day 14	1.000

N30	Baseline *vs* Day 1	<0.001 *
	Baseline *vs* Day 4	<0.001 *
	Baseline *vs* Day 7	<0.001 *
	Baseline *vs* Day 14	<0.001 *
	Day 1 *vs* Day 4	0.132
	Day 1 *vs* Day 7	<0.001 *
	Day 1 *vs* Day 14	<0.001 *
	Day 4 *vs* Day 7	1.000
	Day 4 *vs* Day 14	0.288
	Day 7 *vs* Day 14	0.535
N35	Baseline *vs* Day 1	<0.001 *
	Baseline *vs* Day 4	<0.001 *
	Baseline *vs* Day 7	<0.001 *
	Baseline *vs* Day 14	<0.001 *
	Day 1 *vs* Day 4	0.017 *
	Day 1 *vs* Day 7	<0.001 *
	Day 1 *vs* Day 14	0.001 *
	Day 4 *vs* Day 7	0.480
	Day 4 *vs* Day 14	0.722
	Day 7 *vs* Day 14	1.000

C4 TIME COURSE OF EFFECTS OF OK STUDY

CHANGE IN CORNEAL REFRACTIVE POWER WITH OK

Pairwise comparisons to compare corneal refractive powers at different positions along the horizontal corneal chord during different days of OK treatment.

Position	Comparison	Significance
1.5mm on the temporal cornea	Baseline *vs* Day 1	<0.001 *
	Baseline *vs* Day 4	<0.001 *
	Baseline *vs* Day 7	<0.001 *
	Baseline *vs* Day 14	<0.001 *
	Day 1 *vs* Day 4	<0.001 *
	Day 1 *vs* Day 7	<0.001 *
	Day 1 *vs* Day 14	<0.001 *
	Day 4 *vs* Day 7	0.015 *
	Day 4 *vs* Day 14	0.006 *
	Day 7 *vs* Day 14	1.000
1.1mm on the temporal cornea	Baseline *vs* Day 1	<0.001 *
	Baseline *vs* Day 4	<0.001 *
	Baseline *vs* Day 7	<0.001 *
	Baseline *vs* Day 14	<0.001 *
	Day 1 *vs* Day 4	<0.001 *
	Day 1 *vs* Day 7	<0.001 *
	Day 1 *vs* Day 14	<0.001 *
	Day 4 *vs* Day 7	0.016 *
	Day 4 *vs* Day 14	0.013 *
	Day 7 *vs* Day 14	1.000
0.5mm on the temporal cornea	Baseline *vs* Day 1	<0.001 *
	Baseline *vs* Day 4	<0.001 *
	Baseline *vs* Day 7	<0.001 *
	Baseline *vs* Day 14	<0.001 *
	Day 1 *vs* Day 4	0.001 *
	Day 1 *vs* Day 7	0.001 *
	Day 1 *vs* Day 14	<0.001 *
	Day 4 *vs* Day 7	0.117
	Day 4 *vs* Day 14	0.038 *
	Day 7 *vs* Day 14	1.000

0.1mm on the temporal cornea	Baseline *vs* Day 1	<0.001 *
	Baseline *vs* Day 4	<0.001 *
	Baseline *vs* Day 7	<0.001 *
	Baseline *vs* Day 14	<0.001 *
	Day 1 *vs* Day 4	0.169
	Day 1 *vs* Day 7	0.063
	Day 1 *vs* Day 14	0.001 *
	Day 4 *vs* Day 7	1.000
	Day 4 *vs* Day 14	0.016 *
	Day 7 *vs* Day 14	0.900
0.5mm on the nasal cornea	Baseline *vs* Day 1	<0.001 *
	Baseline *vs* Day 4	<0.001 *
	Baseline *vs* Day 7	<0.001 *
	Baseline *vs* Day 14	<0.001 *
	Day 1 *vs* Day 4	0.368
	Day 1 *vs* Day 7	0.100
	Day 1 *vs* Day 14	0.002 *
	Day 4 *vs* Day 7	1.000
	Day 4 *vs* Day 14	0.051
	Day 7 *vs* Day 14	0.236
1.1mm on the nasal cornea	Baseline *vs* Day 1	0.001 *
	Baseline *vs* Day 4	<0.001 *
	Baseline *vs* Day 7	<0.001 *
	Baseline *vs* Day 14	<0.001 *
	Day 1 *vs* Day 4	1.000
	Day 1 *vs* Day 7	1.000
	Day 1 *vs* Day 14	0.075
	Day 4 *vs* Day 7	1.000
	Day 4 *vs* Day 14	0.381
	Day 7 *vs* Day 14	0.418
1.7mm on the nasal cornea	Baseline *vs* Day 1	0.279
	Baseline *vs* Day 4	0.510
	Baseline *vs* Day 7	1.000
	Baseline *vs* Day 14	0.013 *
	Day 1 *vs* Day 4	1.000
	Day 1 *vs* Day 7	1.000
	Day 1 *vs* Day 14	1.000
	Day 4 *vs* Day 7	1.000
	Day 4 *vs* Day 14	1.000
	Day 7 *vs* Day 14	1.000

2.4mm on the nasal cornea	Baseline *vs* Day 1	0.041 *
	Baseline *vs* Day 4	0.018 *
	Baseline *vs* Day 7	0.003 *
	Baseline *vs* Day 14	0.001 *
	Day 1 *vs* Day 4	0.629
	Day 1 *vs* Day 7	0.027 *
	Day 1 *vs* Day 14	0.113
	Day 4 *vs* Day 7	1.000
	Day 4 *vs* Day 14	1.000
	Day 7 *vs* Day 14	1.000
2.8mm on the nasal cornea	Baseline *vs* Day 1	0.011
	Baseline *vs* Day 4	0.284
	Baseline *vs* Day 7	0.101
	Baseline *vs* Day 14	0.003 *
	Day 1 *vs* Day 4	0.284
	Day 1 *vs* Day 7	0.101
	Day 1 *vs* Day 14	0.003 *
	Day 4 *vs* Day 7	1.000
	Day 4 *vs* Day 14	0.757
	Day 7 *vs* Day 14	1.000

C5 OK PARAMETERS AND PERIPHERAL REFRACTION STUDY

CHANGE IN M WITH OK

Pairwise comparisons to compare M at different positions along the horizontal VF with standard OK lens wear (Phase 1) in the eye assigned to wear an altered OZD OK lens and in the eye assigned to wear an altered tangent OK lens.

		Eye assigned to wear altered OZD OK lens	Eye assigned to wear altered tangent OK lens
Position	**Comparison**	**Significance**	**Significance**
T35	Baseline *vs* Day 1	0.890	0.726
	Baseline *vs* Day 4	1.000	0.564
	Baseline *vs* Day 7	1.000	1.000
	Baseline *vs* Day 14	1.000	1.000
	Day 1 *vs* Day 4	1.000	1.000
	Day 1 *vs* Day 7	0.655	1.000
	Day 1 *vs* Day 14	1.000	1.000
	Day 4 *vs* Day 7	1.000	0.042 *
	Day 4 *vs* Day 14	1.000	0.119
	Day 7 *vs* Day 14	1.000	1.000
T30	Baseline *vs* Day 1	1.000	0.705
	Baseline *vs* Day 4	0.517	0.524
	Baseline *vs* Day 7	0.426	0.163
	Baseline *vs* Day 14	1.000	0.020 *
	Day 1 *vs* Day 4	0.594	1.000
	Day 1 *vs* Day 7	0.119	1.000
	Day 1 *vs* Day 14	1.000	0.096
	Day 4 *vs* Day 7	1.000	1.000
	Day 4 *vs* Day 14	1.000	0.036 *
	Day 7 *vs* Day 14	1.000	1.000

