PERIPHERAL AUTOREFRACTION REPEATABILITY AND PERIPHERAL DEFOCUS OF MYOPIC EYES WITH SPHERICAL SOFT CONTACT LENSES

By

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THESIS

In partial satisfaction of the requirements for the degree of

MASTERS OF SCIENCE

In

PHYSIOLOGICAL OPTICS

Presented to the Graduate Faculty of the

College of Optometry
University of Houston

May 2016

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Acknowledgements

I would like to thank my advisor, Dr. David Berntsen, for his hours of teaching, assistance, encouragement, and guidance in conducting and presenting research. I am inspired by his commitment to and passion for thorough and relevant research in the field of myopia progression. I would not have the same appreciation for research if it were not for the example he set and time he took to show me how to set up proper experimental designs, analyze data and write or present it in a clear manner. I am so thankful for the support of both Dr. Berntsen and his wife, Monique.

I would also like to thank the UHCO graduate faculty. I thoroughly enjoyed my graduate classes and appreciated our discussions. I was appropriately challenged to discuss and defend my experimental question and methods in my experimental design class. My analytical skills were enhanced in Quantitative Methods. I also improved my public speaking skills and approach to presenting in my teaching and communications class.

I would like to extend gratitude to Dr. Frishman for her assistance with the graduate program and my thesis committee for their input and guidance in interpreting results and reviewing my thesis. I would also like to thank Dr. Benoit for her much appreciated assistance in statistical analysis of my data. I would like to thank the NIH/NEI for providing grant support (T35-EY007088 (KEM) and P30-EY07551) and Chris Kuether for his assistance with instrument modifications.

Finally, I would like to thank my husband, Steven, for his great support. He spent many evenings reading or studying with me while I worked on research. I would not be where I am today without his enthusiasm and encouragement. I would also like to thank my parents for their years of encouragement and helping to make my education possible.

Abstract

Purpose: Peripheral retinal defocus has been implicated in the progression of myopia. The purpose of this thesis was to assess the repeatability of peripheral autorefraction, and to determine the effect of commercially-available soft contact lenses on peripheral defocus of myopic eyes.

Methods: Twenty-five young adults with spherical equivalent refractions between –0.50 D and –6.00 D were enrolled. Cycloplegic autorefraction of the right eye was measured centrally and ±20°, ±30°, and ±40° from the line of sight along the nasal and temporal retina using a modified Grand Seiko WAM-5500 autorefractor. **Experiment 1)** The between-visit repeatability of peripheral autorefraction measurements using the Grand Seiko was determined in normal eyes. Measurements were made at two visits separated by 1 to 15 days. Five autorefraction measurements at each location were converted to vector space and averaged. Between-visit repeatability was evaluated by plotting the difference versus the mean of the measurements at the two visits (bias) and by calculating the 95% limits of agreement (LoA). **Experiment 2)** Four commercially-available spherical soft contact lenses (Biofinity, Acuvue2, PureVision2, and Air Optix Night & Day Aqua) were used to correct each subject. Five measurements per location were converted to power vectors and averaged. Spherical equivalent defocus (M) was used to calculate relative peripheral defocus (RPD) while wearing each contact lens and relative peripheral refraction (RPR) with no lens on the eye by taking the difference between each peripheral measurement and the central measurement. Analyses were conducted using repeated-measures analyses of variance (RM-ANOVA) and Benjamini-Hochberg adjusted post-hoc t-tests, when indicated.

Results: The mean age (±SD) and central spherical equivalent refractive error were 24.0 ± 1.3 years and -3.45 ± 1.42 D, respectively. **Experiment 1)** There was no significant between-visit bias for any refractive component evaluated (M, J_0, J_{45}, and RPR) at any location measured (all $p > 0.05$). The 95% LoA (repeatability) for defocus (M) was ±0.21 D centrally. RPR repeatability decreased with increasing eccentricity to ±0.67 and ±0.82 D at 40 degrees nasally and temporally on the retina, respectively. **Experiment 2)** PureVision2 did not change relative peripheral defocus ($p=0.33$). Acuvue2, Biofinity, and Air Optix Night & Day Aqua caused a significant myopic shift on the temporal retina (all $p<0.02$).

Conclusion: With knowledge of the repeatability of on- and off-axis cycloplegic autorefraction with the Grand Seiko, changes in peripheral measurements can be properly interpreted in longitudinal studies. Overall, these results show that the design of spherical soft contact lenses can influence the peripheral defocus profile experienced by a myopic eye. Though spectacles have been reported to increase peripheral hyperopia, several contact lenses tested reduced peripheral hyperopia. Longitudinal studies are required to more fully understand the impact of peripheral defocus on myopia progression and eye shape.

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Chapter 1: Introduction

The general goals of this thesis are to determine the effect of spherical soft contact lenses on peripheral defocus of the myopic eye, and to determine the repeatability of peripheral autorefraction. If peripheral defocus influences eye growth, understanding how standard corrections influence peripheral defocus is important when it comes to optimizing optical designs with the intent of slowing myopia progression. Knowing the repeatability of peripheral autorefraction is also necessary when planning for and interpreting peripheral refraction data in future myopia studies.

1.1 Prevalence of myopia

The prevalence of myopia is increasing in the United States and has reached epidemic levels in parts of Asia, which makes the progression of myopia a serious health concern (Lin et al. 1999; Morgan et al. 2012). The prevalence of myopia has increased in the United States from an estimated 25% in the 1970s to more than 40% today (Vitale et al. 2008). At the current rate of progression, myopia is estimated to affect approximately 5 billion people by 2050, with almost 1 billion of those being high myopes with refractive errors of or greater than 5 diopters (Holden et al. 2016). Myopia is a health concern because as it progresses, it causes increased risk for ocular diseases such as chorioretinal atrophy, choroidal neovascularization, foveal retinoschisis, open angle glaucoma, and retinal detachment (Saw et al. 2005; Cho et al. 2016).

1.2 Animal studies on influence of optical treatment

Animal studies have shed light on how the visual experience can regulate eye growth during emmetropization and what visual signals may be involved in the development of refractive errors after emmetropization. These studies have also given clues as to how visual signals might influence how myopia progresses over time. Firstly, animal studies have shown that ocular growth is dependent on visual feedback, meaning that the type of defocus experienced by the retina is critical in determining the axial length and thus refractive outcome of the eye. The initial evidence that supports this concept of visual feedback comes from studies that show the eye will grow in an unregulated manner, developing form-deprivation myopia, when completely deprived of visual input (Wiesel and Raviola 1977; Smith et al. 1987). The growth mechanisms are localized to the eye and are not dependent on the transmission of visual signals to the brain; form-deprivation myopia will still occur after severing of the optic nerve and pharmacological blocking of the nerve signals (Troilo et al. 1987; Norton et al. 1994). Additionally, lens compensation experiments have been conducted to evaluate the eye's response to different altered refractive states during development (Schaeffel et al. 1988). Monkeys reared experiencing full-field, lens-induced myopic defocus developed hyperopia, while full-field hyperopic defocus induced myopia (Smith and Hung 1999).

Further studies have shown that defocus impacts localized retinal areas and that different parts of the retina can respond independently to local defocus signals (Wallman et al. 1987). One study involving rhesus monkeys that induced different peripheral defocuses on hemifields of the retina resulted in differing shapes of the globe and differing vitreous chamber depths (Smith et al. 2010). In this study, the nasal hemi-field of infant monkeys was exposed to a -3 D spectacle lens, inducing peripheral hyperopia in half the visual field while the other half of the field was left unaltered. This produced an eye that was myopic predominantly in the nasal field (temporal retina). On the other hand, monkeys reared with +3 diopter spectacle lenses in the nasal hemifield developed hyperopia in this region (Smith 2011). In both cases, the unrestricted temporal visual field (corresponding to the nasal retina) was similar to the refractive state of control monkeys. This supports the idea that local defocus signals isolated to particular parts of the retina can result in isolated changes in eye growth such that hyperopic defocus acts as a growth signal while myopic defocus is a stop signal only in the particular portion of the retina that experiences the defocus.

Smith et al. also showed that the fovea is not essential in emmetropization (Smith 2011). In one study on infant monkeys, ablation of the fovea in one eye did not alter the final refractive state as compared to the control eye (Smith et al. 2007). Lens designs tested on chicks showed that altering peripheral retinal defocus had a larger influence on axial elongation than central retinal defocus (Liu and Wildsoet 2011). Furthermore, hyperopic defocus on the peripheral retina accelerates axial eye growth in primates, even in the presence of clear, unrestricted central vision (Smith et al. 2009).

Based on these results in animal models, peripheral defocus is suspected to be influential in human emmetropization and peripheral myopic defocus is hypothesized to slow axial eye growth and myopia progression.

1.3 Peripheral defocus in myopic eyes

The importance of peripheral defocus in myopic eyes and its role in the progression of myopia was first suggested after a longitudinal study performed on young pilots by Hoogerheide et al. published in 1971 (Hoogerheide et al. 1971). Pilots of many commercial airlines and in the military were not permitted to have myopia. In this study, on-axis and peripheral retinoscopy was performed. Many key findings were discovered that helped to guide further research. The first main finding was the percentage of subjects that converted from hyperopes or emmetropes to myopes after their initial examination. While only 5 percent of 295 hyperopes became myopes, 31 percent of 80 emmetropes became myopes.

In this study by Hoogerheide et al., it was discovered that most myopic eyes had peripheral refractions that became increasingly hyperopic at greater eccentricities from the central refraction. It was also shown that a peripheral hyperopic refraction and small interval of Sturm was associated with the greatest percentage of eyes that had experienced more myopic shifts in central refraction over time. Among those that had a hyperopic peripheral refraction were 45 percent of the once hyperopes that had become myopic, 40 percent of the hyperopes that became emmetropic, and 77 percent of the emmetropes that became myopic. Other common peripheral defocus profiles of myopic eyes or subjects that had a myopic shift in central refraction were a larger interval of Sturm with one plane of the astigmatic image more hyperopic and the other along the plane of the retina in addition to a hyperopic defocus with small interval of Sturm nasally and larger interval of Sturm temporally. More emmetropic and myopic eyes had one of these three peripheral defocus profiles with hyperopic defocus in the periphery.

Contrastingly, the majority of hyperopic eyes had at least part of the interval of Sturm in the myopic range peripherally. It was suggested in the paper that peripheral defocus may be a predictor of a person's chance of becoming myopic over time. A manuscript by Rosen et al. contests this point, claiming that perhaps the peripheral defocus skiagrams are not predictive of myopia progression (Rosen et al. 2012). These researchers claim that Hoogerheide et al. did not report the timeline over which measurements were taken and that subjects with the peripheral defocus associated with myopia progression were most likely already myopic at the time the skiagrams were measured. They speculate that the initial refractive values may have been taken from archived records and that the changes in peripheral defocus were in fact not measured over time. Regardless, the initial report by Hoogerheide et al. suggested a potential role for the peripheral retina in refractive error development.

