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Spherical Aberration, Accommodation and Myopia

By

Janice Marie Tarrant

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Vision Science

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor Christine F. Wildsoet, Chair

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Fall 2010

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Abstract

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Professor Christine Wildsoet, Chair

Myopia is a condition in which the eye grows too long to match its optical focal length and represents a failure in both structure and function. Because of the potential risks of vision loss associated with high myopia, and also with corrective treatments such as refractive surgery and occasionally also with contact lenses, myopia should not be considered a benign condition. The hypothesis that hyperopic defocus from under-accommodation during near work is the driving stimulus in the progression of myopia, motivated studies of bifocal spectacles and progressive addition lenses, as optical treatments for the control of myopia progression, with limited success. In contrast, multifocal (MF) soft contact lenses (SCL) and orthokeratology (ortho-k) have proven to be more beneficial although the mechanisms underlying their anti-myopia effects are not understood. This dissertation, which describes 4 main studies, represents efforts to understand how spherical aberration influences the accommodative response and examines as an explanation for the myopia control effects of MF SCLs and ortho-k the possibility that induced changes in ocular spherical aberration decreases the lag of accommodation.

First the effects of bifocal (BF) SCLs on the accommodative responses of young adult emmetropes and myopes were measured using a refractometer. Interpretation of these results proved to be problematic because direct measurements could not be made through the BF SCLs necessitating an assumption to be made about the effective add provided by the lenses.

To address the above issues, in a follow-up study MF SCLs were used in conjunction with a wavefront sensor, allowing direct measurements of accommodative responses through the lenses. To analyze the collected data, the problem of determining a suitable method for calculating accommodative responses from wavefront aberrations had to be solved. Thus a second complementary study evaluated some of the methods used to calculate objective refractions from wavefront aberrations. The best results were obtained with a through-focus procedure, which used an optical quality metric to determine the best image plane and then calculated the accommodative error relative to this plane. The latter findings enabled a comprehensive analysis of the accommodative response data obtained in the MF SCL study, which demonstrated that spherical aberration and pupil diameter independently influence the accommodative response. Both center-distance and center-near MF lenses produced myopic shifts in the best image plane, the former by adding positive spherical aberration and the latter

with the added power of the near addition. For pupils larger than approximately 5 mm, both MF lenses resulted in increased accommodative responses determined by a neural sharpness metric compared with those for a single vision distance lens.

A fourth study measured the change in ocular aberrations induced by ortho-k and assessed the long term effect of ortho-k on the accommodative response of young adult myopes. This study found that ortho-k had similar effects to the center-distance MF SCL on aberrations and accommodative responses. An intriguing long-term outcome of this treatment was a dramatic increase in pupil size for all tested vergences. Explanations in terms of changes in both the pupillary light and near reflexes were considered.

In summary, the studies reported in this dissertation point to complex interactions between spherical aberration, pupil size and the accommodative response, which may be deliberately manipulated in designing novel optical treatments for the control of myopia progression.

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LIST OF ABBREVIATIONS

ANOVA	analysis of variance
AO	adaptive optics
BF	bifocal
CAG	contrast amplitude and gradient
COAS	complete ophthalmic analysis system
COMET	correction of myopia evaluation trial
CRT	corneal refractive therapy
CSF	contrast sensitivity function
DOF	depth of focus
HOA	high order aberrations
LED	light emitting diode
LORIC	longitudinal orthokeratology research in children
MF	multifocal
MFD	center-distance multifocal
MFN	center-near multifocal
MTF	modulation transfer function
NS	neural sharpness
OQM	optical quality metric
OTF	optical transfer function
PAL	progressive addition lens
PFCc	pupil fraction for curvature
PFS _c	pupil fraction for slope
PFW _c	pupil fraction for wavefront
PRK	photorefractive keratectomy
PSF	point spread function
RMS	root mean square
SA	spherical aberration
SCL	soft contact lens
SD	standard deviation
S _E	spherical equivalent refractive error
SEM	standard error of the mean
SLD	super luminescent diode
SV	single vision
SVD	single vision distance
SVL	single vision lens
SVN	single vision near
VA	visual acuity
VSMTF	visual Strehl ratio for MTF
VSOTF	visual Strehl ratio for OTF

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Chapter 1

Introduction – Spherical Aberration, Accommodation and Myopia

Abstract

Myopia should not be considered a benign condition because of the potential risks of vision loss associated not only with high myopia but also with the procedures used to correct myopia. Results from animal studies demonstrating that emmetropization is an active rather than a passive process and the induction of myopic refractive errors with imposed hyperopic defocus underlie the hypothesis that hyperopic defocus resulting from under-accommodation during near work is the driving factor in the development and progression of myopia in susceptible individuals. Based on this premise both bifocal spectacles and progressive addition lenses have been investigated, with limited success, as potential treatments to slow myopia progression. However, alternative treatment modalities such as bifocal and multifocal contact lenses and orthokeratology have proved more effective in slowing myopic eye growth. An understanding of the aberrations induced by the latter treatments and their effects on retinal image quality and accommodative responses can significantly increase our understanding of the optical factors driving myopia progression and guide the design parameters of future optical treatments.

1.1 Etiology of Myopia

Myopia is often considered to be a benign condition that can be corrected as needed with spectacles or contact lenses, or permanently, with refractive surgery. However, it is more appropriately viewed as a failure in both structure and function, a product of the eye growing too long to match its optical focal length. The myopic eye has an increased risk of developing ocular pathology that may lead to vision loss, including retinal detachment, glaucoma, cataract and myopic degeneration with the potential sequela of choroidal neovascularization (Curtin, 1985). The odds ratio for rhegmatogenous retinal detachment with myopia of 1.33/Diopter reported in a recent study (Chou *et al.*, 2007) implies that even moderate levels of myopia carry a significantly increased risk of detachment, i.e. by 4 times for a -3.00 D myope compared with someone with no refractive error. Myopes may also lose vision as a consequence of complications of refractive surgery and more rarely, contact lens use.

Epidemiological studies provide strong evidence that the prevalence of myopia is increasing worldwide, with the most rapid increase being in East Asian countries. Morgan and Rose (2005) have written a comprehensive review of this subject, providing the following data for 12 to 13 year old children:

- Japan 39% in 1984 and 59% in 1996 (Matsumura and Hirai, 1999)
- Taiwan 36.7% in 1983 and 60.7% in 2000 (Lin *et al.*, 2004, Lin *et al.*, 2001)
- Hong Kong 53% in 1991 and 83% in 2001 (Lam and Goh, 1991, Lam *et al.*, 2004)
- United States 12.3% in 1953-54 and 28% in 1993 (Blum *et al.*, 1959, Zadnik, 1997)
- Sweden 49.7% in 2000 (Villarreal *et al.*, 2000)

Not only is the prevalence of myopia increasing in teenagers, it is also increasing in younger age groups, implying that the age of onset of myopia is also decreasing. Earlier onset is also associated with progression to higher levels, with increased prevalence of high myopia (> -6.00 D) being the salient feature.

Animal studies have demonstrated that emmetropization is an active rather than a passive process (Wallman and Winawer, 2004). External optical influences can affect eye growth; for example, when a minus lens is placed in front of the eye it imposes hyperopic defocus, causing the eye to grow longer to compensate for the decrease in overall optical power. When the minus lens is removed, the focal plane of the eye is now in front of the retina, i.e. the eye is now myopic. This lens paradigm involving imposed hyperopic defocus to induce myopic refractive errors is widely used in animal myopia research.

One theory proposed to explain the development of myopia in humans is based on the above observation from animal experiments. Specifically, that hyperopic defocus resulting from reduced accommodation during near tasks is the driving factor underlying the development and progression of myopia in susceptible individuals. Accommodation serves to bring into focus objects at close distances. However, if the eyes under-accommodate, the focal plane conjugate to the near object of regard will lie behind the retina. Because of accommodative lag, extended periods of near work will be associated with extended exposure to hyperopic defocus, a myopia-inducing stimulus. While subjects report seeing clearly and thus the lag of accommodation is assumed to match the ocular depth of focus, it is possible that this defocus error is detectible by the retina, the presumed source of ocular regulating eye growth (Wallman and Winawer, 2004).

The etiology of myopia has been studied extensively, with the relative importance of heredity versus environmental influences being the subject of much debate. However, the preponderance of evidence suggests that environmental influences are more important,

specifically urbanization, education and occupation. Populations in urban areas have been found to have a higher prevalence of myopia compared to those in rural areas. In one study from China, Zhan *et al.* (2000) found that the prevalence of myopia in 6 to 7 year old children was 3.9% in the rural region of Xiamen and 9.1% in Xiamen city. There is also a strong correlation between level of education and prevalence of myopia as evidenced in Singapore military conscripts; 17% of those with no formal education were myopic as opposed to 65% of those with a university education (Au Eong *et al.*, 1993). Whilst the increasing prevalence of myopia is often considered to be a problem confined to east Asian countries, that it is a more general problem is evidenced by the myopia prevalence figure of 60% reported in a recent study of third year law students in the United States (Loman *et al.*, 2002), as well as recently published statistics from a large scale US-based population study by Vitale *et al.* (2009).

Accommodative lag is considered to be an important factor in the pathogenesis of myopia because of the association between myopia progression and near work. While there is not unanimous agreement across all studies, some indicate a tendency for myopes to have a larger lag of accommodation compared to emmetropes (Gwiazda *et al.*, 1995, Gwiazda *et al.*, 1993, McBrien and Millodot, 1986, Abbott *et al.*, 1998, Vera-Diaz *et al.*, 2002) and larger accommodative lags have been linked to both the development (Drobe and de Saint-Andre, 1995, Goss, 1991, Gwiazda *et al.*, 2005) and progression of myopia (Abbott *et al.*, 1998, Allen and O'Leary, 2006, Gwiazda *et al.*, 1995, Mutti *et al.*, 2006).