T20	Baseline *vs* Day 1	0.057	<0.001 *
	Baseline *vs* Day 4	0.017 *	<0.001 *
	Baseline *vs* Day 7	0.001 *	<0.001 *
	Baseline *vs* Day 14	<0.001 *	<0.001 *
	Day 1 *vs* Day 4	0.347	0.348
	Day 1 *vs* Day 7	0.002 *	0.077
	Day 1 *vs* Day 14	<0.001 *	0.001 *
	Day 4 *vs* Day 7	1.000	1.000
	Day 4 *vs* Day 14	0.025 *	0.029 *
	Day 7 *vs* Day 14	0.377	0.517
T10	Baseline *vs* Day 1	0.001 *	<0.001 *
	Baseline *vs* Day 4	0.001 *	<0.001 *
	Baseline *vs* Day 7	0.001 *	<0.001 *
	Baseline *vs* Day 14	<0.001 *	<0.001 *
	Day 1 *vs* Day 4	0.026 *	0.036 *
	Day 1 *vs* Day 7	0.013 *	0.003 *
	Day 1 *vs* Day 14	0.001 *	0.001 *
	Day 4 *vs* Day 7	0.666	0.332
	Day 4 *vs* Day 14	0.332	0.024 *
	Day 7 *vs* Day 14	1.000	0.713
Centre	Baseline *vs* Day 1	0.003 *	<0.001 *
	Baseline *vs* Day 4	0.001 *	<0.001 *
	Baseline *vs* Day 7	0.002 *	<0.001 *
	Baseline *vs* Day 14	<0.001 *	<0.001 *
	Day 1 *vs* Day 4	0.016 *	0.005 *
	Day 1 *vs* Day 7	0.038 *	<0.001 *
	Day 1 *vs* Day 14	0.001 *	<0.001 *
	Day 4 *vs* Day 7	1.000	0.016 *
	Day 4 *vs* Day 14	0.015 *	0.001 *
	Day 7 *vs* Day 14	0.452	0.725
N10	Baseline *vs* Day 1	0.018 *	0.001 *
	Baseline *vs* Day 4	0.004 *	<0.001 *
	Baseline *vs* Day 7	0.001 *	<0.001 *
	Baseline *vs* Day 14	<0.001 *	<0.001 *
	Day 1 *vs* Day 4	0.079	0.086
	Day 1 *vs* Day 7	0.002 *	<0.001 *
	Day 1 *vs* Day 14	0.001 *	<0.001 *
	Day 4 *vs* Day 7	0.096	0.169
	Day 4 *vs* Day 14	0.001 *	0.003 *
	Day 7 *vs* Day 14	0.215	0.143

N20	Baseline *vs* Day 1	0.070	1.000
	Baseline *vs* Day 4	0.474	0.026 *
	Baseline *vs* Day 7	0.283	0.075
	Baseline *vs* Day 14	0.175	0.313
	Day 1 *vs* Day 4	1.000	0.135
	Day 1 *vs* Day 7	1.000	0.596
	Day 1 *vs* Day 14	0.626	1.000
	Day 4 *vs* Day 7	0.926	1.000
	Day 4 *vs* Day 14	0.682	1.000
	Day 7 *vs* Day 14	1.000	1.000
N30	Baseline *vs* Day 1	0.573	0.038 *
	Baseline *vs* Day 4	0.960	0.018 *
	Baseline *vs* Day 7	0.659	0.008 *
	Baseline *vs* Day 14	0.751	0.082
	Day 1 *vs* Day 4	1.000	1.000
	Day 1 *vs* Day 7	1.000	1.000
	Day 1 *vs* Day 14	1.000	1.000
	Day 4 *vs* Day 7	1.000	1.000
	Day 4 *vs* Day 14	1.000	1.000
	Day 7 *vs* Day 14	1.000	1.000
N35	Baseline *vs* Day 1	0.627	0.001 *
	Baseline *vs* Day 4	0.534	<0.001 *
	Baseline *vs* Day 7	0.229	<0.001 *
	Baseline *vs* Day 14	0.247	<0.001 *
	Day 1 *vs* Day 4	1.000	1.000
	Day 1 *vs* Day 7	1.000	1.000
	Day 1 *vs* Day 14	1.000	0.483
	Day 4 *vs* Day 7	1.000	1.000
	Day 4 *vs* Day 14	1.000	0.424
	Day 7 *vs* Day 14	1.000	0.364

C6 OK PARAMETERS AND PERIPHERAL REFRACTION STUDY

CHANGE IN J_{180} WITH OK

Pairwise comparisons to compare J_{180} at different positions along the horizontal VF with standard OK lens wear (Phase 1) in the eye assigned to wear an altered OZD OK lens and in the eye assigned to wear an altered tangent OK lens.

		Eye assigned to wear altered OZD OK lens	Eye assigned to wear altered tangent OK lens
Position	**Comparison**	**Significance**	**Significance**
T35	Baseline *vs* Day 1	0.004 *	0.001 *
	Baseline *vs* Day 4	<0.001 *	<0.001 *
	Baseline *vs* Day 7	<0.001 *	<0.001 *
	Baseline *vs* Day 14	0.001 *	<0.001 *
	Day 1 *vs* Day 4	1.000	0.035 *
	Day 1 *vs* Day 7	0.215	0.007 *
	Day 1 *vs* Day 14	0.131	0.072 *
	Day 4 *vs* Day 7	0.801	1.000
	Day 4 *vs* Day 14	0.542	1.000
	Day 7 *vs* Day 14	1.000	1.000
T30	Baseline *vs* Day 1	0.034 *	0.007 *
	Baseline *vs* Day 4	0.099	<0.001 *
	Baseline *vs* Day 7	0.015 *	<0.001 *
	Baseline *vs* Day 14	0.018 *	<0.001 *
	Day 1 *vs* Day 4	1.000	0.184
	Day 1 *vs* Day 7	0.818	0.002 *
	Day 1 *vs* Day 14	0.085	0.020 *
	Day 4 *vs* Day 7	1.000	0.421
	Day 4 *vs* Day 14	0.234	0.645
	Day 7 *vs* Day 14	1.000	1.000

T20	Baseline *vs* Day 1	1.000	1.000
	Baseline *vs* Day 4	1.000	0.678
	Baseline *vs* Day 7	0.741	0.015 *
	Baseline *vs* Day 14	0.584	0.007 *
	Day 1 *vs* Day 4	1.000	1.000
	Day 1 *vs* Day 7	0.200	0.588
	Day 1 *vs* Day 14	0.602	0.540
	Day 4 *vs* Day 7	0.232	1.000
	Day 4 *vs* Day 14	0.060	1.000
	Day 7 *vs* Day 14	1.000	1.000
T10	Baseline *vs* Day 1	0.894	1.000
	Baseline *vs* Day 4	1.000	0.981
	Baseline *vs* Day 7	1.000	1.000
	Baseline *vs* Day 14	1.000	1.000
	Day 1 *vs* Day 4	1.000	1.000
	Day 1 *vs* Day 7	1.000	1.000
	Day 1 *vs* Day 14	1.000	1.000
	Day 4 *vs* Day 7	1.000	1.000
	Day 4 *vs* Day 14	1.000	0.870
	Day 7 *vs* Day 14	1.000	0.742
Centre	Baseline *vs* Day 1	1.000	1.000
	Baseline *vs* Day 4	1.000	0.390
	Baseline *vs* Day 7	1.000	1.000
	Baseline *vs* Day 14	1.000	1.000
	Day 1 *vs* Day 4	0.695	0.954
	Day 1 *vs* Day 7	1.000	1.000
	Day 1 *vs* Day 14	1.000	1.000
	Day 4 *vs* Day 7	1.000	1.000
	Day 4 *vs* Day 14	1.000	0.191
	Day 7 *vs* Day 14	1.000	1.000
N10	Baseline *vs* Day 1	0.030 *	1.000
	Baseline *vs* Day 4	0.189	0.118
	Baseline *vs* Day 7	0.239	0.040 *
	Baseline *vs* Day 14	0.037 *	0.070
	Day 1 *vs* Day 4	1.000	1.000
	Day 1 *vs* Day 7	1.000	0.907
	Day 1 *vs* Day 14	1.000	1.000
	Day 4 *vs* Day 7	1.000	1.000
	Day 4 *vs* Day 14	1.000	1.000
	Day 7 *vs* Day 14	1.000	1.000