In 2002, Seidemann et. al. published a report outlining the peripheral refractions of different refractive groups measured by various techniques (Seidemann et al. 2002). This study enrolled 56 subjects that were either emmetropic, myopic, or hyperopic. Peripheral refraction was collected by one of two instruments. The first was the PowerRefractor, which is an automated infrared photorefractor that measured out to 22 degrees in the periphery in the horizontal and vertical meridians of the eye. Data were also collected by a double-pass He-Ne laser instrument that measured out to 45 degrees in the temporal meridian of the eye. The main takeaways of the Seidemann et al. study that are relevant to this current work were that, relative to the fovea, peripheral defocus is more hyperopic in myopic eyes and more myopic in hyperopic eyes. Although myopic eyes were more hyperopic in the periphery, they still showed absolute myopia in the periphery at all but one location. This overall myopic peripheral refractive error was attributed to the high astigmatism that was measured peripherally. Additionally, the superior retina of myopes was more myopic compared to the inferior retina, which shifted in the expected hyperopic direction. It was suggested that perhaps this myopia in the superior field was a "lower-field myopia" adaptation to optically correct the eye for the relatively closer ground in the lower portion of the visual field (Hodos and Erichsen 1990). Other studies showed similar trends in peripheral defocus based on central refractive error (Millodot 1981; Mutti et al. 2000; Atchison et al. 2006). In these studies by Millodot et al., Mutti et al., and Atchison et al., myopic eyes were generally reported to have peripheral refractive errors that are relatively more hyperopic in the horizontal meridian of the eye while emmetropic and hyperopic eyes generally had relative peripheral myopic defocus.

Measurements of peripheral refractive error are frequently conducted using the Grand Seiko autorefractor. While the Grand Seiko autorefractor is widely used in clinical studies of refractive error and to measure peripheral defocus, there is limited information regarding the repeatability of the instrument when used for off-axis measurements. The previously reported on-axis 95% limits of agreement for the between-visit repeatability of the Grand Seiko autorefractor range from ±0.47 with cycloplegia, after LASIK surgery (Bailey et al. 2005), to ±0.86 with no cycloplegia (Cleary et al. 2009). In previous studies utilizing cycloplegia, the eye had undergone refractive surgery, which could influence repeatability. The only previous study to evaluate off-axis repeatability of the Grand Seiko autorefractor did so on eyes that had undergone orthokeratology (Lee and Cho 2012), which could influence repeatability because of the significant changes in corneal shape caused by orthokeratology. Determining central and peripheral autorefraction repeatability on normal eyes is important for future work involving peripheral refraction measurements with this instrument.

1.4 Types of optical treatments used to manage myopia progression

The evidence for the influence of peripheral defocus in animal studies has encouraged researchers to explore novel optical corrections in an attempt to slow the progression of myopia. Optical interventions for myopia control have included under correction, gas permeable contact lenses, bifocal spectacles, orthokeratology, and bifocal or novel soft contact lenses.

Under correction and gas permeable contact lenses have been shown to be ineffective or not clinically significant in controlling myopia progression (Chung et al. 2002; Katz et al. 2003; Walline et al. 2004; Adler and Millodot 2006). Progressive addition lenses generally have been found to cause clinically small reductions in myopia progression (Edwards et al. 2002; Gwiazda et al. 2003; Hasebe et al. 2008). A large, well-conducted study by Gwiazda et al. evaluating the effect of progressive addition spectacle lenses on myopia progression compared to single vision spectacle lenses showed the greatest treatment effect over the first year, followed by little additional slowing of progression over the next two years (Gwiazda et al. 2003). In the Gwiazda et al. study, the treatment effect was approximately 33% in the first year, comparable to another 1-year study of progressive addition lenses compared to single vision lenses that showed a treatment effect of 35% (Berntsen et al. 2012). However, in the study by Gwiazda et al., the treatment effect did not continue to increase in the following two years, resulting in an overall treatment effect of 14% over the full three years. Therefore, it is important to consider the duration of treatment when considering the influence of an optical treatment on myopia progression.

While progressive addition lenses have not been found to cause a clinically-meaningful reduction in myopia progression when worn over multiple years, there is some evidence that executive bifocals might be more effective at slowing myopia progression (Cheng et al. 2014). Cheng et al. compared single-vision spectacle wear to executive bifocal and prismatic executive bifocal lens wear over three years. Compared to single vision lenses, the study reported slower refractive error change (slower myopia progression) over three years with executive bifocals (39%) and prismatic executive bifocals (51%); however, they found no significant difference in myopia progression between the two executive bifocal groups (i.e., no statistical evidence that adding base in prism was beneficial). Though the authors reported that executive bifocals slowed axial growth over three years compared to single vision lenses, they also found no significant difference in the amount by which axial eye growth was slowed between the executive bifocal group (30%) and the prismatic executive bifocal group (34%). It is possible that the larger treatment effect found with executive bifocals in their study is due to executive bifocals having a much larger add area than standard bifocal spectacles, which would cause myopic defocus on a larger area of the peripheral retina than standard bifocal lenses.

Orthokeratology (OK) and bifocal soft contact lenses have shown promise for slowing myopia progression. Both of these optical treatments can induce a peripheral myopic shift in retinal defocus (Kang and Swarbrick 2011; Berntsen and Kramer 2013).

A reduction in axial eye growth ranging from 36 to 55 percent has been reported with OK treated eyes over a period of two years with continued treatment accumulation beyond the first year (Cho et al. 2005; Walline et al. 2009; Kakita et al. 2011; Cho and Cheung 2012). The effect of bifocal soft contact lenses for myopia control is more varied, ranging from 25 to 50 percent in two-year studies to over 70 percent reduction in myopia progression in a one-year study (Walline et al. 2013; Lam et al. 2014; Aller et al. 2016). A study by Aller et al. (2016) found a more than 70 percent reduction in myopia progression in a clinical trial conducted over a one-year period. However, as described above, the duration of treatment should be considered when comparing and evaluating different studies as treatment efficacy may decrease over time (i.e., the treatment effect may not continue to build at the same rate in subsequent years). The more variable results with soft bifocal contact lenses compared to OK could be due to overall duration in treatment, differences in lens design, differences in sample size and methods, as well as compliance with wearing the contact lenses. For example, Lam et al. (2014) reported that myopia was slowed by 25% with bifocal soft contact lenses in a two-year randomized study, but noted a 46% reduction in children who wore lenses at least 5 hours per day.

The efficacy of particular optical designs in slowing myopia progression over time calls for the question of the mechanism behind these treatment effects. As described above in Section 1.3, relative peripheral refraction (RPR) studies measuring central and peripheral refraction of uncorrected eyes generally find that myopic eyes have hyperopic RPR. To determine whether hyperopic RPR is able to predict future myopia progression, longitudinal studies have been conducted. Atchison et al. conducted a study of 7-year old and 14-year old subjects over time to assess if RPR that was hyperopic predicts the onset or progression of myopia (Atchison et al. 2015). Data were collected over two years, and the outcome was that relative peripheral hyperopia did not predict the genesis or progression of myopia. Mutti et. al. asked the same question using data from 2043 children who were not myopic initially and later became myopic at follow-up visits conducted annually over a five-year period (Mutti et al. 2011). A statistically significant association was found between the amount of relative peripheral hyperopia and myopia progression (-0.024 D annual myopia progression per diopter relative peripheral hyperopia); however, the amount of progression attributable to hyperopic RPR was not clinically meaningful. Sng et al. came to the same conclusion that RPR did not predict a refractive shift in the myopic direction in a study of 96 Singapore Chinese children with an average follow-up evaluation of 1.26 years after baseline testing (Sng et al. 2011). These studies suggest that the amount of relative peripheral defocus measured on an uncorrected eye does not influence or predict the development or progression of myopia.

While peripheral refraction measured when an eye is not corrected was not associated with myopia progression, studies show that wearing optical correction alters the relative peripheral defocus (RPD) experienced by the eye. In other words, once an eye becomes myopic and requires optical correction to have clear central vision, peripheral defocus will most likely change compared to the uncorrected RPR experienced prior to receiving a first-time correction. A study by Tabernero and Schaeffel in 2009 showed that all subjects had an increase in relative peripheral hyperopia while wearing single-vision spectacles compared to without spectacles, although the amount of hyperopic shift varied considerably among subjects (Tabernero et al. 2009). The same finding of increased peripheral hyperopia when wearing spectacles was shown by Lin et al. for moderate amounts of myopia (Lin et al. 2010). Lin et al. also showed that the amount of hyperopic shift due to spectacles was greater for higher myopes compared to the amount of hyperopic shift in lower myopes. This suggests that the prescribed power of single vision spectacle lenses influences the magnitude of the peripheral hyperopic shift in defocus caused by wearing spectacles.

A study by Berntsen et al. that evaluated the effect of single-vision lenses on myopic children found a significant hyperopic shift in peripheral defocus at 30 degrees nasally, temporally, and superiorly along the retina, as well as 20 degrees inferiorly (Berntsen et al. 2013). On the contrary, the study also found that compared to single vision lenses, progressive addition spectacles with a +2 D add induced a peripheral myopic shift that resulted in relative peripheral myopic defocus in three of the measurement locations (superior, nasal, and temporal retina). Regardless of the lens design, both single vision lenses and progressive addition lenses cause relatively more hyperopic defocus as the amount of negative power in the lens increased (i.e., lenses used to treat more myopia caused a greater hyperopic change in peripheral defocus than lenses used to correct lower amounts of myopia). Although spectacle lenses alter peripheral defocus, the power and design of the lens are both important in determining the direction and amount by which peripheral defocus is shifted.

Not only did the study by Berntsen et al. compare the peripheral defocus experienced in children randomly assigned to wearing single-vision versus progressive addition spectacle lenses, it also reported that myopic defocus on the superior retina was associated with the change in central refraction over a one-year period (Berntsen et al. 2013). Children with hyperopic defocus on the superior retina had a mean progression in myopia of –0.65 D, while children with myopic defocus on the superior retina had significantly less progression of –0.38 D. This is one of few longitudinal studies that have evaluated whether an association exists between peripheral defocus when wearing optical correction and the progression of myopia at the fovea. This finding also supports the idea that myopic defocus acts as a signal to slow human ocular growth, whereas hyperopic defocus encourages growth.

A similar result was found when comparing a novel bifocal contact lens to single-vision spectacle lens wear (Sankaridurg et al. 2011). The novel bifocal contact lens was designed to provide clear central vision and reduce peripheral hyperopia in myopic children. The single-vision spectacles induced relative peripheral hyperopia. After 1 year, children wearing the novel contact lenses showed 34% less myopia progression (-0.57 D progression) compared to the control group wearing single-vision spectacles (-0.86 D progression). The authors also performed peripheral refraction with the study lenses and reported that more relative peripheral hyperopia 30 and 40 degrees in the nasal visual field and 40 degrees temporal in the visual field was associated with faster myopia progression. For example, at 30 degrees in the nasal field, each diopter of peripheral hyperopia was associated with –0.09 D of myopia progression. These findings support the concept that peripheral hyperopic defocus is associated with faster axial elongation.