1.2 Optical Treatments for the Control of Myopia Progression

Based on the premise that the development of myopia is the product of under-accommodation during near tasks, both bifocal spectacles (Fulk *et al.*, 2000, Goss and Grosvenor, 1990) and progressive addition lenses (PALs) (Edwards *et al.*, 2002, Gwiazda *et al.*, 2003, Hasebe *et al.*, 2008, Leung and Brown, 1999) have been investigated in clinical trials as a means of slowing the rate of myopia progression in children. In the largest of these studies, the COMET study (Gwiazda *et al.*, 2003), a small statistically significant treatment effect was reported for PALs. However, this effect was observed only during the first year of the 3-year study and was so small that it was not considered to be clinically significant. Further analyses of the COMET data showed larger treatment effects in individuals with larger accommodative lags in combination with near esophoria, shorter reading distances and lower baseline myopia (Gwiazda *et al.*, 2004).

Studies examining the effectiveness of bifocal (BF) and multifocal (MF) soft contact lenses as myopia control treatments in children and young adults report much greater treatment effects than seen in spectacle lens studies (Aller and Wildsoet, 2007, Aller and Wildsoet, 2006, Howell, 2008, Rodgin, 2001). Two possible reasons for the better results with the BF and MF contact lenses are; i) improved compliance, assuming that the subjects did not use the reading portion of their spectacles as instructed, and ii) the contact lenses affect accommodative responses differently to BF spectacles and PALs. In the first case, it has been demonstrated that children do not consistently use the near addition portion of their spectacles for reading (Hasebe *et al.* 2005). In the second case, bifocal contact lenses not only reduce the accommodative demand but appear to cause subjects to over-accommodate at near distances, as measured by standard refractometry (Tarrant *et al.*, 2005).

Orthokeratology (ortho-k) is a technique that uses reverse geometry rigid gas permeable contact lenses to remodel the anterior corneal surface. Not only can this treatment temporarily

reduce the amount of refractive error in low to moderate myopes, two recent longitudinal studies reported slowed ocular elongation, corresponding to reduced progression of myopia in subjects treated with overnight ortho-k compared to subjects wearing either spectacle correction (Cho *et al.*, 2005) or soft contact lenses (Walline *et al.*, 2009).

Is there a connection between these two different contact lens treatments – multifocal contact lenses and ortho-k lenses - which both appear to reduce myopia progression? Previously published studies have demonstrated a consistent increase in the amount of negative spherical aberration during accommodation (Cheng *et al.*, 2004a), more so in myopes (Collins *et al.*, 1995). Multifocal contact lenses also significantly alter the aberrations of the eye (Peyre *et al.*, 2005), most notably adding spherical aberration and it is plausible that such changes could underlie their observed effects on both accommodation and myopia progression. The same explanation is tenable for the effects of ortho-k because it also affects ocular aberrations. Specifically, ortho-k is reported to induce a positive shift in spherical aberration (Berntsen *et al.*, 2005, Hiraoka *et al.*, 2005, Hiraoka *et al.*, 2008, Hiraoka *et al.*, 2007, Joslin *et al.*, 2003, Stillitano *et al.*, 2008), consistent with the central corneal flattening and relative peripheral corneal steepening produced by the treatment.

In understanding why multifocal and ortho-k lenses may slow myopia progression, it is important to consider the effect on retinal image quality of interactions between defocus and spherical aberration. For example, it has been demonstrated that specific combinations of negative spherical aberration and negative defocus (hyperopic defocus), and positive spherical aberration and positive defocus (myopic defocus) produce images that are seen as subjectively less blurred than the same amounts of either defocus or spherical aberration alone (Applegate *et al.*, 2003, Cheng X *et al.* 2004, Chen *et al.* 2005). The prediction for accommodation based on these observations would be that images will appear least blurred with negative defocus (a lag of accommodation) due to the shift in spherical aberration from positive to negative values with accommodation. Similarly, optical treatments such as multifocal and ortho-k contact lenses, which add positive spherical aberration to the eye, could be expected to produce the best image when combined with positive defocus (a lead of accommodation).

The statistically significant but clinically unimpressive treatment effects reported by previous clinical trials of bifocal spectacles and PALs indicate that whilst decreasing the lag of accommodation may have some benefit on myopia progression, this approach is not effective enough. Based on animal studies, optical treatments that produce leads of accommodation should be more effective because the hyperopic stimulus to growth is removed. While noncompliance is a likely factor contributing to these disappointing results, none of the clinical trials involving bifocal spectacles and PALs measured accommodative behavior through the reading addition, and the influence of accommodative feedback mechanisms was not considered.

When young subjects use a reading addition the lag of accommodation decreases and higher adds can result in a lead of accommodation for some near distances due to the over-riding influence of proximal cues (Seidemann and Schaeffel, 2003). However, because accommodation is controlled by a feedback system, it seems unlikely that such leads would be sustained in the longer term. In this context, it is interesting that the treatment effect of PALs reported in the COMET study was observed only during the first year. Perhaps after this period, the accommodative system had returned to its usual posture and the initial reduction achieved in the lag of accommodation had diminished. Because over-accommodation with a near add does not make the retinal image clearer there would be no reason for the accommodative system to maintain this level of accommodation. However, over-accommodation resulting from an

interaction with the spherical aberration induced by multifocal contact lenses or orthokeratology would likely be more enduring, assuming as predicted it resulted in a sharper retinal image. For this reason multifocal contact lenses and orthokeratology would be expected to have longer-term benefits on myopia progression compared to PALs.

1.3 Dissertation Outline

In this dissertation, the feasibility of manipulating the ocular spherical aberration to induce changes in the accommodative response is investigated. A plausible strategy for slowing myopic eye growth proposed in this dissertation involves understanding how spherical aberration influences the accommodative response and utilizing this effect to decrease the lag of accommodation. The treatment modalities used to alter ocular spherical aberration are bifocal and multifocal soft contact lenses and orthokeratology.

1.3.1 Specific Aims

Chapters 2, 3, 4 and 5 of this dissertation are divided and ordered according to the specific aims as follows:

1. To assess the effect of bifocal soft contact lenses on the accommodative responses of young adult emmetropes and myopes. Consensual accommodative responses were measured with a Grand Seiko WR-5100k refractometer with 3 types of lenses: single vision distance contact lenses, single vision near contact lenses (+1.50 D added to the distance prescription) and bifocal contact lenses (+1.50 D add). This work was published in *Ophthalmic and Physiological Optics* (Tarrant *et al.*, 2008).
2. To evaluate some of the methods used to calculate objective refractions from wavefront aberrations, to determine their applicability for accommodation research. A COAS wavefront analyzer was used to measure ocular aberrations at distance and 4 near target vergences. The accommodative responses were calculated using the following techniques: least squares fitting, paraxial curvature matching, 5 optical quality metrics (PFWc, PFSc, PFCc, NS, and VSMTF) and a task-specific method of determining optimum focus that used a through-focus procedure to select the image that best optimized both contrast amplitude and gradient. This work was published in the *Journal of Vision* (Tarrant *et al.*, 2010).
3. To investigate the effects of multifocal soft contact lenses on the ocular aberrations and accommodative responses of young adult emmetropes and myopes. Monocular accommodative responses were measured using a COAS wavefront sensor with 6 different contact lenses: single vision distance contact lenses, single vision near contact lenses (+1.50 D added to the distance prescription), 2 center-distance multifocal contact lenses (+1.50 and +2.00 D adds), and 2 center-near multifocal contact lenses (+1.50 and +2.00 D adds). This work has been submitted for publication.
4. To measure the changes in ocular aberrations induced by orthokeratology and to assess their long-term effect on the accommodative response. Ocular aberrations were measured with a COAS wavefront sensor for distance and 4 near target vergences. Measurements were made prior to and 4 weeks, 6 months and 1 year after being fit with orthokeratology lenses. Paraxial curvature matching and a neural sharpness

metric were used to calculate the accommodative responses. This work has been reported at 2 conferences and will be submitted for publication.

These individual specific aims are expanded and discussed in further detail in chapters 2-5. In chapter 6, the major findings of the dissertation are summarized, and the clinical implications and possible future directions for this research discussed.

Chapter 2

Accommodation in Emmetropic and Myopic Young Adults wearing Bifocal Soft Contact Lenses

Abstract

Purpose: To assess the effect of bifocal soft contact lenses on the accommodative errors (lags) of young adults. Recent studies suggest that bifocal soft contact lenses are an effective myopia control treatment although the underlying mechanism is not understood.

Methods: Accommodation responses were measured for 4 target distances: 100, 50, 33 and 25 cm in 35 young adult subjects (10 emmetropes and 25 myopes; mean age: 22.8 ± 2.5 years). Measurements were made under both monocular and binocular conditions with 3 types of lenses: single vision distance soft contact lenses (SVD), single vision near soft contact lenses (SVN; +1.50 D added to the distance prescription) and bifocal soft contact lenses (BF; +1.50 D add).

Results: For the SVD lenses, all subjects exhibited lags of accommodation with myopes accommodating significantly less than emmetropes for the 100 and 50 cm target distances ($p < 0.05$). With the SVN lenses, there was no significant difference in accommodative responses between emmetropes and myopes. With the BF lenses, both emmetropic and myopic groups exhibited leads in accommodation for all target distances, with emmetropes showing significantly greater leads for all distances ($p < 0.005$).

Conclusions: Overall, myopes tended to accommodate less than emmetropes, irrespective of the contact lens type, which significantly affected accommodation for both groups. The apparent over-accommodation of myopes when wearing the BF contact lenses, may explain their reported efficacy as a myopia control treatment although further studies are required to elucidate the mechanism underlying this accommodative effect.

2.1 Introduction

The etiology of myopia has been studied extensively, with the relative importance of heredity versus environmental influences being the subject of on-going debate for the more common juvenile (early) - and young adult (late)-onset forms of myopia. The well-established association between myopia progression and near work has led to speculation that the larger accommodative lags reported in myopes may be an important factor in its pathogenesis (reviewed in Rosenfield and Gilmartin, 1998, Saw, 2003). This conclusion is also consistent with reports of robust responses to hyperopic defocus, imposed experimentally in animal myopia studies, with myopia being the end result for all species tested to-date (Wallman and Winawer, 2004).