N20	Baseline *vs* Day 1	0.010 *	0.009 *
	Baseline *vs* Day 4	0.001 *	<0.001 *
	Baseline *vs* Day 7	<0.001 *	<0.001 *
	Baseline *vs* Day 14	<0.001 *	0.001 *
	Day 1 *vs* Day 4	0.019 *	0.177
	Day 1 *vs* Day 7	0.257	0.025 *
	Day 1 *vs* Day 14	0.066	0.013 *
	Day 4 *vs* Day 7	1.000	0.551
	Day 4 *vs* Day 14	1.000	0.159
	Day 7 *vs* Day 14	1.000	1.000
N30	Baseline *vs* Day 1	<0.001 *	0.001 *
	Baseline *vs* Day 4	<0.001 *	<0.001 *
	Baseline *vs* Day 7	<0.001 *	<0.001 *
	Baseline *vs* Day 14	<0.001 *	<0.001 *
	Day 1 *vs* Day 4	0.112	0.602
	Day 1 *vs* Day 7	0.026 *	<0.001 *
	Day 1 *vs* Day 14	0.001 *	0.001 *
	Day 4 *vs* Day 7	1.000	0.079
	Day 4 *vs* Day 14	1.000	0.044 *
	Day 7 *vs* Day 14	1.000	1.000
N35	Baseline *vs* Day 1	<0.001 *	0.016 *
	Baseline *vs* Day 4	<0.001 *	<0.001 *
	Baseline *vs* Day 7	<0.001 *	<0.001 *
	Baseline *vs* Day 14	<0.001 *	<0.001 *
	Day 1 *vs* Day 4	0.236	0.032 *
	Day 1 *vs* Day 7	0.006 *	0.001 *
	Day 1 *vs* Day 14	0.025 *	<0.001 *
	Day 4 *vs* Day 7	1.000	0.842
	Day 4 *vs* Day 14	1.000	0.027 *
	Day 7 *vs* Day 14	1.000	1.000

C7 OK PARAMETERS AND PERIPHERAL REFRACTION STUDY

CHANGE IN CORNEAL REFRACTIVE POWER WITH OK

Pairwise comparisons to compare corneal refractive powers at different positions along the horizontal corneal chord with standard OK lens wear (Phase 1) in the eye assigned to wear an altered OZD OK lens and in the eye assigned to wear an altered tangent OK lens.

		Eye assigned to wear altered OZD OK lens	Eye assigned to wear altered tangent OK lens
Position	**Comparison**	**Significance**	**Significance**
1.5mm temporal cornea	Baseline *vs* Day 1	0.001 *	<0.001 *
	Baseline *vs* Day 4	<0.001 *	<0.001 *
	Baseline *vs* Day 7	<0.001 *	<0.001 *
	Baseline *vs* Day 14	<0.001 *	<0.001 *
	Day 1 *vs* Day 4	0.003 *	0.009 *
	Day 1 *vs* Day 7	<0.001 *	0.003 *
	Day 1 *vs* Day 14	<0.001 *	<0.001 *
	Day 4 *vs* Day 7	0.220	0.066
	Day 4 *vs* Day 14	0.084	0.001 *
	Day 7 *vs* Day 14	1.000	1.000
1.1mm temporal cornea	Baseline *vs* Day 1	<0.001 *	<0.001 *
	Baseline *vs* Day 4	<0.001 *	<0.001 *
	Baseline *vs* Day 7	<0.001 *	<0.001 *
	Baseline *vs* Day 14	<0.001 *	<0.001 *
	Day 1 *vs* Day 4	0.004 *	0.005 *
	Day 1 *vs* Day 7	<0.001 *	0.003 *
	Day 1 *vs* Day 14	<0.001 *	<0.001 *
	Day 4 *vs* Day 7	0.044 *	0.116
	Day 4 *vs* Day 14	0.027 *	0.006 *
	Day 7 *vs* Day 14	1.000	1.000

0.5mm temporal cornea	Baseline *vs* Day 1	<0.001 *	<0.001 *
	Baseline *vs* Day 4	<0.001 *	<0.001 *
	Baseline *vs* Day 7	<0.001 *	<0.001 *
	Baseline *vs* Day 14	<0.001 *	<0.001 *
	Day 1 *vs* Day 4	0.025 *	0.014 *
	Day 1 *vs* Day 7	<0.001 *	0.015 *
	Day 1 *vs* Day 14	<0.001 *	<0.001 *
	Day 4 *vs* Day 7	0.110	0.204
	Day 4 *vs* Day 14	0.048 *	0.009 *
	Day 7 *vs* Day 14	1.000	1.000
0.1mm temporal cornea	Baseline *vs* Day 1	<0.001 *	<0.001 *
	Baseline *vs* Day 4	<0.001 *	<0.001 *
	Baseline *vs* Day 7	<0.001 *	<0.001 *
	Baseline *vs* Day 14	<0.001 *	<0.001 *
	Day 1 *vs* Day 4	0.244	0.028 *
	Day 1 *vs* Day 7	0.007 *	0.034 *
	Day 1 *vs* Day 14	0.005 *	<0.001 *
	Day 4 *vs* Day 7	0.569	0.534
	Day 4 *vs* Day 14	0.103	0.004 *
	Day 7 *vs* Day 14	1.000	1.000
0.5mm nasal cornea	Baseline *vs* Day 1	<0.001 *	<0.001 *
	Baseline *vs* Day 4	<0.001 *	<0.001 *
	Baseline *vs* Day 7	<0.001 *	<0.001 *
	Baseline *vs* Day 14	<0.001 *	<0.001 *
	Day 1 *vs* Day 4	0.969	0.020 *
	Day 1 *vs* Day 7	0.038 *	0.020 *
	Day 1 *vs* Day 14	0.015 *	<0.001 *
	Day 4 *vs* Day 7	1.000	0.596
	Day 4 *vs* Day 14	0.170	0.025 *
	Day 7 *vs* Day 14	1.000	1.000
1.1 mm nasal cornea	Baseline *vs* Day 1	<0.001 *	<0.001 *
	Baseline *vs* Day 4	<0.001 *	<0.001 *
	Baseline *vs* Day 7	<0.001 *	<0.001 *
	Baseline *vs* Day 14	<0.001 *	<0.001 *
	Day 1 *vs* Day 4	1.000	0.038 *
	Day 1 *vs* Day 7	1.000	0.013 *
	Day 1 *vs* Day 14	0.082	0.001 *
	Day 4 *vs* Day 7	1.000	0.138
	Day 4 *vs* Day 14	0.174	0.058
	Day 7 *vs* Day 14	0.572	1.000