As discussed above, longitudinal studies on the influence of orthokeratology (OK) correction on myopia progression have been conducted. While these studies did not measure peripheral retinal defocus, it may be conjectured that peripheral defocus is a factor influencing axial growth because the OK design reshapes the cornea and induces relative peripheral myopia (Kang and Swarbrick 2011). Two OK studies showed that not only was OK associated with less myopia progression (slower axial elongation) compared to spectacle wear, but that higher amounts of myopia corrected by OK were associated with less myopia progression. The Longitudinal Orthokeratology Research in Children (LORIC) study in Hong Kong conducted over 2 years compared the axial elongation of 35 myopic children wearing OK contact lenses to that of children with single-vision spectacle correction (Cho et al. 2005). After 2 years, the axial growth in the OK group was significantly less than the spectacle control group, 0.29 ± 0.27 mm versus 0.54 ± 0.27 mm, respectively. Another OK study by Kakita et al. evaluated the change in axial length of myopic eyes of 42 OK treated subjects compared to 50 spectacle-corrected subjects over 2 years (Kakita et al. 2011). They found similar statistically significant results, with a mean axial elongation of 0.39 ± 0.27 mm in the OK group versus 0.61 ± 0.24 mm in the spectacle wearing control group. They also showed a significant correlation between baseline refractive error and axial growth, with higher amounts of baseline myopia being associated with less myopia progression. Although not tested in these OK studies, one may postulate as to why this correlation would be found in these two studies. It may be suggested that higher amounts of myopia require more central corneal flattening and thus more peripheral steepening to correct the myopia. This increased peripheral steepening of the cornea could induce a greater peripheral myopic shift in defocus and thus a greater stop signal to slow myopia progression. Alternatively, the association between higher baseline myopia and slower axial growth could simply be because children with higher myopia were not progressing as quickly because their myopia was already close to stabilizing.

On that note, an orthokeratology treatment study by Zhong et al. showed that greater mid-peripheral corneal steepening caused by OK used to treat higher amounts of myopia were associated with slower axial elongation than OK lenses that caused less mid-peripheral corneal steepening (Zhong et al. 2014). Again, while peripheral retinal defocus was not measured, greater amounts of measured mid-peripheral corneal steepening would induce a greater myopic shift in the periphery of the eye due to the increase in positive power from the steeper cornea. Under the assumption that greater peripheral steepening induces a greater peripheral myopic shift, this result supports the hypothesis that the magnitude of induced myopic defocus is important, with greater myopic defocus acting as a greater stop signal in axial growth.

Considering these studies together, it appears that measuring peripheral defocus while wearing optical correction is important if trying to understand the influence of peripheral defocus on myopia progression. While studies measuring RPR of the uncorrected eye have failed to find meaningful associations between RPR and myopia progression, studies that have measured peripheral defocus while wearing myopic corrections have found associations. Because optical corrections alter the peripheral defocus profile of the eye, relative peripheral refraction of the uncorrected eye does not accurately describe the peripheral defocus experienced by the retina once a child starts wearing correction. Like in animal studies, relative peripheral myopia induced by optical corrections is associated with slower myopia progression over time (Sankaridurg et al. 2011; Berntsen et al. 2013), suggesting that peripheral myopic defocus acts as a stop signal that slows eye growth. Although not directly measured, OK studies provide evidence that greater amounts of optically induced peripheral myopia are associated with slower axial elongation.

1.5 Single-vision contact lenses

While optical strategies for controlling myopia are being explored, the majority of eye care providers still prescribe single vision soft contact lenses or single vision spectacles to correct myopia. While optical interventions such as specialty contact lenses show promise for slowing myopia progression, it is important to understand how current, standard optical corrections impact peripheral defocus in myopic eyes. As described above, standard spectacle lenses commonly used to correct myopia have been reported to cause a hyperopic shift in peripheral defocus (Lin et al. 2010; Berntsen et al. 2013). Based on animal studies, one would expect this to encourage axial elongation and myopia progression.

Soft contact lenses are another standard correction option. The literature reports varied results on the influence of soft contact lenses on peripheral defocus with some contact lenses inducing myopic shifts in defocus (Shen et al. 2010; Backhouse et al. 2012; Kwok et al. 2012; de la Jara et al. 2014) and others producing hyperopic shifts (Kang et al. 2012; de la Jara et al. 2014). There is little information available on the factors that might lead to differences in peripheral defocus with soft contact lenses. There is also little known about the influence of spherical aberration in lenses with aspheric optics on the peripheral defocus caused by soft spherical contact lenses. One study showed that contact lenses induced an increasing amount of spherical aberration (Z(4,0)) with increasing eccentricity out to 30 degrees from the optical axis (Shen and Thibos

2011). It can be inferred that if a contact lens manufacturer is intentionally creating a lens to optimize visual acuity and image quality, they would utilize aspheric optics and manipulate the amount of positive or negative spherical aberration (Z(4,0)) in their lens design since this is the most significant rotationally symmetric aberration term other than defocus.

The average eye has positive spherical aberration (Salmon and van de Pol 2006). This is known to cause the appearance of halos, which can be problematic at night when the pupil is large. Bausch and Lomb and potentially CooperVision and Alcon are introducing spherical aberrations in their contact lenses to minimize these halos and improve the foveal image of the eye. Bausch and Lomb claims to make their PureVision2 contact lens with an aspheric design in an effort to correct for positive spherical aberration (Bausch & Lomb Inc. 2016). Alcon claims to design the Air Optix Night & Day contact lens with aspheric optics that account for spherical aberration in the lens for enhanced vision (Novartis 2016). Coopervision claims to design the Biofinity contact lens with aspheric optics, as well, but with no claim about targeting spherical aberration (CooperVision Inc. 2012). Johnson & Johnson makes no claim that the Acuvue2 lens is made with intentional aspheric optics (Johnson & Johnson Vision Care Inc. 2016). It is likely that when contact lens manufacturers have used aspheric optics in spherical contact lenses to optimize central vision, they have not considered the potential implications of those optics on peripheral defocus. If the company is inducing aspheric optics, it is typically to correct higher-order aberrations (specifically spherical aberration) in order to optimize foveal vision. If peripheral defocus influences the progression of myopia, it is important to study the optical design features of these contact lenses and to determine their peripheral defocus profiles so that eye care providers understand the potential implications of these lenses on myopia progression.

There are two specific experimental aims that are being addressed in this thesis:

Aim 1: To determine the between-visit repeatability of central and peripheral autorefraction in the horizontal meridian of the eye with the Grand Seiko WAM-5500.

Aim 2: To determine the effect of the following commercially-available spherical soft contact lenses on peripheral defocus in the horizontal visual field of myopic eyes: Biofinity (comfilcon A; CooperVision, Fairport, NY, USA), Acuvue2 (etafilcon A; Johnson & Johnson Vision Care, Inc., Jacksonville, FL, USA), PureVision2 (balafilcon A; Bausch + Lomb, Inc., Bridgewater, NJ, USA), and Air Optix Night & Day Aqua (lotrafilcon A; Alcon, Fort Worth, TX, USA) spherical soft contact lenses.

Chapter 2: Peripheral Autorefraction Repeatability

2.1 Introduction

Open-field autorefraction is frequently used in studies to objectively measure changes in central (on-axis) refractive error over time. While central refractive error is commonly measured in studies of myopia, peripheral refractive error is increasingly being measured as well. The suggestion of a potential role of peripheral refractive error on the development of myopia dates back to the 1970’s (Hoogerheide et al. 1971). With recent work in animal models providing convincing evidence that peripheral defocus influences eye growth and that local regions of the retina can respond to local defocus signals (Smith et al. 2010; Smith 2011), open-field autorefractors are commonly being used to measure peripheral refractive error of the eye as a surrogate for eye shape and to determine peripheral defocus (Mutti et al. 2000; Atchison et al. 2006). Several studies have evaluated longitudinal changes in peripheral refractive error and the influence of optical treatments on peripheral defocus (Mutti et al. 2011; Sankaridurg et al. 2011; Sng et al. 2011; Berntsen et al. 2013). As new optical treatments are investigated in myopia control studies, it will be important to know the off-axis repeatability of open-field autorefraction in order to determine whether peripheral defocus caused by optical interventions results in a change in peripheral refractive error over time.

Grand Seiko autorefractors (Grand Seiko Co., Hiroshima, Japan), also marketed under the name Shin-Nippon, are frequently used in longitudinal studies because of their well-documented accuracy and repeatability when measuring central refractive error and the ability to use real targets of the investigator’s choice due to its open-field design

(Chat and Edwards 2001; Mallen et al. 2001; Davies et al. 2003; Bailey et al. 2005; Sheppard and Davies 2010). Despite the instrument increasingly being used to measure off-axis refractive error over time, studies of between-visit repeatability of peripheral measurements are scarce with the only report of which we are aware being in patients who have undergone orthokeratology treatment (Lee and Cho 2012). Myopic orthokeratology reshapes the cornea leading to significant central flattening and mid-peripheral corneal steepening (Charman et al. 2006). These corneal changes may increase sensitivity to misalignment of the autorefractor when making peripheral measurements because the measurement beam passes through the markedly steeper mid-peripheral corneal zone when making these measurements. Knowing the repeatability of off-axis measurements in the presence of a normal corneal shape will allow for proper interpretation of longitudinal peripheral refraction results, which could aid in understanding whether optical corrections other than orthokeratology have a meaningful influence on eye shape.

The purpose of this study was to determine the between-visit repeatability of the Grand Seiko WAM-5500 open-field autorefractor in the horizontal meridian of normal eyes. The between-visit repeatability of both peripheral refraction (the actual refractive error measured at each location) and relative peripheral refraction (RPR) were determined.

2.2 Methods

Subjects

Twenty-five myopic adults (22 to 27 years old) were enrolled. The subjects were recruited from the University of Houston College of Optometry. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the University of Houston Committee for the Protection of Human Subjects. Subjects reviewed and signed an informed consent document before enrollment in the study. All subjects had spherical equivalent correction at the corneal plane of –0.50 D or more myopia and best-corrected visual acuity of better than 20/25 Snellen acuity. All subjects were free of any ocular disease, had no history of ocular trauma or surgery, and had no history of any systemic disease known to cause variability in refractive error. Rigid gas permeable contact lens wearers were excluded. All subjects were instructed to wear glasses on the days of their study appointments.

Autorefraction Measurements

Cycloplegic measurements of the right eye were made using a Grand Seiko WAM-5500 autorefractor that was modified to allow measurements out to ±40° from the line of sight. An attachment added to the top of the instrument held a red light emitting diode (LED) that could be placed centrally (along the line of sight) and out to 40° nasally and temporally from the line of sight in 10° increments. The LED target was projected on a blank wall and was located 1.5 meters from the entrance pupil at each viewing angle. Subjects were instructed to look at the center of the small target. Measurements began 30 minutes after instilling the first of two drops of 1% tropicamide that were separated by 5 minutes. Each subject wore a patch over the left eye to ensure accurate fixation by the tested eye.

Measurements were made centrally and at ±20°, ±30°, and ±40° from the line of sight on the retina in the horizontal ocular meridian. The autorefractor measurement axis was centered horizontally within the entrance pupil for all measurements to maximize peripheral refraction accuracy (Fedtke et al. 2011). Subjects were given clear instructions to point their nose at the peripheral target while keeping their eye in primary gaze. The examiner visually inspected the subject to make sure their head was rotated upon each new viewing angle and that their nose was pointing to the target. If it appeared as if the subject was not rotating their head properly, the examiner viewed the subject's position from above and re-positioned their head so that their nose pointed at the target. The chin rest was expanded to allow for lateral head motion and rotation for proper sight of the target. Approximately 10 measurements were made at each location to ensure that a total of 5 measurements at each location were available that were within 1.00 D of the mode of the sphere and the cylinder readings, a strategy consistent with the approach utilized by other studies to objectively eliminate spurious readings caused by circumstances such as blinks or brief fixation losses (Zadnik et al. 1993; Lee and Cho 2012; Walline et al. 2013). Subjects returned for a second visit 1 to 15 days after their first visit, and the cycloplegic measurements were repeated.