Based on the premise that the development of myopia is triggered by hyperopic defocus arising from reduced accommodation during near tasks, both bifocal spectacles (Goss and Grosvenor, 1990, Fulk *et al.*, 2000) and progressive addition spectacle lenses (PALs) (Leung and Brown, 1999, Edwards *et al.*, 2002, Gwiazda *et al.*, 2003), have been investigated in clinical trials, as treatments to slow the rate of myopia progression in children. In the largest of these studies, the COMET study (Gwiazda *et al.*, 2003), a small but statistically significant treatment effect (slowed progression), was reported with PALs. Nonetheless, this effect was observed only during the first year of the 3-year study and was too small to be considered clinically significant, although further analyses of the COMET study data showed better effects on individuals with larger accommodative lags in combination with near esophoria (Gwiazda *et al.*, 2004).

The effect of optically undercorrecting myopia on its progression rate has also been assessed in 2 small-scale studies, with paradoxical results in one case (Chung *et al.*, 2002), and no statistically significant effect in the other (Adler and Millodot, 2006). Subjects were undercorrected by approximately +0.75 D in the first case and +0.50 D in the second case. The closest parallel in animal studies involves the use of positive lenses to impose myopia for distance vision, this treatment slowing eye growth. However, as noted above, these studies have also described increased ocular elongation with imposed hyperopia. Thus a possible explanation for the cited human studies is that the level of undercorrection was insufficient to significantly reduce accommodative lags. The latter explanation is consistent with the apparent benefit, albeit small, of bifocal and progressive spectacle lenses incorporating adds in the range of +1.50 to +2.00 D, and the monocular slowing of myopia progression in a monovision spectacle correction trial (Phillips, 2005) in which the dominant (distance) eye was fully corrected and the fellow eye either left uncorrected or corrected to keep the refractive imbalance ≤ 2.00 D. The fellow eyes showed significantly slower progression in the latter study.

Although the rationale for prescribing a near addition (add) for control of myopia progression is to reduce the accommodative demand, and consequently also the lag of accommodation, in the cited clinical trials no measurements were made of the effects of prescribed near adds on the subjects' accommodative responses, either prior to, or over the course of such studies. Nonetheless, the acute effects of near adds, measured in 3 independent studies, are consistent with the rationale for their use. In one such study, the effects of adds, ranging from +0.75 to +2.00 D, on the accommodative responses of "youngish" adults (17 to 40 years old; 7 emmetropes, 17 myopes and 4 hyperopes), were assessed (Rosenfield and Carrel, 2001). When viewing a target binocularly at 40 cm, all subjects manifested leads of accommodation that increased monotonically with larger adds. Similar results are reported in the other 2 two studies, both of which involved near-emmetropic, young adults. In one case, subjects

were tested with +2.00 and +3.00 D spectacles; all over-accommodated while reading at 33 cm (Howland *et al.*, 2002). In the second case, positive lenses of +1.00 and +2.00 D in power were found to reduce the lag of accommodation under monocular viewing conditions and reverse it, creating a lead of accommodation, under binocular conditions (Seidemann and Schaeffel, 2003). In the first of these 3 studies, which compared the responses of emmetropes and myopes, no significant difference between these refractive groups was found.

Recent clinical studies investigating the effect of bifocal soft contact lenses on myopia progression in children and young adults (Aller and Grisham, 2000, Aller, 2000, Aller and Wildsoet, 2006, Aller and Wildsoet, 2007), have reported much greater treatment effects than seen in related spectacle lens studies. That the young subjects in previous bifocal and PAL spectacle trials did not use the reading portion of their spectacles correctly is one of a number of possible explanations for the poorer results in these trials, being consistent with observations that children do not consistently use the near addition portion of their spectacles during reading (Hasebe *et al.*, 2005).

A number of studies have reported larger lags of accommodation in myopes compared to emmetropes (McBrien and Millodot, 1986, Gwiazda *et al.*, 1993, Gwiazda *et al.*, 1995, Abbott *et al.*, 1998, Vera-Diaz *et al.*, 2002, Nakatsuka *et al.*, 2005), and a recent study found accommodative lag to be an independent predictor of myopic progression in both juvenile-onset and late-onset myopes (66% & 77% respectively showed significant progression), as well as in non-myopes (44% of whom became myopic)(Allen and O'Leary, 2006). However, not all studies have yielded confirmatory evidence of larger lags of accommodation in myopes compared to emmetropes (Nakatsuka *et al.*, 2003, Seidel *et al.*, 2005, Harb *et al.*, 2006), inter-study differences in the experimental protocols used to measure accommodative lags being a confounding factor. There is also on-going debate as to whether such increases in accommodative lags occur prior to the onset of myopia, consistent with a causal effect, or occur after onset, as a consequence of the myopic changes (Rosenfield *et al.*, 2002, Mutti *et al.*, 2006).

The purpose of the current study was to assess the effect of bifocal soft contact lenses on the accommodative responses of young adult emmetropes and myopes. Specifically, we sought to confirm observations by others that myopes have higher accommodative lags than emmetropes and to investigate whether bifocal contact lenses are effective in correcting such lags. Such evidence would help to explain their apparently greater efficacy as a myopia control treatment and support their more extensive testing in a controlled clinical trial.

2.2 Methods

2.2.1 Subjects

Thirty-five young adult subjects (mean age: 22.8 ± 2.5 years) participated in the study; 10 were emmetropic (mean spherical equivalent refractive error (S_E): -0.09 ± 0.42 D), and 25 were myopic (mean S_E : -3.06 ± 1.34 D), based on non-cycloplegic autorefractor measurements (Grand Seiko WR-5100K). Astigmatism was limited to less than -1.00 D, and anisometropia, to less than 2.00 D. All subjects had normal corrected visual acuity (20/20 or better) and no binocular vision anomalies.

The study protocol conformed to the provisions of the Declaration of Helsinki and was approved by the University of California, Berkeley institutional review board. Informed consent

was obtained from the participants after the nature and possible complications of the study were explained in writing.

2.2.2 Accommodation Measurement Protocol

A Grand Seiko WR-5100K refractometer was used to measure accommodative responses at 4 different near distances: 100, 50, 33 and 25 cm, and measurements were also taken under distant viewing conditions. Reported accommodative responses represent the average of 5 consecutive refractometer readings. The accommodation target was a high contrast Maltese cross positioned on the subject's midline in all cases. Under binocular conditions, both eyes viewed the target but only the non-dominant eye was measured. Under monocular conditions, only the dominant eye viewed the target and the consensual response of the fellow eye was measured through an infrared transmitting filter (700 nm cut-off wavelength), which also served to occlude that eye. Ocular dominance was determined by a sighting test.

2.2.3 Contact Lens Conditions

Accommodation measurements were made with subjects wearing each of 3 different types of soft contact lenses: 1. single vision distance (SVD) contact lenses, 2. simultaneous vision bifocal (BF) contact lenses (+1.50 D near addition), and 3. single vision near (SVN) contact lenses (+1.50 D added to the distance prescription, to match the BF add). The optical design of the BF contact lens consisted of a 2 mm diameter central distance zone with 5 alternating near and distance zones, extending over an 8 mm diameter optic zone. Single vision lenses belonged to the same lens series. Although the prescriptions of the emmetropes were negligible, all were fitted with contact lenses for accommodation measurements, to control for any effect of the lenses on the refractometer measurements; those with plano prescriptions wore +0.25 D lenses as their distance prescription.

Our primary interest was in how bifocal (BF) soft contact lenses affect accommodation, specifically, whether they reduce accommodative lags. However, we were unable to record valid readings through the BF lenses with our refractometer, because of the discontinuities in optical power across them. As a solution to this problem, subjects were tested with a monocular BF lens on one eye, which was used to view the target, and consensual responses were recorded from the occluded, fellow eye, which wore a SVD lens. For comparison, we made both monocular and binocular measurements with the SVD and SVN lenses. For the latter monocular conditions, measurements were limited to consensual responses.

The inclusion of SVN lenses served two purposes. First, by comparing the responses under monocular and binocular conditions with the SVN lenses, it allowed the effect on accommodative responses of disrupting binocular vision, unavoidable in measurements with the BF lens, to be evaluated. Differences in responses recorded under monocular and binocular conditions may occur due to the elimination of convergence influences on accommodation under monocular conditions (Schor, 1999). Second, the optical design of the BF lens may independently affect accommodation. For example, it is likely that the effective add of the BF lenses will vary between subjects, as the improvement in visual performance at near with simultaneous vision BF contact lenses may be due to either actual bifocality or to an increase in the depth of focus, the latter being pupil size-dependent (Martin and Roorda, 2003).

2.2.4 Data Analyses

Accommodative errors, defined mathematically as the difference between the accommodative demand, adjusted for any near addition present during measurement, and the accommodative response, were calculated for all data sets. For the SVD and BF lenses, refractometer readings were taken as direct measures of accommodative responses. However, refractometer readings obtained with the SVN lenses included the near addition provided by them; thus for each subject, the reading for the distance target measured through the same lenses was subtracted from each of the corresponding near target distances, to obtain the respective accommodative responses. The BF lens was assumed to provide the same near add as the SVN lens, i.e. +1.50 D. Thus for the 25 cm target distance, the demand was -2.5 D for both the SVN and BF lenses compared to -4 D for the SVD lenses, and the comparable values for the 33 and 50 cm distances were -1.5 versus -3 D and -0.5 versus -2 D. For the 100 cm target distance, the accommodative demand was 1 D for the SVD lenses and assumed to be 0 D for both the SVN & BF lenses. Because accommodation renders eyes relatively more myopic (negative refractometer readings), lags, i.e. under-accommodation relative to the target demand, will have negative values while over-accommodation or leads of accommodation will have positive values.