1.7mm nasal cornea	Baseline *vs* Day 1	0.001 *	0.015 *
	Baseline *vs* Day 4	0.021 *	0.006 *
	Baseline *vs* Day 7	0.028 *	0.003 *
	Baseline *vs* Day 14	0.007 *	<0.001 *
	Day 1 *vs* Day 4	1.000	0.190
	Day 1 *vs* Day 7	1.000	0.469
	Day 1 *vs* Day 14	0.969	0.013 *
	Day 4 *vs* Day 7	1.000	1.000
	Day 4 *vs* Day 14	0.367	0.973
	Day 7 *vs* Day 14	0.387	1.000
2.4mm nasal cornea	Baseline *vs* Day 1	1.000	1.000
	Baseline *vs* Day 4	1.000	1.000
	Baseline *vs* Day 7	1.000	1.000
	Baseline *vs* Day 14	1.000	1.000
	Day 1 *vs* Day 4	0.355	1.000
	Day 1 *vs* Day 7	1.000	1.000
	Day 1 *vs* Day 14	1.000	1.000
	Day 4 *vs* Day 7	1.000	1.000
	Day 4 *vs* Day 14	0.500	1.000
	Day 7 *vs* Day 14	1.000	1.000
2.8mm nasal cornea	Baseline *vs* Day 1	0.057	0.001 *
	Baseline *vs* Day 4	0.008 *	0.001 *
	Baseline *vs* Day 7	<0.001 *	<0.001 *
	Baseline *vs* Day 14	<0.001 *	<0.001 *
	Day 1 *vs* Day 4	0.572	1.000
	Day 1 *vs* Day 7	0.013 *	0.626
	Day 1 *vs* Day 14	0.037 *	0.006 *
	Day 4 *vs* Day 7	1.000	1.000
	Day 4 *vs* Day 14	1.000	0.050
	Day 7 *vs* Day 14	1.000	0.044 *

C8 PERIPHERAL REFRACTION AND SCL STUDY

REFRACTION ALONG THE HORIZONTAL MERIDIAN

Planned contrasts conducted to compare M, J_{180} and J_{45} at different positions along the horizontal VF in both low and moderate myopes.

M		
Low myopes		
Comparison	**F**	**Significance**
Centre *vs* temporal 10°	0.478	0.499
Centre *vs* temporal 20°	2.665	0.122
Centre *vs* temporal 30°	2.688	0.030 *
Centre *vs* temporal 35°	6.241	0.024 *
Centre *vs* nasal 10°	2.582	0.128
Centre *vs* nasal 20°	1.387	0.256
Centre *vs* nasal 30°	0.857	0.368
Centre *vs* nasal 35°	0.937	0.348
Moderate myopes		
Comparison	**F**	**Significance**
Centre *vs* temporal 10°	2.821	0.112
Centre *vs* temporal 20°	0.034	0.857
Centre *vs* temporal 30°	5.374	0.034 *
Centre *vs* temporal 35°	8.999	0.008 *
Centre *vs* nasal 10°	7.141	0.017 *
Centre *vs* nasal 20°	1.313	0.269
Centre *vs* nasal 30°	5.358	0.064
Centre *vs* nasal 35°	7.356	0.015 *

J_{180}		
Low myopes		
Comparison	**F**	**Significance**
Centre *vs* temporal 10°	10.457	0.005 *
Centre *vs* temporal 20°	45.582	<0.001 *
Centre *vs* temporal 30°	83.178	<0.001 *
Centre *vs* temporal 35°	106.322	<0.001 *
Centre *vs* nasal 10°	6.897	0.018 *
Centre *vs* nasal 20°	49.170	<0.001 *
Centre *vs* nasal 30°	123.645	<0.001 *
Centre *vs* nasal 35°	144.567	<0.001 *
Moderate myopes		
Comparison	**F**	**Significance**
Centre *vs* temporal 10°	24.806	<0.001 *
Centre *vs* temporal 20°	82.034	<0.001 *
Centre *vs* temporal 30°	172.411	<0.001 *
Centre *vs* temporal 35°	205.904	<0.001 *
Centre *vs* nasal 10°	31.239	<0.001 *
Centre *vs* nasal 20°	115.536	<0.001 *
Centre *vs* nasal 30°	265.532	<0.001 *
Centre *vs* nasal 35°	300.522	<0.001 *

J_{45}		
Low myopes		
Comparison	**F**	**Significance**
Centre *vs* temporal 10°	2.952	0.105
Centre *vs* temporal 20°	0.018	0.895
Centre *vs* temporal 30°	11.244	0.004 *
Centre *vs* temporal 35°	10.375	0.005 *
Centre *vs* nasal 10°	1.204	0.289
Centre *vs* nasal 20°	11.754	0.003 *
Centre *vs* nasal 30°	25.038	<0.001 *
Centre *vs* nasal 35°	35.372	<0.001 *
Moderate myopes		
Comparison	**F**	**Significance**
Centre *vs* temporal 10°	2.221	0.156
Centre *vs* temporal 20°	1.487	0.240
Centre *vs* temporal 30°	12.797	0.003 *
Centre *vs* temporal 35°	8.252	0.011 *
Centre *vs* nasal 10°	0.560	0.465
Centre *vs* nasal 20°	17.390	0.001 *
Centre *vs* nasal 30°	28.438	<0.001 *
Centre *vs* nasal 35°	27.788	<0.001 *

APPENDIX D

Participant information statements and consent forms used in the studies described in this thesis received approval from the University of New South Wales Ethics Committee/ Advisory Panel.

D1 CHAPTER 3 STUDY

THE UNIVERSITY OF NEW SOUTH WALES

SCHOOL OF OPTOMETRY
AND VISION SCIENCE

PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM
Peripheral refraction and ethnicity

Approval number: (HREA 084066)

You are invited to participate in a study to investigate the influence of ethnicity on refractive error in the periphery. We will be testing the current hypothesis that Asians have less relative myopia or short sightedness in the periphery than Caucasians. It is hypothesised that this relative refractive error may contribute to the high prevalence of myopia in Asian countries. You are selected as a possible participant in this study as you fulfill the inclusion criteria listed below;

- Age between 18-40 years
- Either Asian or Caucasian ethnicity
- Refraction between +4.00 and -4.00 DS and less than -1.50DC
- No previous rigid contact lens wear
- No ocular disease or history of ocular injury
- Good health and no medications which may influence ocular health

If you decide to participate, we will require you to attend one measurement session of approximately 30mins duration to collect the following measurements. All procedures are non-invasive and do not require contact between the instrument and your eye:

- Visual acuity, using standard eye test charts,
- Central and peripheral refraction using an autorefractor to determine the refractive error of one eye along the horizontal meridian
- Corneal curvature and topography, using a computerised corneal mapping instrument,

If you have any concerns or questions, you may contact us during working hours on 9385 4613.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission, except as required by law. If you give us your permission by signing this document, we plan to present selected information obtained from this study in the scientific press or at

Peripheral refraction and ethnicity

scientific conferences. The nature of the information disclosed will be the group average and individual responses of interest. In any publication, information will be provided in such a way that you cannot be identified.

Enquiries about your rights as a research study participant, and all complaints may be directed to the Ethics Secretariat, The University of New South Wales, Sydney 2052, Australia (phone 9385 4234, fax 9385 6648, email ethics.sec@unsw.edu.au). Any complaint you make will be treated in confidence and investigated, and you will be informed of the outcome.

Your decision whether or not to participate will not prejudice your future relations with the University of New South Wales. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without prejudice. If you have any questions, please feel free to ask us. If you have any additional questions later, A/Prof. Helen Swarbrick (9385 4373, h.swarbrick@unsw.edu.au) will be happy to answer them. You will be given a copy of this form to keep.

You are making a decision whether or not to participate. Your signature indicates that, having read the Participant Information Statement, you have decided to take part in the study.