Data Analysis

Autorefraction values at each retinal location were transposed into vector components (M, J_0, and J_{45}) using previously described methods and were averaged (Thibos et al. 1997). RPR at each peripheral location was calculated by subtracting the mean central defocus (M) from the mean peripheral defocus.

Statistical analyses were performed using STATA 13.1 (Stata Corp., College Station, TX). Between-visit repeatability was assessed using methods described by Bland and Altman (Bland and Altman 1986). The difference between each pair of measurements at the two visits was calculated for each refractive value (M, J_0, J_{45}, and RPR) at each retinal location. The mean of the differences between visits describes the bias. Each mean difference was compared to zero using a t-test with the exception of when differences were found not to be normally distributed by a Shapiro-Wilk test, in which case a non-parametric sign test was used instead. The relationship between the differences and means for each refractive value at each location was also evaluated using either a Pearson correlation or a Spearman correlation (when non-parametric testing was appropriate). The 95% limits of agreement (LoA) were calculated as the mean difference ±1.96 x standard deviation of the differences.

2.3 Results

The mean (± SD) age and central cycloplegic spherical equivalent autorefraction (at visit 1) of the subjects were 24.0 ±1.3 years and –3.45 ±1.42 D, respectively. Of the 25 subjects, 18 (72%) were female. Central and peripheral autorefraction results, bias, and repeatability (±1.96 x SD of the differences) are shown in Table 2.1. RPR results, bias, and repeatability are shown in Table 2.2.

Table 2.1. Mean ± SD central and peripheral autorefraction values (in diopters) at each visit, bias, and repeatability.

	Retinal Location						
	40° Nasal	**30° Nasal**	**20° Nasal**	**Central**	**20° Temporal**	**30° Temporal**	**40° Temporal**
M							
Visit 1	-2.95 ± 1.91	-3.39 ± 1.79	-3.49 ± 1.70	-3.45 ± 1.42	-3.51 ± 1.49	-3.11 ± 1.67	-2.55 ± 2.01
Visit 2	-2.87 ± 1.95	-3.32 ± 1.77	-3.51 ± 1.67	-3.47 ± 1.41	-3.51 ± 1.53	-3.18 ± 1.67	-2.54 ± 2.01
Bias*	-0.08 ± 0.37	-0.07 ± 0.31	0.02 ± 0.21	0.02 ± 0.11	0.00 ± 0.18	0.06 ± 0.24	-0.02 ± 0.45
Repeatability†	± 0.73	± 0.60	±0.42	± 0.21	± 0.36	± 0.47	± 0.88
J_0							
Visit 1	-0.92 ± 0.59	-0.53 ± 0.28	-0.13 ± 0.29	0.01 ± 0.19	-0.54 ± 0.29	-1.03 ± 0.36	-1.66 ± 0.59
Visit 2	-0.86 ± 0.61	-0.45 ± 0.28	-0.24 ± 0.24	0.02 ± 0.18	-0.51 ± 0.27	-1.05 ± 0.40	-1.70 ± 0.55
Bias*	-0.07 ± 0.36	-0.08 ± 0.23	0.11 ± 0.26	-0.01 ± 0.12	-0.04 ± 0.16	0.02 ± 0.22	0.04 ± 0.20
Repeatability†	± 0.71	± 0.45	± 0.51	± 0.23	± 0.32	± 0.44	± 0.39
J_{45}							
Visit 1	-0.35 ± 0.31	-0.21 ± 0.27	-0.16 ± 0.20	0.02 ± 0.19	0.14 ± 0.25	0.19 ± 0.33	0.25 ± 0.46
Visit 2	-0.32 ± 0.32	-0.21 ± 0.25	-0.20 ± 0.24	-0.01 ± 0.15	0.16 ± 0.26	0.18 ± 0.34	0.23 ± 0.48
Bias*	-0.04 ± 0.15	0.00 ± 0.13	0.04 ± 0.11	0.03 ± 0.09	-0.02 ± 0.08	0.01 ± 0.17	0.02 ± 0.19
Repeatability†	± 0.30	± 0.25	± 0.22	± 0.17	± 0.16	± 0.33	± 0.36

*Difference between visits (visit 1 – visit 2)

† 1.96 x standard deviation of mean difference between visits

Table 2.2. Mean ± SD relative peripheral refraction (RPR) in diopters at each visit, bias, and repeatability.

	Retinal Location					
	40º Nasal	**30º Nasal**	**20º Nasal**	**20º Temporal**	**30º Temporal**	**40º Temporal**
RPR						
Visit 1	0.49 ± 0.90	0.06 ± 0.79	-0.04 ± 0.58	-0.06±0.41	0.33 ± 0.60	0.89 ± 1.19
Visit 2	0.59 ± 0.98	0.15 ± 0.71	-0.04 ± 0.56	-0.04±0.40	0.29 ± 0.64	0.93 ± 1.21
Bias*	-0.10 ± 0.34	-0.09 ± 0.29	0.00 ± 0.19	-0.02±0.16	0.04 ± 0.20	-0.04 ± 0.42
Repeatability†	± 0.67	± 0.57	± 0.37	± 0.31	± 0.40	± 0.82

*Difference between visits (visit 1 – visit 2)

† 1.96 x standard deviation of mean difference between visits

The bias (difference between visits) was not significantly different than zero for M, J_0, J_{45}, or RPR at any location measured (all $p > 0.08$). A difference versus mean plot of the central spherical-equivalent defocus (M) between-visits is shown in Figure 2.1, and difference versus mean plots for peripheral defocus (M) between visits are shown in Figure 2.2 at each peripheral location measured. For all refractive values (M, J_0, J_{45}, and RPR), repeatability was best centrally and became less repeatable as eccentricity increased.

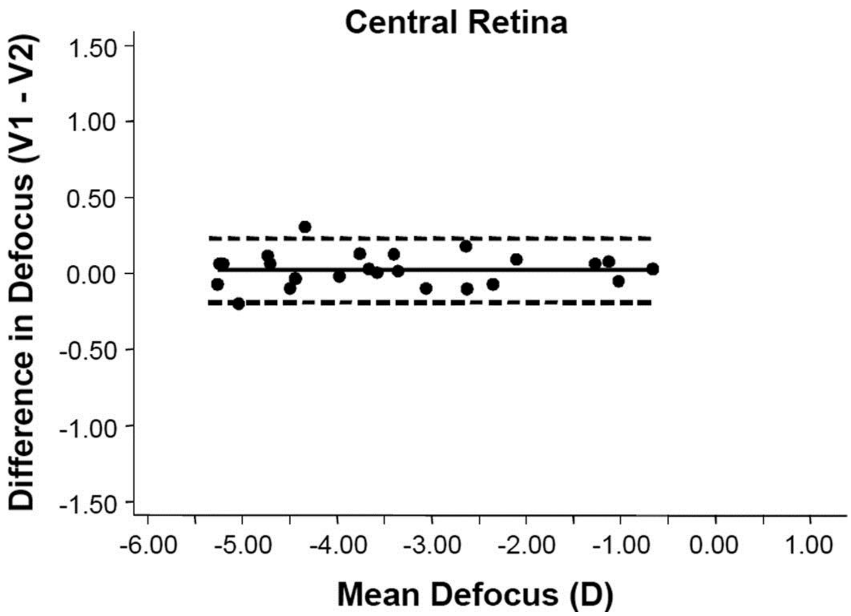

Figure 2.1. Difference versus mean plot of central spherical-equivalent defocus (in diopters) measured at two separate visits. The solid line represents the mean difference between the two visits (bias), and the dashed lines represent the 95% limits of agreement.

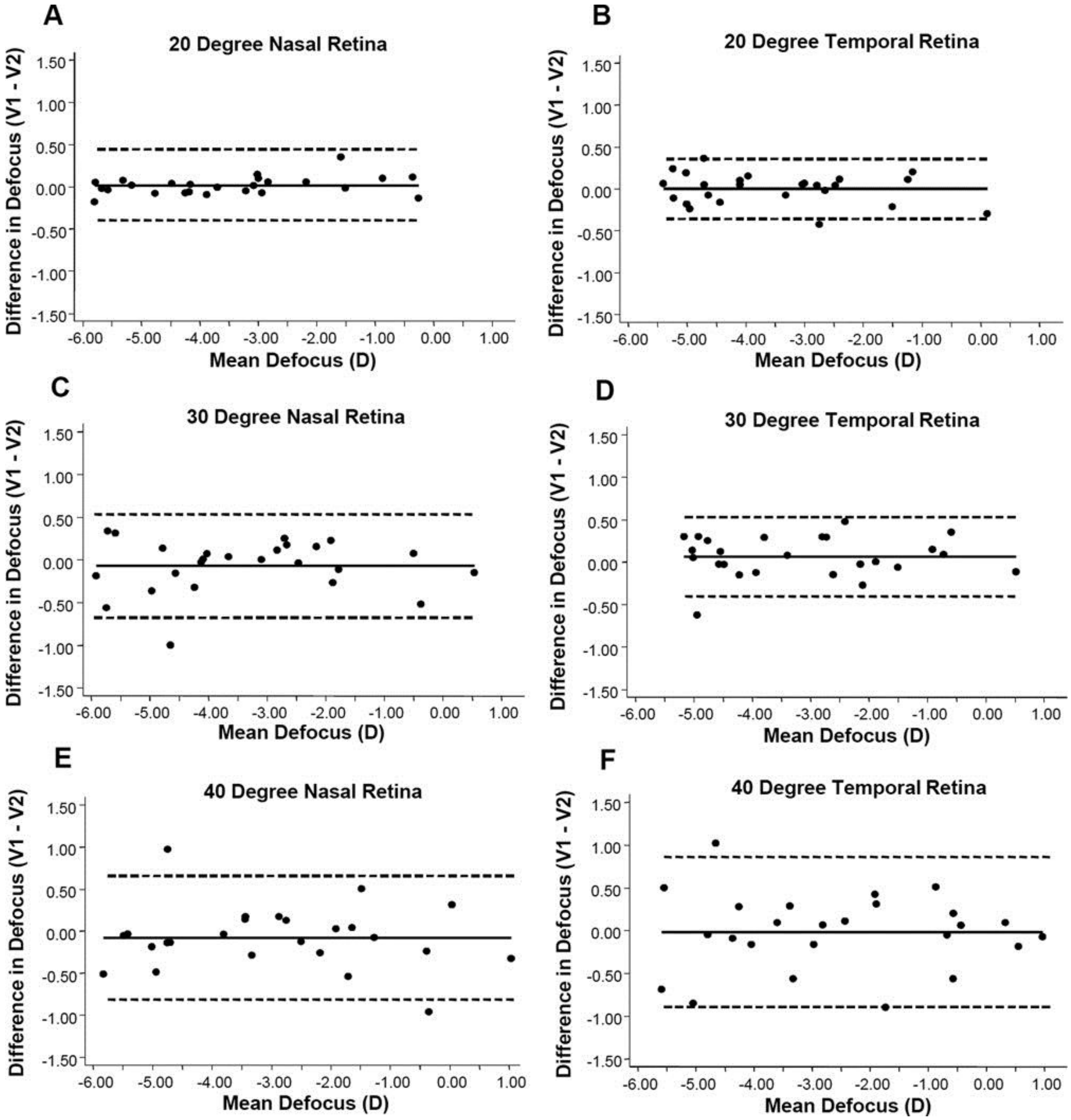

Figure 2.2. Difference versus mean plots for repeated measurements of peripheral spherical-equivalent defocus (in diopters) measured at (A) 20° nasally, (B) 20° temporally, (C) 30° nasally, (D) 30° temporally, (E) 40° nasally, and (F) 40° temporally on the retina at two separate visits. The solid lines represent the mean difference between the two visits (bias), and the dashed lines represent the 95% limits of agreement. (V1 = Visit 1 and V2 = Visit 2)

As expected, relative peripheral hyperopic defocus was found in these myopic eyes, and relative peripheral hyperopia was greatest at the most eccentric measurement location (Table 2.2). At more peripheral locations along the horizontal meridian of the eye, J_0 astigmatism also increased as measurements were made through more peripheral portions of the cornea and crystalline lens (Table 2.1). Small increases in J_{45} (oblique) astigmatism were observed as eccentricity increased, though changes in oblique astigmatism were relatively small (just over 0.25 D at 40°).