Paired t-tests were used to compare accommodative responses measured under binocular and monocular conditions. Differences in monocular accommodative errors, between emmetropes and myopes, were assessed using Student's t-tests, for both the SVD and SVN lenses, and the Aspin-Welch unequal variance t-test for the BF lenses (for all viewing distances). Repeated measures ANOVAs were used to compare the effects of the different corrective lenses on the monocular accommodative errors, for both groups, with the Bonferroni adjustment for all paired comparisons (for all viewing distances).

2.3 Results

Overall, the myopes generally accommodated less than the emmetropes, irrespective of the lens type worn and for all viewing distances. However the inclusion of a near addition reduced the lag and in some cases, leads rather than lags of accommodation were seen. The results for monocular testing conditions are summarized graphically in Figures 2-1 and 2-2.

For all 3 lens types, accommodative responses increased with increased target vergence overall although there was minimal response to the 1 D vergence demand with the SVN lens and the range of responses was reduced for both the SVN and BF lenses compared to that of the SVD lenses (compare Fig. 1A vs. Figs. 1B & C, left panel). The accuracy of these accommodative responses was quantified in terms of accommodative errors. For the SVD lenses (Fig. 1A, right panel), all subjects exhibited lags of accommodation for all target distances, with the myopes recording larger lags than the emmetropes. The differences between the two groups are also statistically significant for the 50 and 100 cm target distances ($p < 0.05$). With the SVN lenses (Fig. 1B, right panel), the myopes again showed lags of accommodation for all target distances. On the other hand, the emmetropes exhibited leads for the two farthest distances (50 and 100 cm), although they again exhibited lags for the two closest target distances (25 and 33 cm). However, these differences in accommodative responses between the two groups are not statistically significant. With the BF lenses (Fig. 1C, right panel), both the emmetropes and myopes exhibited leads of accommodation at all target distances, with the differences between the two groups being statistically significant for all distances ($p < 0.005$).

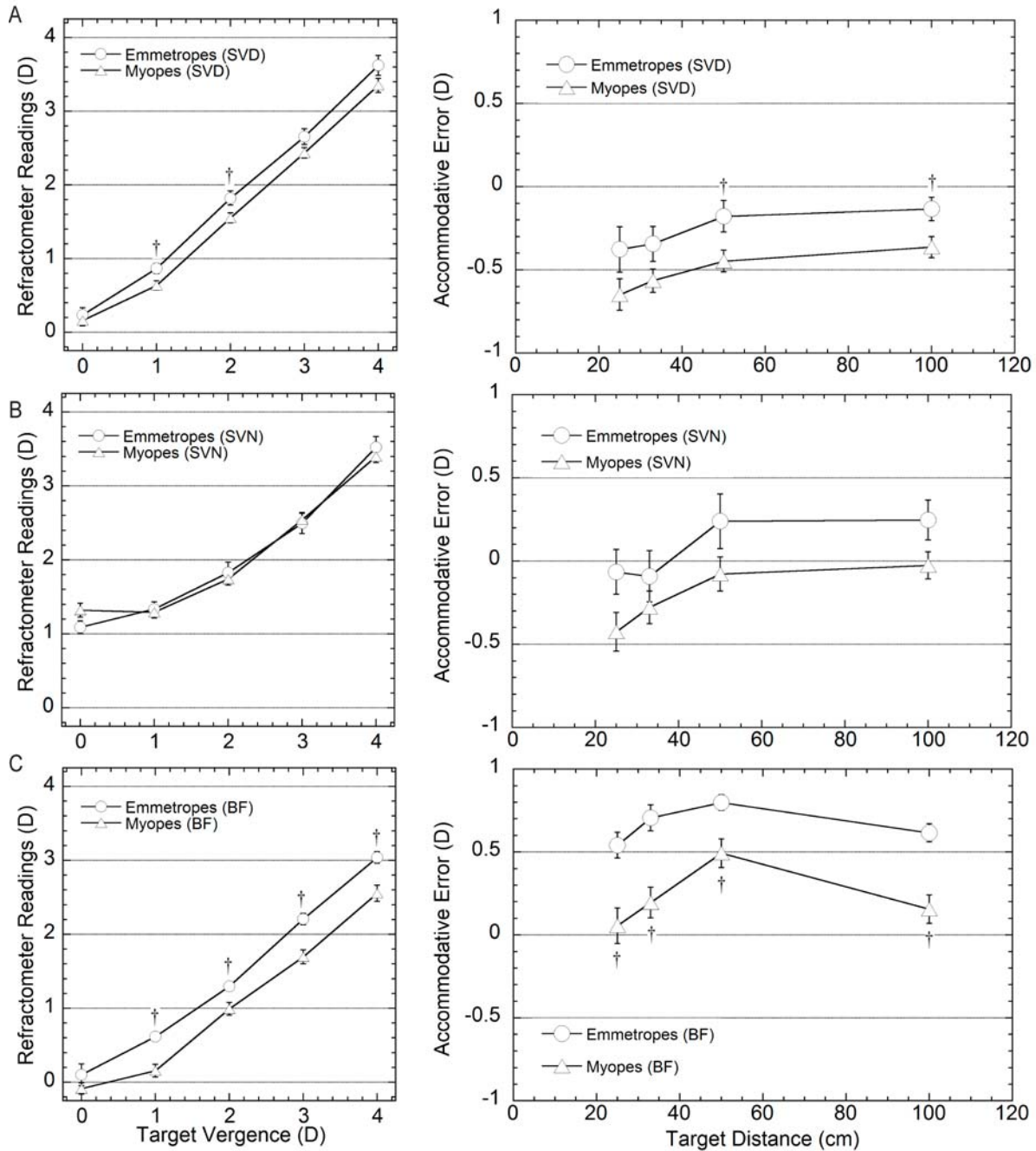


Figure 2-1. Refractometer readings (left panel) and accommodative errors (right panel; lags or leads; mean \pm SEM) measured through either (A) single vision distance contact lenses (SVD), (B) single vision near contact lenses (SVN), or (C) bifocal contact lenses (BF). Emmetropes consistently exhibited less accommodative lag (negative values) and/or more lead (positive values) than myopes. † significant intergroup differences ($p < 0.05$).

Compared to the accommodative lags recorded with the SVD lenses, both the SVN and BF lenses produced positive shifts in accommodative errors for both the myopic and emmetropic

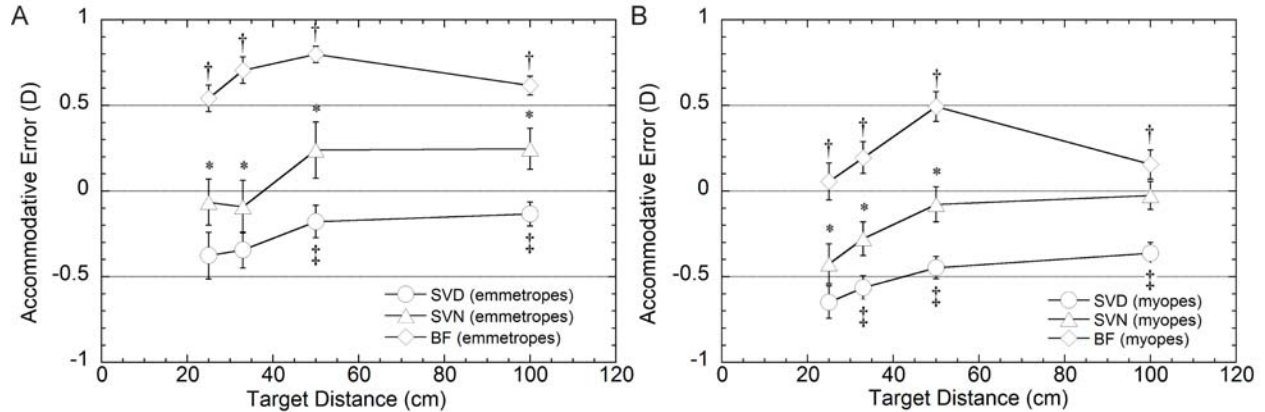


Figure 2-2. Data from *Figure 2-1* replotted to contrast the effect of lens type on accommodation for (A) emmetropes and (B) myopes. Single vision near (SVN) and bifocal (BF) lenses reduced accommodative lags and or resulted in accommodative leads; differences significant for single vision distance (SVD) vs BF ($\dagger p < 0.017$), SVD vs SVN ($\ddagger p < 0.017$), SVN vs BF ($* p < 0.017$).

groups. To better illustrate these effects of lens design on accommodation performance, the data shown in *Figure 2-1* are replotted in *Figure 2-2*, organized by refractive error group. For the emmetropic group (*Fig. 2A*), the differences in accommodative errors recorded with the SVN lenses compared to those recorded with the SVD lenses are statistically significant only for the two farthest target distances, 50 and 100 cm ($p < 0.017$), while the equivalent differences for BF compared to both the SVD and SVN lenses are significantly different for all target distances ($p < 0.017$). For the myopes (*Fig. 2B*), differences between accommodative errors with the SVN lenses compared to the SVD lenses are statistically significant for all but the closest target distance (i.e. 33, 50 and 100 cm; $p < 0.017$); for the SVD compared to the BF lenses, there are significant differences in accommodative errors for all target distances ($p < 0.017$), and for the SVN compared to the BF lenses there are significant differences in accommodative errors for the three closest target distances, 25, 33 and 50 cm.

For reasons explained in the methods section, only monocular (consensual) measurements were possible with the BF lenses. However, comparison of measurements made under monocular and binocular conditions with the SVD lens revealed no significant difference between binocular versus monocular measurements, and the equivalent comparison for the SVN lenses revealed only small differences in performance. Specifically, there is no difference between the binocular and monocular responses for the 100 cm target distance, and while the binocular accommodative responses are slightly larger (i.e. less lag), than the monocular responses for the three closest distances, the average differences are less than 0.125 D for the 33 and 25 cm target distances, and 0.57 D for the 50 cm target distance. These trends also are in the wrong direction to explain the leads of accommodation observed with the BF lenses.