……..	……..
Signature of Research Participant	Signature of Witness
……..	……..
(Please PRINT name)	Please PRINT Name
……..	……..
Date	Nature of Witness

……..
Signature(s) of Investigator(s)

……..
Please PRINT Name

REVOCATION OF CONSENT
Peripheral refraction and ethnicity

I hereby wish to WITHDRAW my consent to participate in the research study described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with The University of New South Wales.

…….. ……..
Signature Date

……..
Please PRINT Name

The section for Revocation of Consent should be forwarded to A/Prof Helen Swarbrick, School of Optometry and Vision Science, The University of New South Wales, Sydney NSW 2052.

D2 CHAPTER 4 STUDY

THE UNIVERSITY OF NEW SOUTH WALES

SCHOOL OF OPTOMETRY
AND VISION SCIENCE

PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM
Peripheral axial length and refraction

Approval number: (HREA 10059)

You are invited to participate in a study to investigate the relationship between eye length and refractive error at corresponding peripheral locations. From this study, we hope to gain an understanding of differing eye shapes between different refractive groups. You are selected as a possible participant in this study as you fulfill the inclusion criteria listed below;

- Age between 18-40 years
- Refraction between +4.00 and -4.00 DS and less than -1.50DC
- No previous rigid contact lens wear
- No ocular disease or history of ocular injury
- Good health and no medications which may influence ocular health

If you decide to participate, we will require you to attend one measurement session of approximately 45mins duration to collect the following measurements. Most procedures do not require contact between the instrument and your eye:

- Visual acuity, using standard eye test charts
- Intraocular pressure, using the Goldmann tonometer – a contact procedure routinely used in optometric practice
- Central and peripheral axial length measurement using the Zeiss IOL Master along the horizontal meridian
- Central and peripheral refraction using the Shin-Nippon NVision K5001 autorefractor to determine the refractive error in one eye along the horizontal meridian,

At this session, eye drops (0.5% proparacaine hydrochloride – a topical anaesthetic, and 1mg fluorescein sodium – a non-toxic dye) will be instilled to measure intraocular pressure. 1% cyclopentolate will then be instilled to temporarily dilate your pupils. You may experience mild discomfort on instillation of these drops and your vision may be slightly blurry particularly at close distances with slight light sensitivity for up to 24 hours.

There are potential side effects such mild allergic, toxic and systemic reactions and possible angle-closure glaucoma with the use of the listed ocular drugs. ***However, numerous studies have demonstrated that the risks of such adverse effects occurring***

Peripheral axial length and refraction

are very rare. Intraocular pressure is measured by an instrument which comes in contact with the eye. There is a slight risk of epithelial disturbance, and very rarely inflammation and infection. In the context of this closely monitored study involving a registered optometrist, the risks of such complications are minimal. Additionally, intraocular pressure measurement and the listed eye drops are regularly used in optometric practices as a part of a routine eye examination. In the unlikely event that ocular or other complications occur which will require medical intervention, you will be referred immediately to an appropriate health care practitioner ***at no cost to yourself***. You may contact a 24 hour contact phone number 0414 843 121 for emergencies. If you have any concerns or questions, you may contact us during working hours on 9385 4613.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission, except as required by law. If you give us your permission by signing this document, we plan to present selected information obtained from this study in the scientific press or at scientific conferences. The nature of the information disclosed will be the group average and individual responses of interest. In any publication, information will be provided in such a way that you cannot be identified.

All complaints may be directed to the Ethics Secretariat, The University of New South Wales, Sydney 2052, Australia (phone 9385 4234, fax 9385 6648, email ethics.sec@unsw.edu.au). Any complaint you make will be treated in confidence and investigated, and you will be informed of the outcome.

Your decision whether or not to participate will not prejudice your future relations with the University of New South Wales. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without prejudice. If you have any questions, please feel free to ask us. If you have any additional questions later, A/Prof. Helen Swarbrick (9385 4373, h.swarbrick@unsw.edu.au) will be happy to answer them. You will be given a copy of this form to keep.

You are making a decision whether or not to participate. Your signature indicates that, having read the Participant Information Statement, you have decided to take part in the study.

……..	……..
Signature of Research Participant	Signature of Witness
……..	……..
(Please PRINT name)	Please PRINT Name
……..	……..
Date	Nature of Witness

……..
Signature(s) of Investigator(s)

……..
Please PRINT Name

REVOCATION OF CONSENT
Peripheral axial length and refraction

I hereby wish to WITHDRAW my consent to participate in the research study described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with The University of New South Wales.

…….. ……..
Signature Date

……..
Please PRINT Name

The section for Revocation of Consent should be forwarded to A/Prof Helen Swarbrick, School of Optometry and Vision Science, The University of New South Wales, Sydney NSW 2052.

D3 CHAPTER 5 STUDY

THE UNIVERSITY OF NEW SOUTH WALES

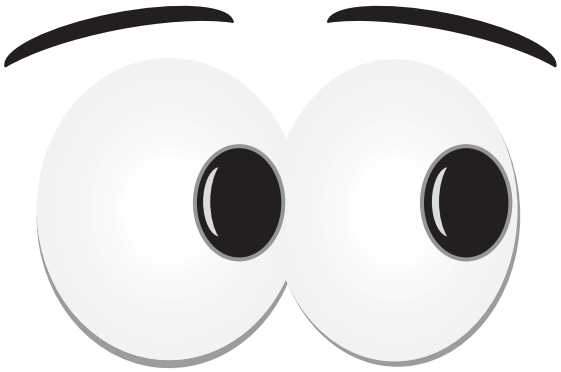
SCHOOL OF OPTOMETRY
AND VISION SCIENCE

PARTICIPANT INFORMATION STATEMENT (8-14 years)

The future of corneal reshaping: can we control myopia or is the risk of corneal compromise too great?

Approval number (HREC 07032)

We would like to invite you to participate in an addition to the study in which you are currently enrolled. We will check the amount of short sightedness on the sides of the eye. If you agree to participate, we will take these measurements by using an instrument that will have no contact with your eye and carries no risk of discomfort. This instrument is commonly used at other optometric practices. It will take an extra 3 minutes of your time at your already scheduled visits in our clinic.



We cannot and do not guarantee or promise that you will receive any benefits from this study.

We will send you a newsletter during and at the end of the study. Some information from this study will be published in scientific journals and will be available to the public.

All your personal information will be confidential and no one will identify you from the information published in scientific journals. If you give us your permission by signing this document, we plan to report the results of this research in the scientific literature, or at scientific conferences. We will give some results from this study to our industry partners BE Enterprises (Queensland, Australia), Capricornia Contact Lens (Queensland, Australia) and The Boston Products Group of Bausch & Lomb (Massachusetts, USA). In any publication or presentation of study results, information will be presented in such a way that you will not be able to be identified.

Any complaints about this study may be directed to the Ethics Secretariat, The University of New South Wales, Sydney 2052, Australia (phone 9385 4234, fax 9385 6648, email ethics.sec@unsw.edu.au).

Your decision whether or not to participate will not affect your future relations with The University of New South Wales. If you decide to participate, you are free to withdraw your consent and to discontinue your participation at any time without prejudice. If you have any questions, please feel free to ask us now or as the study progresses. If you have any additional questions later, Associate Professor Helen Swarbrick (02-9385 4373 or h.swarbrick@unsw.edu.au), the Chief Investigator on this project, will be happy to answer them.

You will be given a copy of this form to keep.

PARTICIPANT INFORMATION STATEMENT (8-14 years)

The future of corneal reshaping: can we control myopia or is the risk of corneal compromise too great?

You are making a decision whether or not to participate. Your signature indicates that, having read the information provided above, you have decided to participate in this study.