2.4 Discussion

Repeatable measurements of central refractive error have long been important in longitudinal studies of refractive error development. With both animal (Smith et al. 2010; Smith 2011) and human (Berntsen et al. 2013) studies suggesting a role for peripheral defocus in myopia progression, an increasing number of studies are measuring peripheral refraction. Because local retinal regions have been shown to respond to local defocus signals in animal models (Smith et al. 2010; Smith et al. 2013), determining whether changes in peripheral refractive error occur over time in studies of optical interventions is important (Smith 2013). Previous studies have shown the Grand Seiko to have good on-axis, between visit repeatability (Davies et al. 2003; Bailey et al. 2005; Cleary et al. 2009), and the Grand Seiko has been used as the standard against which to compare other methods of measuring peripheral refractive error (such as aberrometry-based methods) (Atchison 2003; Berntsen et al. 2008). That being said, to our knowledge, the between-visit repeatability of peripheral refraction measurements using the Grand Seiko autorefractor has not been reported in normal eyes that have not undergone any type of refractive surgery or corneal reshaping.

The Grand Seiko showed excellent central, between-visit repeatability for spherical-equivalent defocus, J_0, and J_{45}, which became progressively less repeatable with increasing eccentricity. The central 95% LoA for cycloplegic spherical-equivalent defocus in our study of normal eyes (±0.21 D) was better than previously reported in several studies without cycloplegia (range: ±0.43 to ±0.86 D) (Mallen et al. 2001; Davies et al. 2003; Cleary et al. 2009; Sheppard and Davies 2010) and with cycloplegia in eyes after LASIK surgery (±0.47 D) (Bailey et al. 2005). An advantage of our study is that measurements were made under cycloplegia and eyes had not undergone refractive surgery. These factors likely account for the better central repeatability found in our study because the typical prolate shape of the cornea was unaltered and cycloplegia eliminated the potential for variable accommodation.

The between-visit 95% LoA for spherical-equivalent defocus in the far periphery (±0.73 D nasally and ±0.88 D temporally) were still good when compared to the reported between-visit 95% LoA of cycloplegic subjective refraction (±0.94 D) (Zadnik et al. 1992). The repeatability of J_0 astigmatism in the periphery was similar to that of defocus. The repeatability of J_{45} astigmatism in the horizontal meridian of the eye was better than the repeatability of M and J_0 in the periphery with a smaller decrease in repeatability at higher eccentricities. The better repeatability for J_{45} astigmatism is likely because measurements were made in the horizontal meridian of the eye where peripheral increases in astigmatic error are expected to be due to differences in power along the horizontal and vertical meridian. Had peripheral measurements been made along an oblique meridian, we might expect the repeatability of J_{45} to decrease more similarly to the change seen in J_0 astigmatism along the horizontal meridian.

One contributing factor to the decrease in repeatability of defocus, J_0, and J_{45} measurements further in the periphery may be the reported influence of lateral pupil misalignment when autorefractor measurements are made at higher eccentricities. Fedtke et al. reported that even a 0.27 mm lateral misalignment of the pupil center with the instrument axis when measuring 30° in the periphery of a myopic eye could cause a 0.25 D change in peripheral defocus (Fedtke et al. 2011). This might be due to increased higher-order aberrations at more eccentric locations of the visual field when light travels through the peripheral cornea and crystalline lens (Shen and Thibos 2011). Despite taking great care to ensure that the Grand Seiko measurement beam was centered in the pupil before taking measurements, subtle misalignment errors not detected by the examiner may have contributed to the increased variability observed in the far periphery.

There was a slight asymmetry in the repeatability of defocus measurements between the nasal and temporal retinal locations. One might hypothesize that because peripheral astigmatism is typically less in the nasal retina (Seidemann et al. 2002; Atchison et al. 2006; Berntsen et al. 2008), the lower amount of astigmatism nasally accounts for the slightly better repeatability found at the 40° nasal retinal location in this study compared to that found at the 40° temporal retinal location. The asymmetry in astigmatism can be explained by angle lambda (the roughly 5º difference between the line of sight and the pupillary axis). Because measurements were made relative to the line of sight, central measurements were slightly temporal on the retina compared to the pupillary axis. Thus, measurements 40º temporal on the retina from the line of sight were actually more than 40º (closer to 45º) from the pupillary axis, which can explain the greater amount of astigmatism measured temporally on the retina than nasally in this study and by others (Millodot 1981; Shen et al. 2010). That being said, the repeatability of defocus measurements at 30º was better temporally than nasally despite astigmatism being lower at the nasal location. Thus, while astigmatism likely plays a role in repeatability, other factors such as off-axis higher-order aberrations may also play a role.

The only other study that we are aware of that has evaluated off-axis, between-visit repeatability was by Lee et al. after subjects underwent orthokeratology treatment (Lee and Cho 2012). Table 2.3 compares repeatability results for defocus from their study to the results of this study. In their study, the 95% LoA reached ±3.00 D at 30° in the periphery, which is less repeatable than we found in normal eyes at 40° (±0.88 D).

Table 2.3. Comparison of between-visit repeatability of central spherical equivalent autorefraction measurements and relative peripheral refraction (RPR) measurements for the present study (normal eyes) and a previous study (Lee and Cho 2012) of orthokeratology-treated eyes.

	Between-Visit Repeatability* by Retinal Location						
	40º Nasal	**30º Nasal**	**20º Nasal**	**Central**	**20º Temporal**	**30º Temporal**	**40º Temporal**
Present Study (Normal Eyes)	±0.67	±0.57	±0.37	±0.21	±0.31	±0.40	±0.82
Orthokeratology Treated Eyes	N/A†	±1.78	N/A†	±0.51	±1.45	±3.00	N/A†

*1.96 x standard deviation of mean difference between visits

†Repeatability not evaluated at this location by Lee and Cho (2012)

The repeatability of off-axis, between-visit autorefraction in orthokeratology treated eyes is valuable for longitudinal studies examining the effects of orthokeratology on peripheral refraction because the influence of the corneal shape changes that occur with the oblate corneal shape changes caused by the procedure are taken into consideration. However, it is also important to know the off-axis repeatability of peripheral autorefraction in normal eyes that may be wearing either soft contact lenses or spectacles in which the prolate corneal shape is not altered by the optical correction. Based on the results of these two studies, it appears that peripheral autorefraction measurements made through the mid-peripheral cornea where orthokeratology causes rapid steepening is likely the cause of the reduced repeatability found in the study by Lee et al.

Subjects were instructed to point their nose at the fixation target to avoid small eye turns to eliminate the possibility that the extraocular muscles might distort eye shape and thereby alter peripheral refraction. Although head and eye positioning was visually verified by the examiner to ensure that the eye was in primary gaze prior to each set of measurements, it is possible that subtle eye turns may have still been present. That being said, a previous study found no significant difference between peripheral refraction measurements made using the eye and head turn methods (Radhakrishnan and Charman 2008); therefore, small residual eye turns that potentially remained while measurements were made in this study are unlikely to have significantly influenced peripheral refraction and its repeatability.

A limitation of this study is that between-visit repeatability was only evaluated on measurements made in the horizontal meridian of the eye. Repeatability could have been assessed in the vertical meridian, as well. We assume that the repeatability in the vertical meridian would have been comparable to what it is in the horizontal meridian because symmetry of the optics of the eye means that we would encounter the same misalignment errors in measuring through an off-axis pupil both vertically and horizontally. Additionally, the vertical and horizontal meridians show a similar increase in astigmatism as measured by aberrometry out to 30 degrees in the nasal and temporal fields, 30 degrees superior, and 20 degrees inferior to the central retina (Berntsen et al. 2013). While vertical measurements were not made in this study, between-visit autorefraction in the vertical meridian could be assessed in the future because changes in the vertical refraction is an important indicator of ocular changes due to optical treatment along this meridian. A recent study by Atchison et al. showed that the Grand Seiko produced reliable off-axis measurements in the horizontal and vertical meridians, but became unreliable in oblique meridians due to the influence of higher-order aberrations (Atchison et al. 2015). This report should be considered when designing and interpreting studies of peripheral defocus.

Another limitation of this study is that measurements were only made under cycloplegic conditions. Non-cycloplegic measurements could have been made; however, we anticipate that this would have decreased the repeatability found at all locations given the reported central, non-cycloplegic autorefraction between-visit repeatability of ±0.72 D (Zadnik et al. 1992). Non-cycloplegic measurements risk fluctuation or variability in accommodation given different target distances or target surfaces and shapes and, thus, greater variability in measurements. When longitudinal studies are performed, especially multi-center studies, repeatability is maximized if measurements are made under cycloplegic conditions.

Peripheral autorefraction with the Grand Seiko WAM-5500 showed good repeatability, though repeatability did decrease as eccentricity increased. While the repeatability of peripheral autorefraction measurements was not as good as that of central autorefraction, the between-visit repeatability of peripheral autorefraction was still superior to the previously reported repeatability of on-axis, cycloplegic subjective refraction. With clear knowledge of the repeatability of on- and off-axis cycloplegic autorefraction, peripheral measurements can be properly interpreted in longitudinal studies to determine whether treatments that induce myopic peripheral defocus in an attempt to slow the progression of myopia result in a meaningful influence on peripheral refraction.

Chapter 3: Peripheral Defocus with Spherical Soft Contact Lenses

3.1 Introduction

Animal studies have shown that ocular growth is dependent on visual feedback, meaning that the type of defocus experienced by the retina is important in determining the axial length of the eye. The evidence for the influence of peripheral defocus in animal studies has encouraged researchers to explore novel optical corrections in an attempt to slow the progression of myopia. Myopic eyes typically have peripheral hyperopic defocus in the horizontal meridian of the eye (a potential grow signal) (Mutti et al. 2000; Seidemann et al. 2002); optically creating peripheral myopic defocus is hypothesized to slow the progression of myopia in humans.

While optical interventions such as bifocal contact lenses and orthokeratology contact lenses show promise for slowing myopia progression, it is important to understand how commonly prescribed standard optical corrections impact peripheral defocus in myopic eyes. The purpose of this study was to determine the change in peripheral defocus in the horizontal meridian of myopic eyes caused by multiple, commonly-prescribed, commercially-available, spherical soft contact lenses.

3.2 Methods

Subjects

The same twenty-five myopic young adults with spherical equivalent (SE) refractive error at the corneal plane of between -0.50 D and -6.00 D with less than -1.25

D of astigmatism participated in this study. The SE refractive error range was chosen because it is a myopic range that would most likely be used for future myopia studies. This investigation adhered to the tenets of the Declaration of Helsinki and was approved by the University of Houston Committee for the Protection of Human Subjects. All subjects provided written informed consent prior to any testing.