2.4 Discussion

The principal findings of the current study are: 1. that accommodation becomes increasingly inaccurate with increasing demand (reduced target distance), 2. that myopes accommodate less than emmetropes, recording larger accommodative lags as a consequence, and 3. both near addition single vision lenses and bifocal lenses incorporating the same effective add

can reduce or eliminate accommodative lags although there are differences between the effects of these 2 types of lenses.

Neither the observed interaction between target distance and accommodative lag nor the observed accommodative performance differences between myopes and emmetropes represents a new finding. Nonetheless, that we were able to confirm the findings of others is important in the context of the current study and also in the context of myopia pathogenesis. Specifically, our results indicate that myopes tend to accommodate less than emmetropes for all target distances when wearing distance corrective lenses. Among previous, related studies, different measurement paradigms are encountered, with some studies fixing the target distance and using negative lenses of increasing power to stimulate accommodation and others manipulating the target distance, as in the current study. Nonetheless, most report similar trends, for both children and young adults (McBrien and Millodot, 1986, Gwiazda *et al.*, 1993, Gwiazda *et al.*, 1995, Abbott *et al.*, 1998), although the use of negative defocusing lenses appears to exaggerate the difference between myopes and emmetropes (Gwiazda *et al.*, 1995, Abbott *et al.*, 1998).

Because our subjects wearing their distance corrective lenses showed lags of accommodation, we predicted a reduction in their accommodative lags when they wore optical corrections that incorporated near adds, thereby reducing the accommodative demand at all target distances. Our results confirmed our prediction. All subjects showed reductions in their lags of accommodation with SVN contact lenses compared to SVD contact lenses. For the emmetropes and the 2 farthest target distances, lags of accommodation were replaced by leads of accommodation, and for the same target distances myopes showed negligible accommodative lags.

There are 3 earlier studies reporting the effects of near additions on accommodative lags. Findings from one study involving young adults wearing single vision spectacle lenses (Seidemann and Schaeffel, 2003) are consistent with our findings although this study was confined to “near-emmetropic” subjects. Under monocular viewing conditions, leads of accommodation were observed for their three farthest target distances (1.5, 2 and 3 D accommodative demands) with a +1.00 D near add, and at all target distances (1.5, 2, 3, 4 and 5 D accommodative demands) with a +2.00 D add. Another closely related study (Howland *et al.*, 2002) is more difficult to interpret as inter-subject differences in distance refractive errors were not taken into account in the study design. In contrast to the current result, no effect of refractive error was found in a third study, the only previous one to examine refractive error-related differences in the effects of near adds on the accommodative responses (Rosenfield and Carrel, 2001); myopes, emmetropes and hyperopes were tested with +0.75, +1.50, +2.00, and +2.50 D adds, and one test distance, 40 cm. All adds produced leads of accommodation, with larger adds resulting in larger leads.

Because our choice of near addition for the SVN contact lenses was intended to match the effective add of the BF contact lenses used, by analogy, the accommodative errors measured with the BF and SVN lenses were expected to be similar. However, our analyses indicate that the BF lenses had a much larger effect on the accommodation responses of our subjects than the SVN lenses. Notably, the BF lenses resulted in leads of accommodation at all target distances for both groups, whereas only the emmetropes experienced leads with the SVN lenses, for the two farthest targets in this case.

One possible explanation for observed differences in accommodative responses measured with the BF and SVN lenses is that the BF lenses did not provide a +1.50 D add, as assumed.

Our calculations of accommodative errors, which were based on the consensual responses of the fellow SVD lens-wearing eyes, required an assumption to be made about the effective add produced by the BF contact lenses. While we used a value of +1.50 D, substituting a smaller value (i.e. <+1.50 D), would bring the calculated errors closer to those calculated for the SVN lenses. Note that our working model also assumes that all subjects experienced true bifocality with the BF contact lenses, with the two optical powers incorporated into the lenses having independent influences on their vision. Other explanations for the differences in accommodative responses seen with the SVN and BF lenses are considered below.

That simultaneous vision contact lenses increase the static ocular depth of focus has been considered as a possible explanation for associated improvements in the reading ability of presbyopes (Chateau and Baude, 1997, Ares *et al.*, 2005), and also may explain the results of the current study. Such increases in the ocular depth of focus provide what is referred to as an extended pseudoaccommodation range, reducing the need for accommodation, just like near addition lenses. For our young adult subjects, BF lens-induced increases in depth of focus are likely to be smaller than for their presbyopic counterparts for which the lenses were designed, because of the typically larger pupils of young adults. Assuming that some accommodation was required at each target distance, albeit reduced in magnitude compared to that required with SVD lenses and greater than that required with SVN lenses, the effective add experienced with the BF lens would have been smaller than that of the SVN lenses, and the effect on the calculated error of accommodation would be an apparent increase in the lead of accommodation with BF lenses compared to SVN lenses, as observed.

While the above explanations can account for differences in the leads of accommodation recorded with the BF and SVN lenses, they do not readily account for apparent differences in the shape of the response curves (Fig. 1), and related differences between the emmetropic and myopic groups (Fig. 2). For example, with the BF lenses, the largest leads were recorded with an intermediate target distance (50 cm), with the decrease in lead for the larger target distance being particularly prominent for the myopes (Fig. 1C, right panel). The results for the SVN lenses were more predictable; here, increasing the target distance from 50 to 100 cm resulted in either no change or a further slight increase in lead (Fig. 1B, right panel). The latter results are also comparable with those of Rosenfield and Carrel (2001), who found increasing leads with increasing near adds, for a fixed testing distance.

Observed differences between the BF and SVN lens results could reflect differences in the optical designs of the lenses and thus differences in optical aberrations so introduced. While spherical soft contact lenses are expected to add small amounts of positive spherical aberration (SA), the BF would likely have added much more positive SA due to the more positive power in the near ring surrounding the central distance zone. If accommodation optimizes retinal image quality, then these altered ocular aberrations can be expected to alter accommodation responses. This prediction also is consistent with demonstrations from several visual performance studies that specific combinations of positive Zernike SA and positive Zernike defocus (myopic defocus) produce images that appear less subjectively blurred than the same amounts of either defocus or SA alone (Applegate *et al.*, 2003, Cheng *et al.*, 2004b, Chen *et al.*, 2005). This interaction between Zernike defocus and SA is illustrated in Figure 2-3, which shows the wave aberrations over a 5 mm pupil for 0.4 μm rms Zernike defocus and 0.15 μm rms Zernike SA, alone and combined, and simulations of their effects on the retinal image of a 20/50 Snellen E. Note that the individual wave aberration patterns are similar in shape over the central region of the pupil but opposite in sign; thus they interact to produce a flatter wave aberration and consequently,

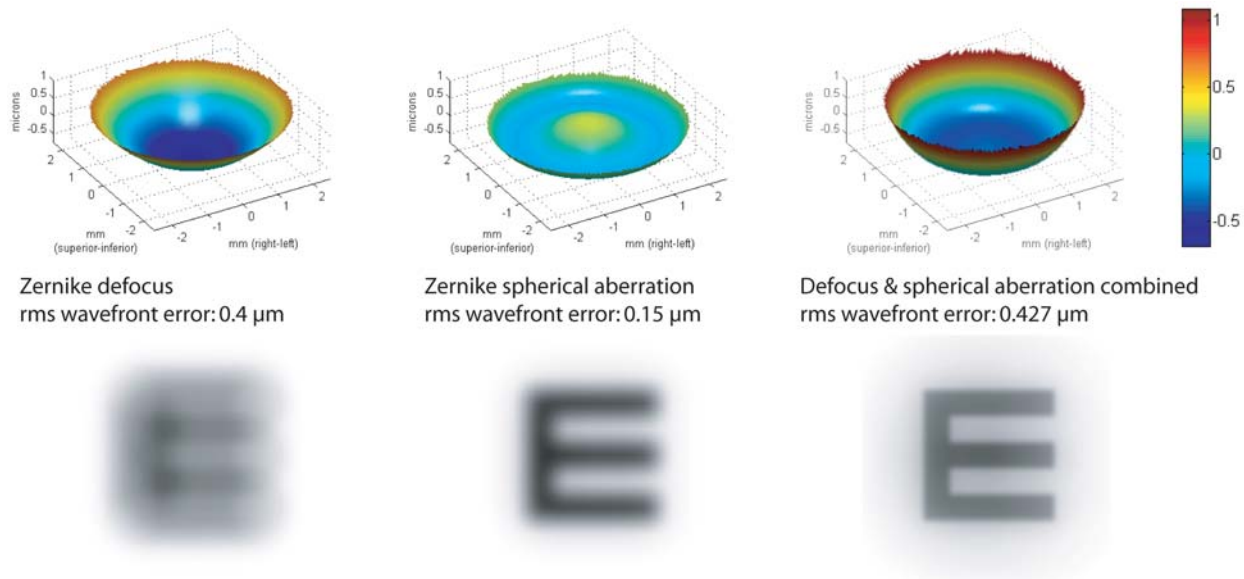


Figure 2-3. Ocular wave aberrations calculated over a 5 mm pupil for 0.4 μm of Zernike defocus, 0.15 μm of Zernike spherical aberration and the two combined, and simulated retinal images of a 20/50 Snellen E, for each of the three conditions.

a less blurred retinal image, even though the combined rms (0.427 μm) is larger than either individual term.

Could so-called leads and lags of accommodation simply reflect the amount of defocus required to provide the clearest retinal image in the presence of SA? To test this “aberration hypothesis”, we executed 2 simulations that made use of information about changes in SA with accommodation and estimated BF lens-induced changes in ocular SA.