……	……
Signature	Signature of Witness
……	……
Please PRINT Name	Please PRINT Name
……	……
Date	Nature of Witness

……
Signature(s) of Investigator(s)

……
Please PRINT Name

REVOCATION OF CONSENT BY PARENT (OR GUARDIAN)

The future of corneal reshaping: can we control myopia or is the risk of corneal compromise too great?

I hereby wish to **WITHDRAW** my consent for my child/ward to participate in the research project described above and understand that such withdrawal **WILL NOT** jeopardise any treatment, or my child/ward's relationship, with The University of New South Wales.

……...… ……...……
Signature Date

……...
Please PRINT Name

The section for Revocation of Consent should be forwarded to A/Prof Helen Swarbrick, School of Optometry and Vision Science, The University of New South Wales, Sydney NSW 2052.

D4 CHAPTER 5 STUDY

THE UNIVERSITY OF NEW SOUTH WALES

SCHOOL OF OPTOMETRY
AND VISION SCIENCE

PARENTAL (OR GUARDIAN) INFORMATION STATEMENT

The future of corneal reshaping: can we control myopia or is the risk of corneal compromise too great?

Approval number HREC 07032

You are invited to permit your child to participate in an addition to the study in which they are currently enrolled. Recent studies have suggested that peripheral refraction of the human eye may influence the development and progression of myopia. If you permit your child to participate, peripheral refraction will be measured using the Shin-Nippon NVision K-5001 autorefractor. This instrument is non-invasive and requires no contact with the eye. Peripheral refraction measurements with the autorefractor carries no risk of physical injury or discomfort and the autorefractor is commonly used in routine optometric practice. These measurements will take an extra 3 minutes of your child's time at their already scheduled visits.

Feedback will be given to study participants via a newsletter during and at the end of the study, and through updates on our website. Information will also be provided through articles that will be published in the scientific literature and which are therefore available in the public domain.

Any information that is obtained in connection with this study and that can be identified with your child will remain confidential and will be disclosed only with your permission, except as required by law. If you give us your permission by signing this document, we plan to publish the results of this research in the optometric, vision science and/or ophthalmological scientific literature, or at scientific conferences. The results will also be disclosed to our industry collaborators BE Enterprises (Queensland, Australia), Capricornia Contact Lens (Queensland, Australia) and The Boston Products Group of Bausch & Lomb (Massachusetts, USA). In any publication or presentation of study results, information will be presented in such a way that you or your child will not be able to be identified.

Information on your and your child's right as a research subject, and any complaints about this study may be directed to the Ethics Secretariat, The University of New South Wales, Sydney 2052, Australia (phone 9385 4234, fax 9385 6648, email ethics.sec@unsw.edu.au).

PARENTAL (OR GUARDIAN) INFORMATION STATEMENT

The future of corneal reshaping: can we control myopia or is the risk of corneal compromise too great?

Your decision whether or not to permit your child to participate will not prejudice you or your child's future relations with The University of New South Wales. If you decide to permit your child to participate, you are free to withdraw your consent and to discontinue your child's participation at any time without prejudice. If you have any questions, please feel free to ask us now or as the study progresses. If you have any additional questions later, Associate Professor Helen Swarbrick (02-9385 4373 or h.swarbrick@unsw.edu.au), the Chief Investigator on this project, will be happy to answer them. You will be given a copy of this form to keep.

You are making a decision whether or not to permit your child to participate. Your signature indicates that, having read the information provided above, you have decided to permit your child to participate in this study.

……..	……..
Signature of Research Participant	Signature of Witness
……..	……..
(Please PRINT name)	Please PRINT Name
……..	……..
Date	Nature of Witness

……..
Signature(s) of Investigator(s)

……..
Please PRINT Name

REVOCATION OF CONSENT BY PARENT (OR GUARDIAN)

The future of corneal reshaping: can we control myopia or is the risk of corneal compromise too great?

I hereby wish to **WITHDRAW** my consent for my child/ward to participate in the research project described above and understand that such withdrawal **WILL NOT** jeopardise any treatment, or my child/ward's relationship, with The University of New South Wales.

…….. ……..
Signature Date

……..
Please PRINT Name

The section for Revocation of Consent should be forwarded to A/Prof Helen Swarbrick, School of Optometry and Vision Science, The University of New South Wales, Sydney NSW 2052.

D5 CHAPTER 6 STUDY

THE UNIVERSITY OF NEW SOUTH WALES

SCHOOL OF OPTOMETRY
AND VISION SCIENCE

PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM
The effect of orthokeratology lens designs on peripheral refraction

Approval number: HREC 08270

Orthokeratology (OK) is a method of using rigid contact lenses to reshape the front surface of the eye to temporarily reduce myopia (short-sightedness). Recent studies have suggested that peripheral refraction of the human eye may influence the development and progression of myopia. You are invited to participate in a study designed to investigate the effects of different orthokeratology lens designs on peripheral refraction measurements using the Shin-Nippon NVision K-5001 autorefractor. You are selected as a possible participant in this study as you fulfill the inclusion criteria listed below;

- Age between 18-40 years
- Refraction between -0.75 and -4.00D of ***short-sightedness*** and less than -1.50D of ***astigmatism***
- Less than 0.75D of refractive difference between the 2 eyes
- No previous rigid contact lens wear
- No ocular disease or history of ocular injury
- Good health and no medications which may influence ocular health

If you decide to participate, we will require you to attend a preliminary session to collect baseline measurements and to perform lens fitting. The first session will be of approximately 1 hour duration and you will be taught insertion, removal, care and maintenance of the lenses at these visits. Lenses and lens care solutions will be free of charge for the duration of the study. You will then be required to wear the lenses on an overnight (approximately 8 hours) basis for 10 nights, with no lens wear during the day. You will return for follow-up measurements after the first night of lens wear (day 1) within 1 hour of eye opening wearing the lenses. You may be required to repeat the initial night of overnight lens wear so that we can ensure that you are given the best fitting lenses for your eyes. The morning visit schedule will be repeated on days 4, 7, 14, 28, 32, 35 and 48 of lens wear within 1 hour of eye opening wearing the lenses. There will be a period of no lens wear between days 14 to 28. Each of these sessions will take approximately 45 minutes. The following measurements will be taken at each session. All measurements are non-invasive and require no contact between the instrument and your eye:

The effect of orthokeratology lens designs on peripheral refraction

- Visual acuity, using standard eye test charts,
- Central and peripheral refraction to determine the refractive error of one eye along the horizontal meridian using the Shin-Nippon NVision K5001 autorefractor
- Corneal curvature, using a computerised corneal mapping instrument
- Corneal thickness, using an optical pachometer
- Length of the eye using the IOLMaster

None of these measurement procedures carries any risk of physical injury or discomfort. You may experience mild discomfort after lens insertion because of the interaction between the rigid lens edge and your eyelid margins. Your vision may be slightly blurry during and after lens removal, particularly after the first night of lens wear. In the event of the incomplete correction of your refractive error, supplementary disposable soft contact lenses will be provided for day-time wear particularly if you are required to drive. ***Some photographs of the eye may be taken in this study. However, due to the highly magnified nature of the photographs, you will not be able to be identified.***

Wearing rigid lenses overnight carries a slight risk. Mild epithelial disturbances, ocular inflammation, corneal infections and temporary lens adherence to the eye have been reported with overnight lens wear. In the context of this closely monitored study, the risks of such complications are minimal. ***There is an exceptionally rare but possible risk of possible severe infections/blindness. The risk of adverse reactions in rigid contact lens wear is very small (0.44-2.5/10,000 patients per year of lens wear), and significantly lower than the risk posed by soft contact lens use.*** We will teach you how to identify and safely free up an adherent lens, and how to recognise warning signs of other adverse responses. In the unlikely event that ocular or other complications occur which will require medical intervention, you will be referred immediately to an appropriate health care practitioner ***at no cost to yourself***. You may contact a 24 hour contact phone number 0414 843 121 for emergencies. You may also contact us during working hours on 9385 4613 if you have any concerns.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission, except as required by law. If you give us your permission by signing this document, we plan to present selected information obtained from this study in the scientific press or at scientific conferences. The nature of the information disclosed will be the group average and individual responses of interest. In any publication, information will be provided in such a way that you cannot be identified.