An examination that included a standardized manifest refraction (most plus/least minus to best visual acuity) and biomicroscopy was performed to determine eligibility. Subjects were not presbyopic, had no history of ocular surgery or trauma, were free from ocular disease, and did not wear rigid gas permeable contact lenses. All subjects had spherical equivalent corrected visual acuity of 20/25 or better to exclude subjects with meaningful amounts of amblyopia and to ensure that any astigmatism present would not degrade vision to a level below which a spherical contact lens might be prescribed.

Contact Lenses

The right eye of each subject was fitted with each of the following spherical soft contact lenses, in random order: Biofinity (comfilcon A; CooperVision); Acuvue 2 (etafilcon A; Johnson & Johnson Vision Care); PureVision2 (balafilcon A; Bausch + Lomb); and Air Optix Night & Day Aqua (lotrafilcon A; Alcon). The contact lens power chosen for each subject was based on the spherical equivalent of the manifest refraction after vertexing to the corneal plane. Each lens was fitted and allowed to settle for approximately five minutes prior to evaluating the lens fit. The same contact lens power was used for each brand of contact lens fitted on a subject; no over-refraction was performed for each contact lens because subjects were already cyclopleged to allow for more accurate peripheral autorefraction measurements, described below.

Autorefraction

Cycloplegic autorefraction was performed 30 minutes after instilling the first of two drops of 1% tropicamide separated by 5 minutes. Autorefraction of the right eye was performed on each subject using a modified, open-field Grand Seiko WAM-5500 autorefractor (Grand Seiko Co.; Hiroshima, Japan) with each lens on the eye and with no lens on the eye. Measurements were made centrally and at ±20°, ±30°, and ±40° from the line of sight in the horizontal meridian of the eye. The side on which measurements began (nasal or temporal) was randomized for each testing condition. The autorefractor was centered within the entrance pupil for all measurements (Fedtke et al. 2011). Subjects turned their head (not the eye) to view a red LED target projected on a wall for all peripheral measurements to avoid contact lens decentration due to eye rotation. The examiner monitored the subject upon each new target position to ensure an appropriate head movement was made.

The first five autorefraction measurements collected at each retinal location that were within ±1.00 D of the mode for the sphere and cylinder powers of the measurements were transposed to vector form using previously reported methods and averaged to obtain the mean M, J_0, and J_{45} vector components (Thibos et al. 1997). Relative peripheral refraction (RPR) at each retinal location was calculated by subtracting the central spherical equivalent (M) of the unaided eye from the peripheral M component of the unaided eye. Relative peripheral defocus (RPD) was calculated in the same way using measurements made when the subject wore each contact lens.

Aberrometry Measurements

A Discovery System aberrometer (Innovative Visual Systems; Elmhurst, IL) was used to collect cycloplegic aberrometry measurements with each contact lens on the eye and with no lens on the eye. Five measurements each were made along the line of site. Zernike coefficients were calculated over a 7-mm pupil and averaged (American National Standards Institute 2004). The measured spherical aberration of the eye alone (C4,0) was subtracted from the spherical aberration measured while wearing each contact lens to determine the change in spherical aberration induced by each contact lens.

Sample Size

The sample size was determined using a standard deviation estimated from previously reported on-axis repeatability of the Grand Seiko autorefractor. Applying the standard deviation of ±0.24 D from previously reported cycloplegic repeatability of the Grand Seiko (Bailey et al. 2005), assuming a 2-sided alpha of 0.05 and power of 80%, a sample size of 7 subjects was necessary to detect a 0.25 D difference in defocus. Even applying the worst reported on-axis repeatability of the Grand Seiko (standard deviation of ±0.44 D) under non-cycloplegic conditions (Cleary et al. 2009), assuming a 2-sided alpha of 0.05 and power of 80%, a sample size of 24 subjects was adequate to detect a 0.25 D difference in defocus. A total of 25 subjects were enrolled in this study.

Data Analyses

Data analyses were conducted with STATA 13.1 (StataCorp; College Station, TX) and SAS (SAS Institute Inc.; Cary, NC). Repeated-measures analyses of variance (RM-ANOVA) were used to evaluate whether differences existed in RPD, relative peripheral J_0 and J_{45} while wearing each of the contact lenses versus the uncorrected eye (i.e., evaluating whether the optics of each contact lens caused a change in peripheral defocus and astigmatism). Retinal location and testing condition (each contact lens brand or uncorrected eye) were included as factors in the RM-ANOVA. Contact lens spherical power was also included as a covariate to determine whether the magnitude of minus power in the lens influenced changes in RPD caused by the lens. Benjamini-Hochberg corrected post-hoc t-tests were performed when appropriate to test for differences in defocus, J_0, and J_{45} between the contact lens-corrected eye and the uncorrected eye and also to determine if lens decentration was significantly different than zero.

A linear mixed model was used to determine whether there is an association between the change spherical aberration caused by each contact lens and the change in peripheral defocus induced by the contact lens at each eccentricity. The power of the contact lens was included as a covariate in all models.

3.3 Results

The subjects had a mean age ± SD of 24.0 ± 1.3 years and an average spherical equivalent refractive error of -3.45 ± 1.42 D (range: -1.00 to -5.75 D). Of the 25 subjects, 18 (72%) were female.

Refractive changes caused by contact lenses

The mean RPR with no lens on the eye and the mean RPD with each of the four spherical soft lenses on the eye are shown in Figure 3.1. Differences in peripheral defocus depended on the testing condition (lens type) and the location measured (testing condition by location interaction; $p<0.001$). RPD while wearing a contact lenses was significantly different than RPR (no lens) for: Biofinity ($p = 0.003$); Acuvue2 ($p = 0.001$); and Air Optix Night & Day Aqua ($p < 0.0001$). RPD with PureVision2 was not different than RPR of the uncorrected eye ($p = 0.33$).

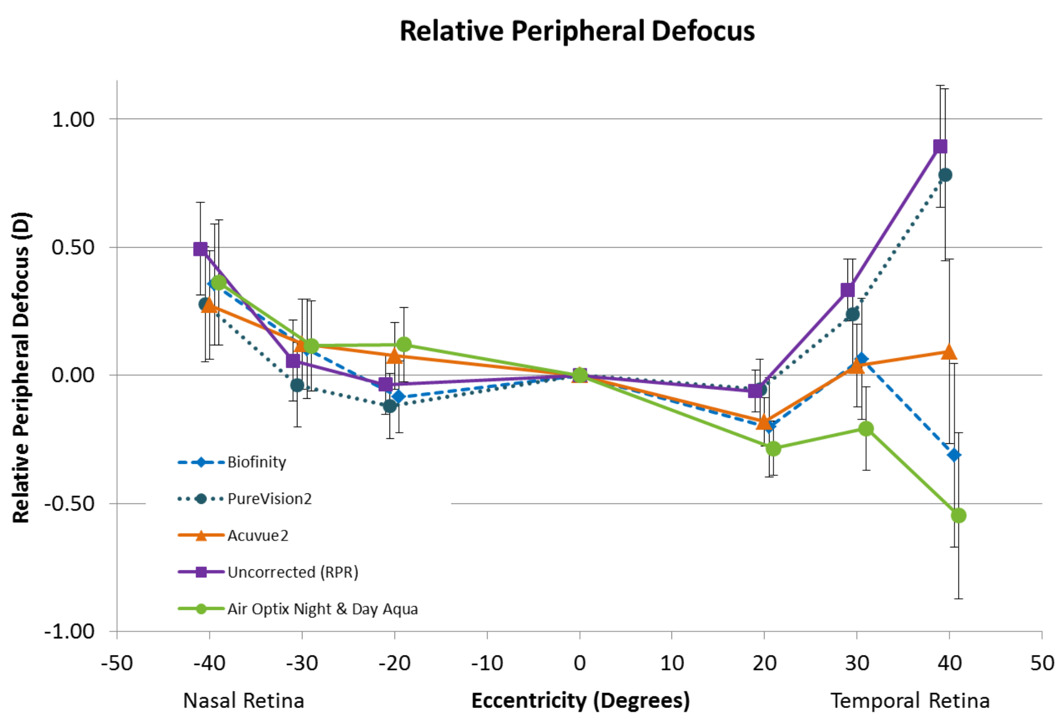

Figure 3.1. Plot of relative peripheral defocus with the four soft contact lenses and relative peripheral refraction with no lens on the eye. Positive defocus represents a hyperopic image shift and negative defocus represents a myopic image shift.

Compared to RPR, a myopic shift was found with contact lenses at the following locations: Biofinity at temporal 40° (-1.21 D), Acuvue2 at temporal 30° (-0.29 D) and temporal 40° (-0.80 D), and Air Optix Night & Day Aqua at temporal 20° (-0.23 D), temporal 30° (-0.48 D), and temporal 40° (-1.50 D; all $p < 0.05$). RPD with contact lenses was not different than RPR (uncorrected eye) along the nasal retina for any retinal location.

J_0 astigmatism is plotted in Figure 3.2. Relative peripheral J_0 astigmatism depended on the contact lens type (lens by location interaction; $p<0.001$). J_0 astigmatism was found to significantly increase compared to that of the uncorrected eye at the 40° temporal retinal location with all contact lenses tested (all $p < 0.03$), except for PureVision2 ($p = 0.97$). There was also a significant difference between the J_0 astigmatism of Air Optix Night & Day Aqua and that of the uncorrected eye at 40 degrees nasal retina ($p = 0.03$) and 30 degrees temporal retina ($p < 0.001$).

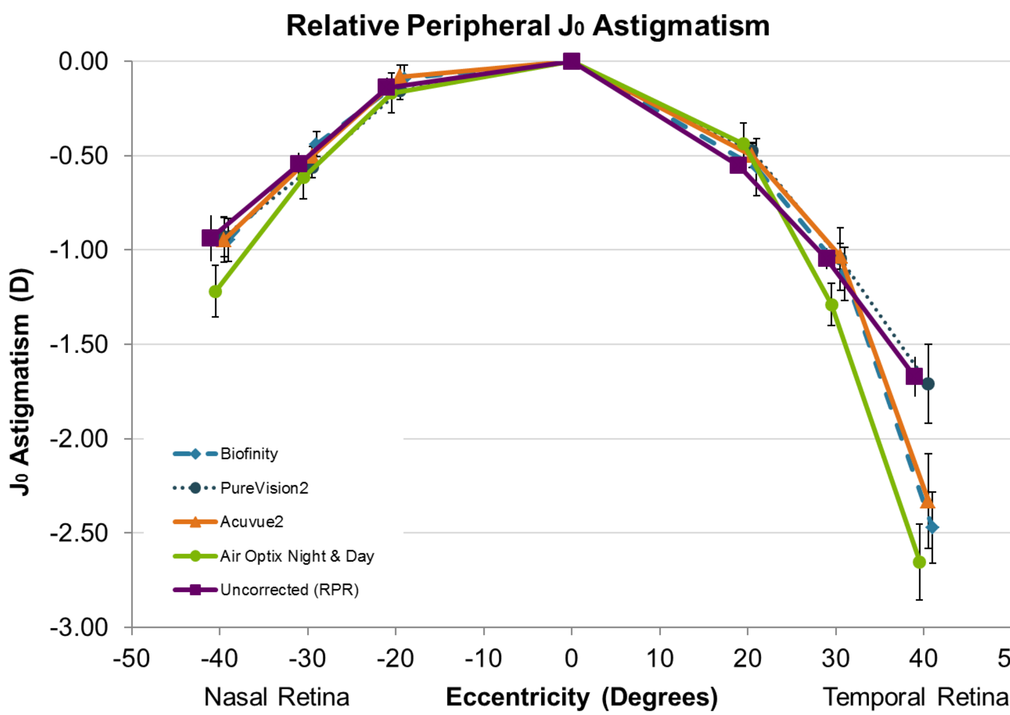

Figure 3.2. Plot of J_0 astigmatism with the four soft contact lenses and with no lens on the eye.