Our first simulation made use of data from an accommodation study of young adults in which it is reported that SA shifts from being positive, when accommodation is relaxed, in the negative direction, increasingly so with increasing accommodation (Cheng *et al.*, 2004a). In this study, the average value of Zernike spherical aberration was around -0.15 μm for an accommodative demand of 3 - 4 D and a 5 mm pupil diameter. For this demand, accommodation typically lags, by approximately 0.5 to 0.6 D, based on the results from the current study. Thus increasing amounts of negative Zernike defocus, i.e. lags of accommodation, were combined with -0.15 μm of SA in our simulation. Figure 2-4 shows the calculated ocular wave aberrations over a 5 mm pupil and the resultant retinal images of a 20/50 Snellen E. When considering the interaction between Zernike defocus and SA alone, the clearest image was obtained with a residual defocus (lag) of around -0.3 to -0.4 D. From this, albeit simplistic simulation, it is apparent that a lag of accommodation can serve to reduce retinal image blur in the presence of negative SA, as seen in accommodating eyes. Furthermore, the report of more negative SA in accommodating myopic compared to emmetropic eyes (Collins *et al.*, 1995), should translate into a difference in the optimal lag of accommodation for these 2 refractive groups, as observed.

In our second simulation, the SA of the BF contact lens was taken into account. It was not possible to measure the aberrations of the BF contact lens used in the current study because of the discontinuities in optical power inherent in its design. Instead, an estimate of the SA

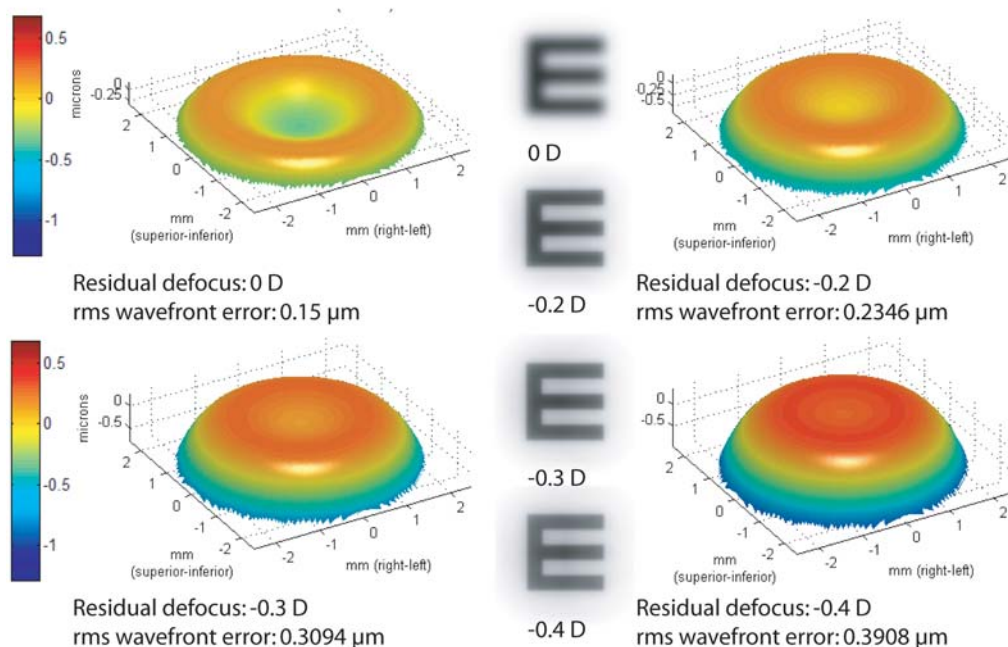


Figure 2-4. Ocular wave aberrations (μm) calculated over a 5 mm pupil for an accommodating eye with -0.15 μm of Zernike spherical aberration (Cheng *et al.*, 2004a) and a range of negative Zernike defocus. Simulated retinal images of a 20/50 Snellen E shown for the same conditions.

induced by this BF lens was obtained by measuring induced changes in ocular SA for another multifocal contact lens of similar design but without discontinuities. For this simulation, +0.45 μm of SA was attributed to the BF contact lens and combined with the same amount of ocular SA used in the first simulation, with a net result of +0.3 μm SA. Figure 2-5 shows the calculated ocular wave aberrations over a 5 mm pupil for this eye (with +0.3 μm of SA), and increasing positive Zernike defocus. For each of six defocus conditions tested, the resultant retinal image of a 20/50 Snellen E is also shown. For these conditions, the clearest image was obtained with a residual Zernike defocus of around 0.6 to 0.8 D, corresponding to a lead of accommodation. Together, these simulations offer further support for accommodative errors, in the latter case, an accommodative lead, being the product of a blur-driven controller; they also predict refractive error-related differences, as observed.

Which, if any of the above explanations for the accommodative data collected with the BF lenses, would predict a slowing of myopia progression, as reported in preliminary clinical tests of the same (Aller, 2000, Aller and Grisham, 2000, Aller and Wildsoet, 2006, Aller and Wildsoet, 2007). The leads of accommodation, such as observed with the BF lenses, could underlie their beneficial effects on myopia progression, given the reports of slowed eye growth with imposed myopic defocus in animal studies (Wildsoet, 1997, Wallman and Winawer, 2004). Animal studies also have established a link between poor retinal image quality and abnormal eye growth. Thus, if the result of interactions between BF lens-induced changes in ocular SA and changes in accommodative errors is a net improvement in retinal image quality, then slowed eye growth also would be predicted. On-going investigations using multifocal lenses in animal studies may provide insight into the mechanism underlying the anti-myopia effect of BF contact lenses.

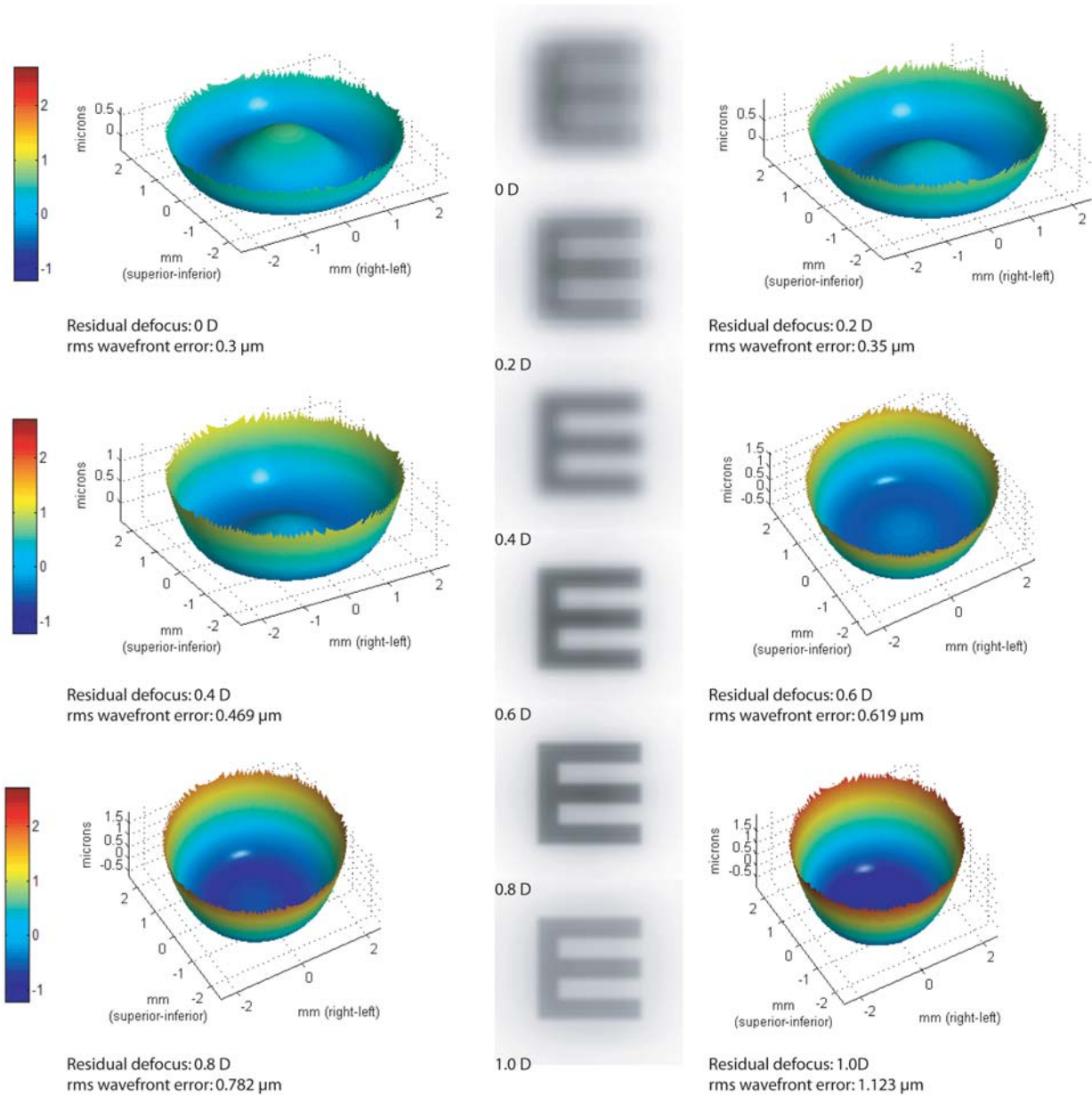


Figure 2-5. Ocular wave aberrations (μm) calculated over a 5 mm pupil for an accommodating eye with 0.3 μm of Zernike spherical aberration, to simulate the effect of a bifocal contact lens, and a range of positive Zernike defocus. Simulated retinal images of a 20/50 Snellen E shown for the same conditions.

2.5 Conclusions

In conclusion, in the presence of distance corrective lenses, young adult subjects show lags of accommodation, myopes recording larger lags than emmetropes. Near additions can reduce accommodative lags and even convert lags to leads. The BF contact lenses used in the current study appear to induce leads of accommodation for both myopes and emmetropes, smaller for the former group. Further research is needed to understand the exact nature and cause of this effect of the BF lenses, and so guide further refinements of this potential myopia control treatment.