All complaints may be directed to the Ethics Secretariat, The University of New South Wales, Sydney 2052, Australia (phone 9385 4234, fax 9385 6648, email ethics.sec@unsw.edu.au). Any complaint you make will be treated in confidence and investigated, and you will be informed of the outcome.

The effect of orthokeratology lens designs on peripheral refraction

Your decision whether or not to participate will not prejudice your future relations with the University of New South Wales. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without prejudice. If you have any questions, please feel free to ask us. If you have any additional questions later, A/Prof. Helen Swarbrick (9385 4373, h.swarbrick@unsw.edu.au) will be happy to answer them. You will be given a copy of this form to keep.

You are making a decision whether or not to participate. Your signature indicates that, having read the Participant Information Statement, you have decided to take part in the study.

……..	……..
Signature of Research Participant	Signature of Witness
……..	……..
(Please PRINT name)	Please PRINT Name
……..	……..
Date	Nature of Witness

……..
Signature(s) of Investigator(s)

……..
Please PRINT Name

REVOCATION OF CONSENT
The effect of orthokeratology lens designs on peripheral refraction

I hereby wish to WITHDRAW my consent to participate in the research study described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with The University of New South Wales.

…….. ……..
Signature Date

……..
Please PRINT Name

The section for Revocation of Consent should be forwarded to A/Prof Helen Swarbrick, School of Optometry and Vision Science, The University of New South Wales, Sydney NSW 2052.

D6 CHAPTER 7 STUDY

THE UNIVERSITY OF NEW SOUTH WALES

SCHOOL OF OPTOMETRY
AND VISION SCIENCE

PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM
The effect of different soft contact lenses on peripheral refraction in myopes

Approval number: (HREA 10058)

You are invited to participate in a study to investigate the effect of optimal, under and over correction of myopia with commercially available spherical soft contact lenses on peripheral refraction along the horizontal meridian. You are selected as a possible participant in this study as you fulfill the inclusion criteria listed below;

- Age 18-40 years of age
- Refraction between -1.00D to -6.00D of short-sightedness and less than -1.50D of astigmatism
- No previous rigid contact lens wear
- No ocular disease or history of ocular injury
- Good health and no medications which may influence ocular health

If you decide to participate, we will require you to attend one measurement session of approximately 60min duration which will include a screening for suitability. You will be fitted with soft contact lenses which will be worn only during this session. The following measurements will be taken. All procedures are non-invasive and do not require contact between the instrument and your eye:

- Visual acuity, using standard eye test charts
- Central and peripheral refraction using the Shin-Nippon NVision K5001 autorefractor to determine the refractive error of one eye along the horizontal meridian
- Corneal curvature using a computerised corneal mapping instrument

None of these measurement procedures carries any risk of physical injury or discomfort. Wearing soft contact lenses carries a minimal risk of mild epithelial disturbances, ocular inflammation and corneal infections. In the context of this closely monitored study and short duration of soft contact lens wear, the risks of such complications are unlikely and very minimal. In the unlikely event that ocular or other complications occur which will require medical intervention, you will be referred immediately to an appropriate health care practitioner ***at no cost to yourself***. You may also contact us during working hours on 9385 4613 if you have any concerns.

The effect of different soft contact lenses on peripheral refraction in myopes

We cannot and do not guarantee or promise that you will receive any benefits from this study.

Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission, except as required by law. If you give us your permission by signing this document, we plan to present selected information obtained from this study in the scientific press or at scientific conferences. The nature of the information disclosed will be the group average and individual responses of interest. In any publication, information will be provided in such a way that you cannot be identified.

All complaints may be directed to the Ethics Secretariat, The University of New South Wales, Sydney 2052, Australia (phone 9385 4234, fax 9385 6648, email ethics.sec@unsw.edu.au). Any complaint you make will be treated in confidence and investigated, and you will be informed of the outcome.

Your decision whether or not to participate will not prejudice your future relations with the University of New South Wales. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without prejudice. If you have any questions, please feel free to ask us. If you have any additional questions later, A/Prof. Helen Swarbrick (9385 4373, h.swarbrick@unsw.edu.au) will be happy to answer them. You will be given a copy of this form to keep.

You are making a decision whether or not to participate. Your signature indicates that, having read the Participant Information Statement, you have decided to take part in the study.

……..	……..
Signature of Research Participant	Signature of Witness
……..	……..
(Please PRINT name)	Please PRINT Name
……..	……..
Date	Nature of Witness

……..
Signature(s) of Investigator(s)

……..
Please PRINT Name

REVOCATION OF CONSENT
The effect of different soft contact lenses on peripheral refraction in myopes

I hereby wish to WITHDRAW my consent to participate in the research study described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with The University of New South Wales.

…….. ……..
Signature Date

……..
Please PRINT Name

The section for Revocation of Consent should be forwarded to A/Prof Helen Swarbrick, School of Optometry and Vision Science, The University of New South Wales, Sydney NSW 2052.

APPENDIX E

Written instructions on lens wearing, cleaning and maintenance given to subjects in studies which involved OK lens wear.

LENS BINDING

It is quite common to find your Ortho-K lenses 'stuck' to your eyes on awakening after overnight wear (lens binding). This is normal and is the result of the changes in the viscosity of your tears together with the molding effect of the lenses. The majority of lenses will automatically become 'unstuck' following several blinks. However, should the lenses still appear bound after few minutes of waking time and repeated blinking, follow the steps as described below. Do not attempt to remove the lens in the usual manner as this may injure the eye.

Place one or two drops of lens lubricant into the eye and blink a few times

Look upwards and press gently but firmly against the lower eyeball with the edge of the lower eyelid three times using the index finger. Be careful not to push the edge of the lens with the lid as this will cause a 'shearing' action between the lens and your eye.

Look downwards and repeat the procedure with the upper eyelid against the top of the eyeball.

LENS CARE AND HANDLING

This is a guide to the insertion, removal, re-centring and general care of your lenses. Each step should be carefully followed in order to avoid lens wear complications such as eye irritations or serious infections.

When inserting, removing or cleaning your lenses, you will need the following items:

- Mirror
- Plastic bowl
- Rigid lens cleaning solution
- Rigid lens conditioning solution
- Saline solution

Please **remove lenses** and **contact us** if

Your eye is **RED** or

Your vision is **BLURRY** or

Your eye is **SORE**

ROK UNSW

Research in Orthokeratology

School of Optometry and Vision Science
UNSW SYDNEY NSW 2052
Telephone 9385 4613
Mobile: 0425 210 681
Email ROKinfo@unsw.edu.au

THE UNIVERSITY OF NEW SOUTH WALES

LENS INSERTION AND REMOVAL

ROK UNSW

Research in Orthokeratology

LENS INSERTION

Wash your hands with soap that does not contain lotions or fragrances. Dry your hands on a lint-free towel
Remove the lens from its storage container. Do not rinse the conditioning solution from the lens as this will have a cushioning effect when placed on the eye.

Place the lens on the fingertip of your index or middle finger of the same hand as the eye into which you will be inserting the lens (i.e. right hand for your right eye). Make sure your fingertips are dry.

Direct your gaze downward. Raise your upper eyelid with your thumb or index finger of the other hand, and hold it firmly against the bony part above your eye. Check that your eyelid is firmly under control by attempting to blink.