J_{45} astigmatism is plotted in Figure 3.3. Relative peripheral J_{45} astigmatism depended on the contact lens type (lens by location interaction; $p = 0.007$). At the 40 degree temporal retinal location, relative peripheral J_{45} astigmatism was significantly different than the uncorrected eye ($p = 0.004$). There were no other statistically significant differences in J_{45} astigmatism for any of the lenses compared to the uncorrected eye ($p \geq 0.21$).

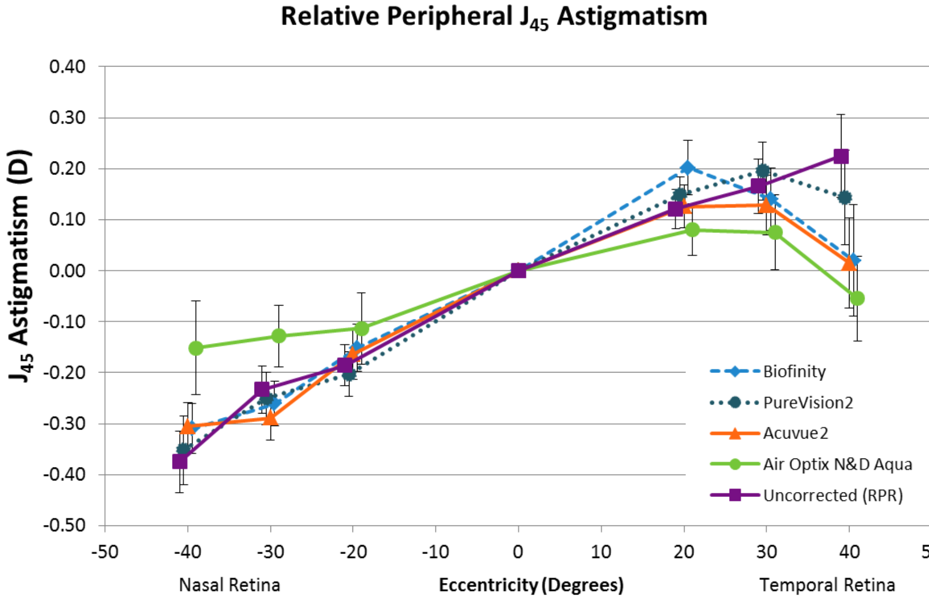

Figure 3.3. Plot of J_{45} astigmatism with the four soft contact lenses and with no lens on the eye.

The average amount of lateral lens decentration for each lens type was not significantly different than zero (mean decentration for each lens brand = 0.1 mm, all $p>0.18$). That being said, the direction of decentration differed among lens types ($p=0.01$). Biofinity, Acuvue2, and PureVision2 on average all decentered 0.1 mm temporal on the cornea. Air Optix Night & Day decentration was significantly different than that of the other three contact lenses (0.1 mm nasal on the cornea; $p<0.05$; Tukey's HSD).

Influence of Contact Lens Power

The change in RPD at each location due to the contact lens optics depended on the power of the contact lens (lens power by location interaction; $p = 0.002$). The change in RPD due to the power of the contact lens did not depend on the lens type (lens type by lens power by location interaction; p=0.58). In Figure 3.4, the defocus profiles of the four contact lenses were averaged based on a split of contact lens power to graphically demonstrate the effect that contact lens power had on the change in peripheral defocus caused by the contact lens. More negative SCL powers caused a more myopic change in RPD than less negative SCL powers at 40° nasal (-0.57 D), 20° temporal (-0.40 D), 30° temporal (-0.79 D), and 40° temporal (-1.38 D) on the retina (all $p < 0.02$).

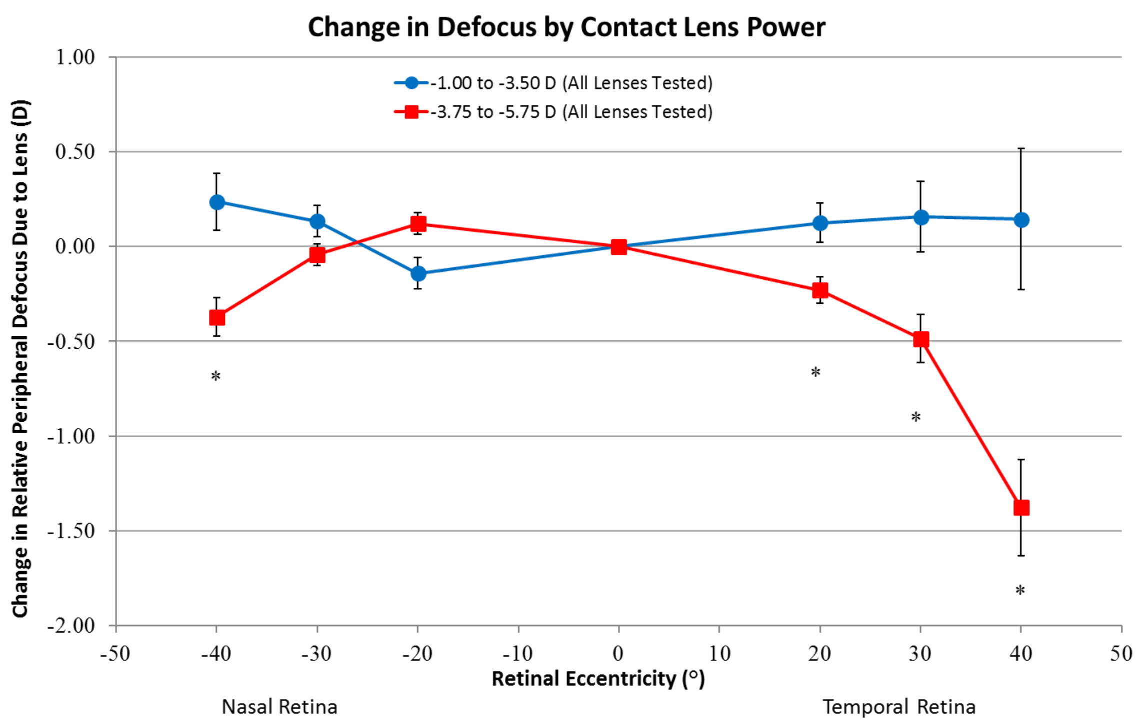

Figure 3.4. Plot of the relative peripheral defocus profiles of the four soft contact lenses averaged based on contact lens power. Positive defocus represents a hyperopic image shift and negative defocus represents a myopic image shift. The asterisks denote eccentricities at which the two groups are significantly different from one another.

Influence of Spherical Aberration

The mean change (± SD) in spherical aberration (C4,0) caused by each contact lens type over a 7-mm pupil was negative: Biofinity: -0.34 ± 0.12 μm; PureVision2: -0.33 ± 0.11 μm; Acuvue2: -0.21 ± 0.12 μm; and Air Optix Night & Day: -0.11 ± -0.09 μm. There were no significant differences between slope estimates for the association between the change in spherical aberration and the change in peripheral defocus at the three nasal retinal locations, so they were averaged in subsequent linear mixed models. The slope estimates (± SE) shown in Figure 3.5 represent the association between a one-micron change in spherical aberration caused by the contact lens and the dioptric change in peripheral defocus. The slope estimates differed by retinal location ($p < 0.001$), becoming more negative with increasing temporal retinal eccentricity. The change in peripheral defocus associated with the mean change in spherical aberration caused by each contact lens brand is shown in Table 3.1 based on the slope estimate at the 40° temporal retinal location of -3.15 D/μm change in spherical aberration. Overall, contact lenses that induced less negative (more positive) changes in spherical aberration were associated with a less hyperopic change in RPD.

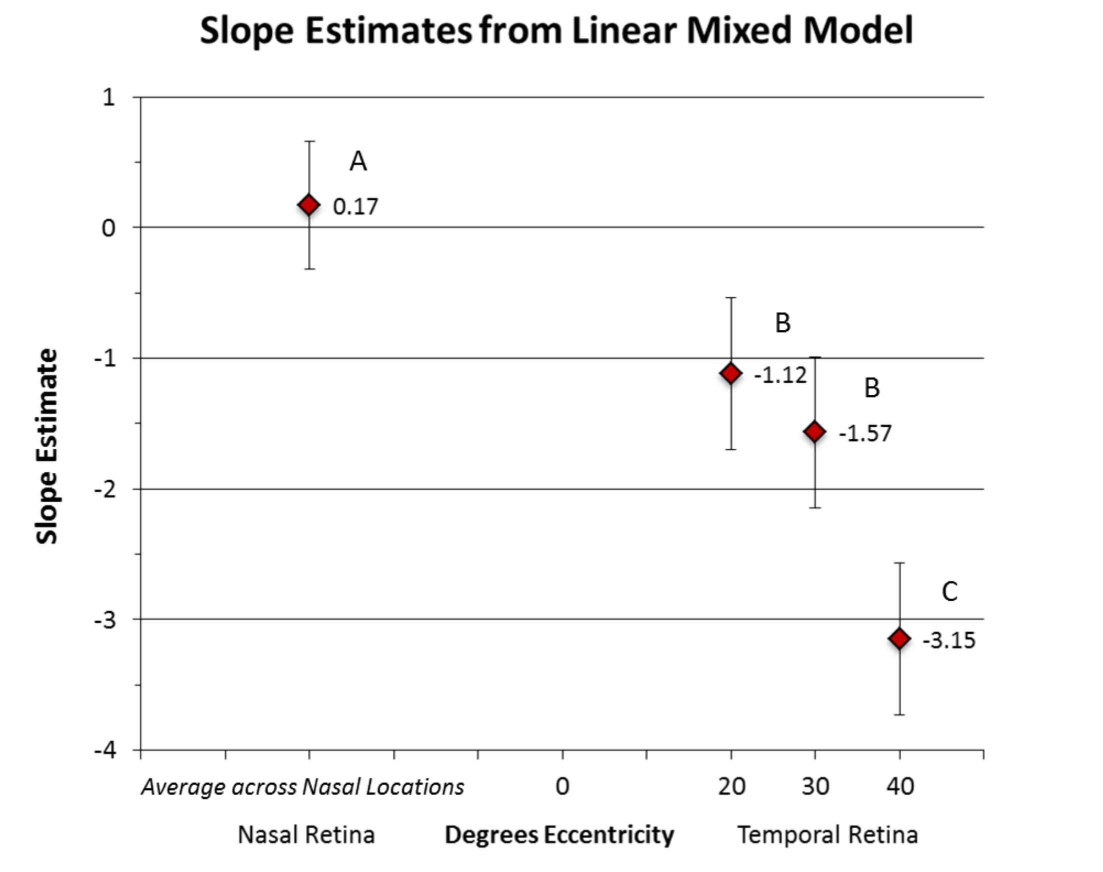

Figure 3.5. Plot of slope estimates from linear mixed model showing the dioptric change in defocus per 1 micron change in spherical aberration due to the contact lens. A shared letter (A, B, or C) indicates no significant difference between slope estimates. Thus, the temporal 20 and 30 degree slope estimates are not significantly different, but both the nasal and the temporal 40 degree estimates are significantly different from all other locations.