Chapter 3

Determining the Accommodative Response from Wavefront Aberrations

Abstract

The purpose of this study was to evaluate some of the methods used to calculate objective refractions from wavefront aberrations, to determine their applicability for accommodation research. A wavefront analyzer was used to measure the ocular aberrations of 13 emmetropes and 17 myopes at distance, and 4 near target vergences: 2, 3, 4 and 5 D. The accommodative response was calculated using the following techniques: least squares fitting (Zernike defocus), paraxial curvature matching (Seidel defocus), and 5 optical quality metrics (PFWc, PFSc, PFCc, NS, and VSMTF). We also evaluated a task-specific method of determining optimum focus that used a through-focus procedure to select the image which best optimized both contrast amplitude and gradient (CAG). Neither Zernike nor Seidel defocus appear to be the best method for determining the accommodative response from wavefront aberrations. When the eye has negative spherical aberration, Zernike defocus tends to underestimate, whereas Seidel defocus tends to overestimate the accommodative response. A better approach is to first determine the best image plane using a suitable optical quality metric, and then calculate the accommodative error relative to this plane. Of the metrics evaluated, both NS and VSMTF were reasonable choices, with the CAG algorithm being a less preferred alternate.

3.1 Introduction

An extensive amount of research has been undertaken to determine the best method for calculating the ocular refractive error from wave aberration measurements. The gold standard for these techniques has been to find agreement with, or improve upon, in terms of accuracy and precision, the results from a subjective refraction. Curiously, an equivalent effort has not been expended on developing methods for determining the accommodative response from wavefront aberrations; instead it has been assumed that methods for calculating refractive error are also applicable to accommodation. Below we first review the methods proven successful in calculating objective refractions, as well as their limitations. Then we discuss their usage in and suitability for accommodation studies.

Initial attempts at predicting refractive errors used the Zernike coefficients from measured second order aberrations expressed in power vector notation (Thibos *et al.*, 2002). Despite the fact that subjects wore prescription lenses that optimized their visual acuity during the measurements, residual defocus was evident in many of their aberration maps. This finding suggested that the method for judging best focus during a subjective refraction was not based on the criterion of minimizing the wavefront variance over the entire uniformly weighted pupil. Furthermore, the Zernike coefficients for this residual defocus varied systematically with the Zernike coefficients for spherical aberration in a way that maximized visual acuity. From these results, it was inferred that the subjective best focus occurred when the wavefront error was minimized over the largest possible area of the central pupil.

A number of alternative methods that take into account the effect of the eye's high order aberrations (HOA) have since been proposed to estimate refractive errors. Guirao and Williams (2003) calculated the combination of sphere and cylinder that optimized different image quality metrics. One class of metrics was based on the wave aberration defined in the pupil plane and another was based on the retinal image plane. The pupil plane metrics minimized either the wave aberration root mean square (RMS) or the sum of all the spherical and cylindrical components. Both pupil plane metrics predicted subjective refraction poorly, with large errors in spherical equivalent refractive error. The retinal image plane metrics optimized one of the following: the Strehl intensity ratio, the entropy and intensity variance of the point spread function (PSF), the volume under the modulation transfer function (MTF), or the volume under the contrast sensitivity function. All performed better than the pupil plane metrics, the differences between predicted and subjective refractions being considerably smaller.

Research into the effects of aberrations on visual performance has found important application in the development of methods for determining objective refractions from wavefront aberrations. Applegate *et al.* (2003) showed that certain Zernike terms, for example spherical aberration and defocus, can interact to improve acuity despite an increase in total wavefront error. When combined in the correct proportions spherical aberration and defocus decrease the wavefront error over the center of the pupil. In agreement with previous research (Thibos *et al.*, 2002), better visual acuity is attained when the wave aberration is reasonably flat over a greater region in the pupil center.

Marsack *et al.* (2004) investigated the interaction of wave aberrations in terms of the correlation of 31 metrics of optical quality to high contrast visual acuity. The metrics were classified into 2 main types, pupil plane metrics, defined by qualities of the shape of the wave aberrations, and image plane metrics, based on either the PSF or the optical transfer function

(OTF), with some of the latter including a neural weighting component. They identified 6 metrics that could account for 70% or more of the variance in visual acuity.

In a related study, Cheng et al. (2004b) used the same 31 metrics of image quality to evaluate the impact of HOA on subjective refractions. To determine which metrics best predicted the subjective refraction, defocus and astigmatism levels that optimized each metric were compared with the corresponding metric values that produced the best visual acuity for degraded retinal images. They found that subjective judgment of best focus does not minimize the RMS wavefront error nor create paraxial focus, but makes the retina conjugate to a plane between these two.

Chen et al. (2005) used an adaptive optics system to manipulate the aberrations of the eye, by way of investigating the ability of different image quality metrics to predict measured subjective image quality. Their results confirmed that some Zernike modes, such as spherical aberration and defocus, interact strongly in determining subjective image quality. Their neural sharpness metric, which captures the effectiveness of a PSF in stimulating the neural portion of the visual system, best described subjective image sharpness.

In a comprehensive study of the ability of optical quality metrics to predict subjective refractions, all 31 metrics (Marsack et al., 2004) were evaluated using a large population of 200 eyes (Thibos *et al.*, 2004). These metrics were compared with 2 surface fitting methods, least squares fitting (Zernike defocus) and paraxial curvature matching (Seidel defocus), designed to find the nearest sphero-cylindrical approximation to the wave aberration map. Five of the optical quality metrics were classified as reasonably accurate and among the most precise; 3 were based on pupil plane metrics and 2 on image plane metrics. Zernike defocus proved to be one of the least accurate methods for determining the spherical equivalent refractive error. Seidel defocus was the most accurate, although it was significantly less precise than some of the optical quality metrics. It was suggested that Zernike and Seidel defocus appear to locate the two ends of the eye's depth-of-focus (DOF), consequently the optimum focus should lie somewhere between these limits.

One problem with utilizing optical quality metrics to calculate objective refractions in a clinical setting is that they are computationally expensive, requiring an iterative process to find the optimal result. To address this issue, Iskander et al. (2007) proposed the use of refractive and curvature Zernike power polynomials, which represent the wave aberration in terms of dioptric power calculated from closed-form expressions derived from the Zernike wavefront coefficients. The refractive Zernike power polynomials are based on an estimated focal length, and the curvature Zernike power polynomials, on an estimated wavefront curvature. These 2 methods were compared with the more familiar least squares and paraxial curvature matching techniques, which are also pupil plane measures with closed-form solutions. Of these 4 methods, the refractive Zernike power polynomials yielded the best correlation between the objective and subjective sphero-cylindrical refraction. This method also achieved a marginally better correlation with subjective refraction compared to the performance of a number of image plane metrics that took into account pupil apodization and neural weighting (Iskander *et al.*, 2008).

Understanding the influences of ocular aberrations on accommodative responses and subjective refraction represents similar problems although the former has received far less research attention. That aberrations change with accommodation is a complicating variable. For example, in a large study of young adults by Cheng et al. (2004a), the wave aberrations were found to vary with accommodation, with Zernike spherical aberration showing the greatest

change, always in the negative direction and in proportion to the change in the accommodative response.

Of direct relevance to the current study, Hazel et al. (2003) investigated the relationship between accommodative accuracy and aberrations using an autorefractor to measure accommodation and a wavefront sensor to measure aberrations. The wavefront sensor data were used to determine the paraxial sphero-cylindrical correction, the sphero-cylindrical correction required to minimize the variance of the HOA and the total sphero-cylindrical correction (paraxial + spherical aberration) for natural and 2.9 mm pupil sizes. For both emmetropic and myopic subjects, the paraxial sphero-cylindrical correction underestimated the accommodative error. The total sphero-cylindrical correction overestimated the accommodative error for both refractive error groups compared with autorefractor readings when calculated with natural pupil sizes, and underestimated it for the 2.9 mm pupil diameter. The authors attributed the discrepancies in accommodative errors measured with an autorefractor versus a wavefront sensor to the influence of HOA.

In another relevant study, Plainis et al. (2005) examined the correlation between accommodative errors and changes in ocular aberrations and retinal image quality during accommodation. Accommodative responses were calculated from the measured wavefront using 2 techniques: the equivalent quadratic of the wave aberration map using paraxial curvature matching, and the power of a focusing lens needed to optimize retinal image quality as quantified by a weighted MTF metric. They found that spherical aberration was the main HOA that contributes to image quality changes during accommodation. Furthermore, with spherical aberration shifting from positive to negative values with increasing accommodation, the one-to-one stimulus-response relationship should not be considered ideal, instead a lag for near targets and a lead for far targets would be predicted.

In a later study, Buehren and Collins (2006) also found an association between accommodative error and spherical aberration under natural pupil conditions. The accommodative response was calculated from the Zernike defocus term for both 3 mm and natural pupil sizes and retinal image quality was quantified using the visual Strehl ratio of the OTF (VSOTF) (Cheng *et al.*, 2004b, Thibos *et al.*, 2004). Because of the good correlation between the location of the peak of the VSOTF and accommodative errors, they concluded that these “errors” serve to optimize retinal image quality.

It is interesting that while the latter two studies (Buehren and Collins, 2006, Plainis *et al.*, 2005) use completely different methods to calculate accommodative responses (Zernike defocus and paraxial curvature matching respectively), both arrive at the same conclusion, that spherical aberration significantly influences accommodative errors. Which of these methods is the more appropriate for determining accommodative errors? Or is neither? The purpose of the current study was to evaluate some of the optical quality metrics (OQM) that have proven successful in determining objective refractions from wave aberrations, to determine their ability to calculate the accommodative response. We also propose an alternate method that may be better suited to quantifying the mechanism of selecting optimum focus utilized by the accommodation system.

3.2 Methods

3.2.1 Subjects

Thirty young adult subjects (mean age: 23.5 ± 2.9 years, range: 19 to 31 years) participated in the study; 13 were emmetropic (mean spherical equivalent refractive error (S_E): 0.21 ± 0.20 D, range: plano to +0.50 D) and 17 were myopic (mean S_E : -3.47 ± 1.47 D, range: -1.25 to -5.75 D). Astigmatism was limited to ≤ 1.00 D, and anisometropia to < 2.00 D. All subjects had normal corrected visual acuity (20/20 or better) and no binocular vision anomalies. Prior to data collection, binocular accommodative amplitudes and facility were assessed to be within normal parameters based on age.