Use the middle or fourth finger of the hand holding the lens to pull down and control the lower lid. Move the lens close to your eye. While looking 'through' the contact lens (with both eyes open) gently place it directly on to the centre of your eye (the cornea).

Slowly release the lower lid, then the upper lid.

During the initial stages, you may feel slight discomfort as your eye needs to adapt to the lens. To reduce the discomfort, lift your chin and look towards their knees (the "comfort position"). This will minimise lens-lid interactions and promote adaptation.

Gently dab any excessive tears with a tissue. Be careful not to press or rub the eyes with the tissue.
Insert the other lens according to the above procedure.

NB. Following your initial adaptation period, if the lens feels irritable after insertion, remove the lens and clean as described below. Then re-insert the lens. If the sensation continues, the lens should not be worn.

Remember: **"when in doubt, take it out"**

LENS REMOVAL

Two Finger Technique:
Wash your hands with soap that does not contain lotions or fragrances. Dry your hands on a lint-free towel.

While looking directly at your eyes in a mirror, place the thumb or index finger against the upper eyelid edge as shown in the image. While maintaining the eyelid edge against the eyeball, pull the eyelid upwards then outwards to stretch the lid margin against the eyeball well above the lens edge.

Then place the thumb or index finger of the opposite hand on the lower eyelid edge, and press this lightly against the eyeball just below the lens edge.

Make sure that both eyelid edges are now located just outside the lens edges, and that the fingers holding the eyelids are directly above and below the lens. Be sure not to allow either eyelids to roll outwards, or the lens edge will slip under the lid.

Gently move the eyelid edges towards the lens edges, pressing lightly on the eyeball, until one lens edge pops away from the eyeball surface. Continue to move the eyelids together until the lens lifts away from the eyeball surface.

Gently close your eyes. The lens should easily lift away from the eyelashes (or locate the lens if it has dropped from the eye).

LENS CLEANING

Clean the lens surface by rubbing it for 5-10 seconds over a bowl with a few drops of the rigid lens cleaner. Rinse the lens thoroughly with saline solution until all of the cleaner is removed. Return the lens to its storage container with a fresh amount of conditioning solution.

LENS RE-CENTRING

Your lenses may occasionally mislocate onto the white part of the eyeball (conjunctiva) due to eye rubbing, excessive tearing or other causes. Irritation may be felt when this happens. Removal of the lens may be difficult as the lens will tend to 'stick' to the eye. Rather, the lens should be recentred by the following method.

Locate the lens on the eye using a mirror. While starring at the reflection of your eye, pivot your head in the same direction as where the dislocated lens is relative to your cornea.

If the lens floats freely on the eyeball, use the eyelid edges, with the two index fingers or with index finger and thumb, to guide the lens towards the cornea. Do not press on the lens itself.

When the lens is close to the cornea, look slowly toward the lens while steadying the lens with the eyelid edges. The lens should re-centre on the cornea.
If the lens has suctioned on to the conjunctiva, use standard lens removal techniques to break the suction and remove the lens from the eye.

Once you become aware of the feeling of the lens moving on your eye, the lens can safely be removed in the usual manner.

THE UNIVERSITY OF
NEW SOUTH WALES
LENS
CLEANING
ROK
UNSW
Research in
Orthokeratology
ROK
UNSW
Research in
Orthokeratology
School of Optometry and Vision Science
UNSW SYDNEY NSW 2052
Telephone 9385 4613
Mobile: 0425 210 681
Email ROKinfo@unsw.edu.au

LENS and CASE CARE

After wearing your lenses they must be cleaned. Use the following steps:

Wash hands

Wash your hands with soap that does not contain lotions or fragrances. Dry your hands on a lint-free towel.

REMOVE YOUR LENSES

Lens cleaning

Clean the lens surface by gently rubbing it for 5-10 seconds over a bowl with a few drops of Boston Advance Cleaner.

Lens rinsing

Rinse the lens thoroughly with Sensitive Eyes Saline until all of the cleaner is removed.

Lens conditioning

Return the lens to its case with a fresh amount of Boston Simplus. Store the lenses for a minimum of 4 hours.

Once your lenses have been soaked for a minimum of 4 hours you can wear them again.

Wash hands

Wash your hands with soap that does not contain lotions or fragrances. Dry your hands on a lint-free towel.

INSERT YOUR LENSES

Take the lenses directly from the case and insert them into your eyes.

Clean your case

Empty the solution from your lens case and rinse it with Sensitive Eyes Saline or lens conditioning solution.

Dry the case and lid by air drying or using a clean tissue and leave the case opened in a safe dry place.

Every week, thoroughly scrub your lens case rinsing it with Sensitive Eyes Saline or lens conditioning solution and leave it to dry as usual.

Please **remove lenses** and **contact us** if

Your eye is **RED** or

Your vision is **BLURRY** or

Your eye is **SORE**

APPENDIX F

F1 PUBLICATIONS ARISING FROM THIS THESIS

JOURNAL ARTICLES

1. KANG, P., GIFFORD, P., MCNAMARA, P., WU, J., YEO, S., VONG, B. & SWARBRICK. H. 2010. Peripheral refraction in different ethnicities. *Invest Ophthalmol Vis Sci*, 51**,** 6059-65.

2. KANG, P. & SWARBRICK, H. 2011. Peripheral refraction in myopic children wearing orthokeratology and gas-permeable lenses. *Opt Vis Sci,* 88**,** 476-82.

PUBLISHED ABSTRACTS

1. KANG, P., GIFFORD, P., MCNAMARA, P., WU, J., YEO, S., VONG, B. & SWARBRICK. H. 2009. Peripheral refraction in East Asians and Caucasians. *Invest. Ophthalmol. Vis. Sci*, 50**,** E-Abstract 3940.
2. KANG, P. & SWARBRICK, H. 2010. Peripheral refraction in myopic children wearing OK and GP contact lenses. *Invest. Ophthalmol. Vis. Sci*, 51**,** E-Abstract 3934.
3. KANG, P. & SWARBRICK, H. 2011. Orthokeratology and peripheral refraction in myopic children. *Optom Vis Sci*, 81**,** 395-403

4. KANG, P., BLOCH, L., GOSLING, S., GRIMSON, D., OWEN, J., ALHARBI, A., GIFFORD, P., & SWARBRICK, H. 2011. Peripheral refraction and axial length at corresponding retinal locations. *Invest. Ophthalmol. Vis. Sci*, 52**,** E-Abstract 2829.

F2 PRESENTATIONS ARISING FROM THIS THESIS

PRESENTATIONS

1. KANG, P. & SWARBRICK, H.
Peripheral refraction and orthokeratology
8th Congress of the Orthokeratology Society of Oceania (OSO)
Goldcoast, Australia, July 2010

2. KANG, P., GIFFORD, P. & SWARBRICK, H. **(presented by GIFFORD, P.)**
Peripheral refraction and orthokeratology
13th Biennial Scientific Meeting, 7th Educators' Meeting in Optometry (SEMO)
Sydney, Australia, September 2010

3. KANG, P. & SWARBRICK, H.
The effect of different soft contact lenses on peripheral refraction
16th meeting of The International Society for Contact Lens Research (ISCLR)
Napa Valley, USA, August 2011

POSTER PRESENTATIONS

1. KANG, P. & SWARBRICK, H.
Correlation between para-central corneal power change and peripheral refraction change after OK
XIX Biennial Meeting of the International Society for Eye Research (ISER)
Montreal, Canada, July 2010

2. KANG, P. & SWARBRICK, H.
Orthokeratology and peripheral refraction in myopic children
13th Biennial Scientific Meeting, 7th Educators' Meeting in Optometry (SEMO)
Sydney, Australia, September 2010