Table 3.1. Dioptric change in peripheral defocus at 40° temporal retina associated with the average change in spherical aberration caused by each contact lens.

Lens Type	Mean ∆ SA (microns)	40T Dioptric ∆ / Avg ∆ SA
Biofinity	-0.34	1.07 D
PureVision2	-0.33	1.04 D
Acuvue2	-0.21	0.66 D
Air Optix Night & Day Aqua	-0.11	0.35 D

3.4 Discussion

Depending on the retinal location measured, the four contact lenses evaluated in this study either induced a myopic shift in peripheral defocus or caused no significant change in the peripheral defocus experienced by the eye. None of the contact lenses caused a hyperopic shift. PureVision2 was the only contact lens that induced no change in peripheral defocus at any measurement location. Biofinity, Acuvue2, and Air Optix Night & Day Aqua caused a myopic shift on the temporal retina at greater eccentricities.

Previous studies evaluating the peripheral defocus profile induced by commercially-available soft contact lenses have found variable results. Peripheral myopic shifts have been reported with Acuvue 1-Day Moist, Acuvue2, and Air Optix Night & Day Aqua contact lenses (Shen et al. 2010; Backhouse et al. 2012; Kwok et al. 2012; de la Jara et al. 2014). A hyperopic shift in peripheral defocus has been reported with Proclear and Acuvue2 contact lenses (Kang et al. 2012; de la Jara et al. 2014). Although a previous study of Biofinity reported no significant differences in peripheral defocus caused by the lens at most retinal locations, a sudden myopic shift in peripheral defocus at 40 degrees temporal on the retina was reported similar to the profile found in this study (Berntsen and Kramer 2013). The sudden myopic shift is hypothesized to be due to the edge of the optic zone of the contact lens.

Of the lenses we tested, Acuvue2 is the only lens where our findings conflict with a previous report of the lens peripheral defocus profile (de la Jara et al. 2014). A study by de la Jara et al. reported a relative peripheral hyperopic shift in defocus produced by Acuvue2. In both our study and another study by Shen et al., a myopic shift in peripheral defocus was found with Acuvue2 (Shen et al. 2010). Possible reasons for the discrepancy between our studies could include methodology (e.g., measurements made with versus without cycloplegia) and differences in lens fit and centration on the eye of study subjects.

At the 40 degree temporal retinal location, Biofinity, Acuvue2, and Air Optix Night & Day Aqua had a myopic shift with a corresponding increase in J_0 astigmatism. The relative peripheral changes in J_{45} astigmatism were minimal. The increase in J_0 astigmatism is hypothesized to be due to the size of the optic zone. The optic zones are reported by the manufacturer for only two of our study lenses: PureVision2 with a 9.0 mm optic zone and Air Optix Night & Day Aqua with an 8.0 mm optic zone (Thompson 2015). In evaluating schematic diagrams of the eye with a contact lens and utilizing the Grand Seiko measurement beam diameter of 2.3mm (Fedtke et al. 2009), the autorefractor's measurement beam at the 40 degree temporal retinal location is partially outside of the smaller optic zone of the Air Optix Night & Day Aqua. Because of its larger optic zone, PureVision2 does not result in measurements made outside of the optic zone when measuring at 40 degrees temporally on the retina, even after accounting for the contact lens centering over the optic axis of the eye rather than the visual axis upon which measurement eccentricity is based. The increase in astigmatism for three of the lenses tested is likely due to the instrument measuring partially through the peripheral curve of the contact lens. The sudden increase in J_0 astigmatism at the 40-degree temporal retinal location most likely accounts for the myopic shift in defocus at this peripheral location. This increase in astigmatism suggests that the optic zone size is an important factor to consider when determining the peripheral defocus induced by a contact lens.

Similar to previously published peripheral defocus profiles with soft contact lenses on the eye (Shen et al. 2010; Kang et al. 2012), there is a nasal-temporal asymmetry in our defocus profiles. The nasal retina remains unchanged from the uncorrected eye while the temporal retina shows a myopic shift in three of the four soft contact lenses. One frequently cited cause for this asymmetry is that lenses center on the cornea and thus sit over the optical axis of the eye as opposed to the visual axis (the difference being angle alpha). One might also wonder whether contact lens decentration was a potential contributing factor to asymmetry in this study. If a contact lens consistently decentered in a particular direction, this could influence the peripheral defocus profile caused by the lens. While the average lens decentration did not differ significantly from zero, three of the lenses decentered temporally on average and the Air Optix Night & Day contact lens decentered nasally on average. Though these contact lenses decentered in opposite directions, there was little difference in the defocus profiles, which is likely because of the small amounts of decentration measured in this study. The measured increase in J_0 astigmatism that corresponds to the myopic shift in defocus at the 40 degree temporal location provides convincing evidence that measurements are occurring outside of the controlled optics (i.e., optic zone) of the contact lens and are responsible for the most peripheral asymmetric myopic shifts measured in this study.

The power of the contact lens had a significant effect on the peripheral defocus power of the contact lens. On average, across all four contact lenses, a higher power (more minus) contact lens was associated with a greater myopic shift in the periphery. This finding of more negative contact lens powers causing a greater myopic shift in peripheral defocus has been reported before with the Biofinity lens (Berntsen and Kramer 2013). Our findings demonstrate that in addition to variations in contact lens designs between manufacturers, contact lens power can have a significant influence on the change in peripheral defocus caused by a contact lens of any brand. It is also important to note that while more minus power contact lenses in this study increased peripheral myopic defocus, more minus power spectacle lenses have been previously reported to increase peripheral hyperopic defocus (Lin et al. 2010). Based on these results, it seems that spherical soft contact lenses may provide a more favorable peripheral defocus profile than spectacle lenses from a myopia progression standpoint.

Though multiple contact lens manufacturers report that their lenses include aspheric optics, it is not always clear what goal the manufacturer is trying to achieve. Because spherical aberration is a rotationally symmetric aberration, it can be manipulated when designing a spherical contact lens. On average, the general population has positive spherical aberration (Salmon and van de Pol 2006), so one might infer that manufacturers designing aspheric soft contact lenses are either attempting to control induced spherical aberration in the contact lens or have the goal of eliminating the eye's inherent spherical aberration in an attempt to improve visual quality. It is important to note that attempting to correct positive spherical aberration in a person that does not have the population average of spherical aberration could result in an overall increase in spherical aberration. Additionally, if a contact lens containing spherical aberration decenters, it will induce additional higher-order aberrations such as coma.

The average change in spherical aberration caused by the contact lenses measured in this study was negative, which would contribute to a more hyperopic shift in the periphery. Despite finding that the lenses in this study contained negative spherical aberration, we observed myopic changes in peripheral defocus in three of the lenses. That being said, a closer evaluation of the influence of spherical aberration suggests that any hyperopic shift was outweighed by the large impact of contact lens power on peripheral defocus. For example, when considering Air Optix Night & Day, our model results show that at the 40 degree temporal retina, the average spherical aberration induced by this particular lens brand accounts for approximately a 0.35 D hyperopic shift in peripheral defocus. When looking at the effect of prescribed contact lens power on peripheral defocus (Figure 3.4), higher powered (more minus) lenses are approximately 1.5 D more myopic at 40 degrees temporal retina than lower powered contact lenses. This shows that although negative spherical aberration in this study contributed to a hyperopic shift in the defocus profile, the myopic shifts associated with increasingly negative contact lens power was greater and produced an overall net myopic shift on the temporal retina for three of the four contact lenses.

Overall, there were differences in the change in peripheral defocus caused by each spherical soft contact lens. The differences in the defocus profiles seen between different brands of contact lenses are likely due to differences in contact lens optical design (including aspheric optics and optic zone diameter), the influence of prescribed contact lens power, and overall fit of the lens on the eye. If peripheral defocus influences myopia progression, the influence of these lens design differences should be kept in mind.

Chapter 4: Conclusions

The purpose of this thesis was to determine the repeatability of peripheral autorefraction with the Grand Seiko WAM-5500 and to investigate the relative peripheral defocus profiles of four commercially-available spherical soft contact lenses on myopic eyes.

The repeatability of peripheral autorefraction measurements using the Grand Seiko WAM-5500 autorefractor had not been reported for normal eyes. Peripheral autorefraction is commonly employed in refractive error studies and is considered a surrogate for eye shape. Longitudinal studies measuring peripheral refraction are becoming increasingly common as research is performed that manipulates peripheral optics in an attempt to reduce myopia progression. Knowledge of the between-visit repeatability of a commonly used open-field autorefractor for longitudinal refractive error studies will allow for better planning for and interpretation of experimental results.

In this thesis, changes in peripheral defocus induced by contact lenses were measured, and reasons why peripheral defocus was or was not altered by the contact lenses were explored by analyzing optical features and the fit of the contact lenses. These contact lens characteristics included spherical aberration, contact lens power, optic zone size, and lens decentration. If peripheral defocus influences myopia progression, the influence of commonly prescribed spherical soft contact lenses on peripheral defocus is important information for both clinicians prescribing the contact lenses and manufacturers who design contact lenses.

The main findings of this thesis are as follows:

- Repeatability of the Grand Seiko autorefractor was best centrally, and became gradually less repeatable as eccentricity increased. Even at 40° eccentricity, cycloplegic peripheral autorefraction repeatability was better than the previously-reported central repeatability of cycloplegic subjective refraction and was comparable to the previously reported repeatability of central non-cycloplegic autorefraction.
- Repeatability may be reduced in the periphery when measuring with the Grand Seiko autorefractor due to the reported increasing influence of autorefractor lateral pupil misalignment as eccentricity increases.
- PureVision2 did not affect peripheral defocus. However, Air Optix Night & Day Aqua, Acuvue2, and Biofinity each caused a temporal myopic shift on at least one location tested.
- At 40° temporal retina, Air Optix Night & Day Aqua, Acuvue2, and Biofinity had a myopic shift with a corresponding increase in J_0 astigmatism. This increased astigmatism is hypothesized to be due to the size of optic zone. PureVision2 has a larger optic zone and had no increase in peripheral astigmatism, while Air Optix Night & Day Aqua has a smaller optic zone and modeling of measurements through the periphery of the contact lens suggests that the increased astigmatism is due to measurements crossing outside the edge of the optic zone.
- More negative (higher minus) power spherical soft contact lenses caused a greater myopic change in peripheral defocus than less negative (lower

minus) power contact lenses. This is the opposite of the effect seen with higher minus spectacles.

- Overall, the spherical aberration induced by the spherical soft contact lenses was negative. Negative spherical aberration causes a hyperopic shift in peripheral defocus. It is assumed that the myopic shift in defocus measured for three of the four contact lenses was due to the greater influence of contact lens power on peripheral defocus than spherical aberration. However, less negative (more positive) SA was associated with a less hyperopic change in RPD. For example, Air Optix Night & Day had the greatest myopic shift at 40 degrees temporal retina as well as the least negative spherical aberration induced by the contact lens.

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