The study protocol conformed to the provisions of the Declaration of Helsinki and was approved by the University of California, Berkeley institutional review board. Informed consent was obtained from the participants after the nature and possible complications of the study were explained in writing.

3.2.1 Data Collection

A COAS wavefront analyzer (Abbott Medical Optics, Albuquerque, NM) was used to measure ocular aberrations at distance and 4 near target vergences: 2, 3, 4 and 5 D. Measurements were made of the dominant eye under monocular viewing conditions. All subjects wore single vision soft contact lenses to correct their ametropia. To control for any effect of the contact lenses on aberration measurements the emmetropes were also fitted with contact lenses; those with plano prescriptions wore +0.25 D lenses as their distance prescription.

The near target was an external letter chart, viewed monocularly through a beam splitter, and positioned at the appropriate distance for each target vergence. It consisted of 4 lines, each made up of 5 high contrast letters, and decreasing in size, such that at each of the 4 near viewing distances, one line had an angular subtense of 12.5 minutes of arc. Subjects were instructed to look at the middle letter of the appropriate line of letters and to keep the letters as clear as possible. For each test condition, 20 data sets were obtained from approximately 2 seconds of continuous recordings. Measurements were taken in the dark, with a small LED providing the illumination for the near target.

3.2.3 Data Analysis

The wavefront data were exported as the Zernike coefficients, up to sixth order, calculated for a wavelength of 550 nm and natural pupil sizes. Accommodative responses for each target vergence were calculated using 3 methods adapted from those used in determining objective refractions (Thibos et al., 2004), and another method developed specifically for this project. Two of these methods are closed-form solutions (least-squares fitting and paraxial curvature matching) and the other two are iterative procedures.

The refractive state of the eye can be calculated directly from the measured wavefront using either of the closed- form solutions. For an accommodating eye the refractive state determined by these 2 metrics provides a measure of the accommodative response.

The wave aberration is the difference between the measured wavefront and the reference wavefront for the target vergence. For example, for the distance target the reference wavefront is a plane wave and for the near targets it is a spherical wavefront with a radius of curvature equal to the target distance. The accommodative error is the difference between the accommodative response and the stimulus vergence. Therefore because the accommodative response is

determined from the measured wavefront, the wave aberration provides a measure of the accommodative error.

The accommodative error can be calculated directly from the wave aberration using either of the closed-form solutions, or it can be derived from the accommodative response determined by these 2 metrics by calculating the difference between the response and the stimulus vergence. The accommodative error can also be calculated from the wave aberration using the through-focus procedure described below, and the accommodative response can then be derived from the accommodative error.

3.2.3.1 Least squares fitting (Zernike defocus)

This is a surface fitting procedure designed to find the quadratic surface that best fits the wave aberration map by minimizing the sum of squared deviations between the two surfaces. It is given by the second order Zernike coefficients and minimizes the RMS of the wave aberration:

$$M = \frac{c_2^0 4\sqrt{3}}{r^2} \quad (3-1)$$

where c_2^0 is the second order Zernike coefficient for defocus and r is the pupil radius.

3.2.3.2 Paraxial curvature matching (Seidel defocus)

This is another surface fitting procedure that matches the curvature of two surfaces at the pupil center. It is given by the Zernike expansion of the Seidel formula for defocus (truncated here at the fourth order):

$$M = \frac{c_2^0 4\sqrt{3} - c_4^0 12\sqrt{5}}{r^2} \quad (3-2)$$

where c_2^0 is the second order Zernike coefficient for defocus, c_4^0 is the fourth order Zernike coefficient for spherical aberration and r is the pupil radius.

3.2.3.3 Maximizing optical or visual quality

This procedure mathematically adds or subtracts specific amounts of a spherical wavefront (Zernike defocus) to the measured aberration map, which includes all aberrations from 2nd to 6th order. Using a suitable metric of optical quality (OQM), the optimum power M needed to maximize optical quality for the accommodating eye was determined. The OQM we evaluated were 5 identified as reasonably accurate and among the most precise: PFWc, PFSc, PFCc, NS and VSMTF (Thibos et al., 2004).

Brief descriptions of these OQMs are given in Table 3-1. The first 3 metrics quantify optical quality based on wavefront quality, in terms of the flatness of the aberration map, measured by RMS error, slope or curvature. The last 2 metrics quantify the visual effectiveness of the retinal image, taking into account the Stiles-Crawford effect. NS uses retinal image quality for point objects, weighting the PSF with a spatial sensitivity function that represents the neural visual system. VSMTF uses retinal image quality for grating objects, weighting the MTF by the neural contrast sensitivity function (CSF). Programs for computing the metrics were written in Matlab (The Mathworks, Inc.) and verified using known examples.

Table 3-1. Acronyms and descriptions for the optical quality metrics.

Acronym	Description
PFWc	Pupil fraction for wavefront when critical pupil is defined as the concentric area for $RMS_w < \text{criterion } (\lambda/4)$
PFSc	Pupil fraction for slope when critical pupil is defined as the concentric area for $RMS_s < \text{criterion } (1 \text{ arc min})$
PFCc	Pupil fraction for curvature when critical pupil is defined as the concentric area for $B_{ave} < \text{criterion } (0.25 \text{ D})$
NS	Neural sharpness
VSMTF	Visual Strehl ratio for MTF

The wave aberration was calculated, then for each metric the through-focus analysis determined the amount of additional defocus required to maximize the metric over a nominal range of -0.5 to $+0.6$ D. This was accomplished by mathematically adding a spherical wavefront to the measured aberration map in 0.1 D increments, then computing the PSF, MTF, retinal image and the corresponding OQM. The defocus level with the maximum metric value was defined as the plane of best focus and the accommodative error was defined as the additional defocus required to optimize the metric. An example of the through-focus analysis is shown in Figure 3-1 for one of our myopic subjects and the 5 D target vergence.

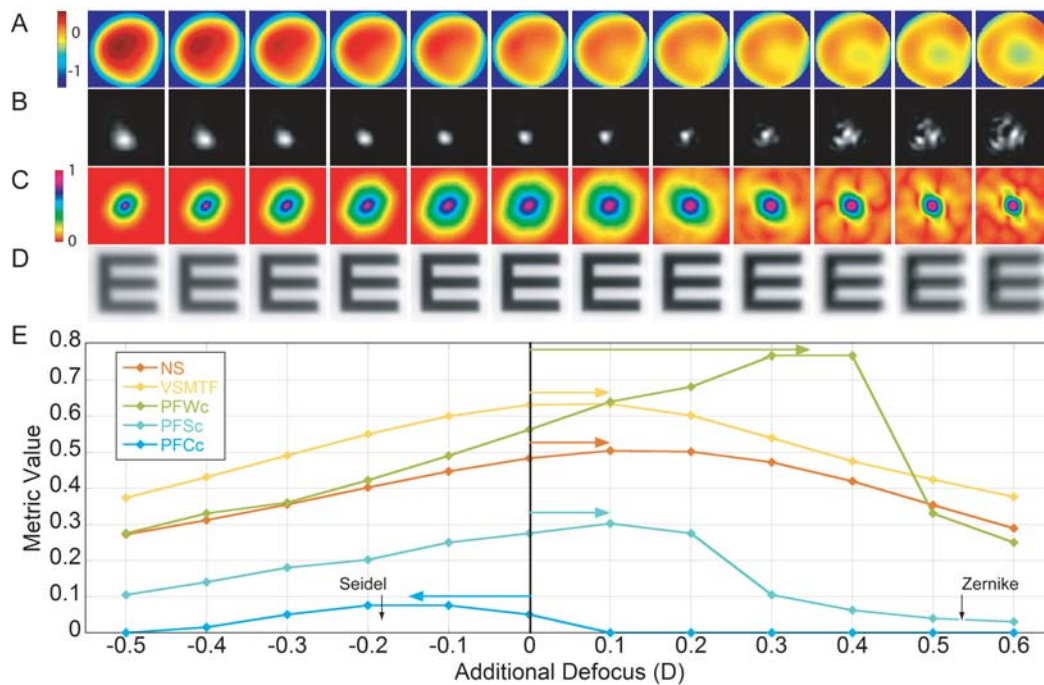


Figure 3-1. An example of the results from the through-focus analysis for a myopic subject and the 5 D target vergence. The image sequences are calculations of: (A) the wave aberration contour map, (B) the PSF, (C) the MTF, (D) the retinal image of a 20/50 Snellen letter, and (E) the OQM values, adding defocus incrementally to the measured wave aberration. Colored arrows show the accommodative error determined by each metric. Metrics that peak to the right of the zero line indicate that additional defocus was needed to optimize image quality, corresponding to a lag of accommodation. Metrics that peak to the left of the zero line indicate a lead of accommodation. The black arrows show the accommodative errors calculated for Seidel and Zernike defocus.

Data analyses with the pupil fraction metrics proved to be problematic in that, for some subjects and stimuli the location of the best image plane was not well defined and the metric did not converge to an optimum value, i.e. all 12 defocus values in the through-focus sequence resulted in the same value for the OQM. This problem was attributed to residual aberrations, such as astigmatism and spherical aberration, limiting the area over the center of the pupil where the wave aberration was sufficiently flat to meet the criterion specified for each metric. The PFSc metric proved to be the most robust of the 3 pupil fraction metrics and was considered a reasonable metric to use for calculating accommodative responses. The failure rate for the PFCc metric was very high, reaching 67% for the 4 D test condition and thus the results for this metric were not further analyzed. The performance of the PFWc metric, while better than that of the PFCc metric, was much poorer than that of the PFSc metric. Its results are presented later for interest; however other metrics are considered better choices.

3.2.3.4 Contrast amplitude and gradient (CAG)

Because of the problems with the pupil fraction metrics just outlined a new approach was developed based on the mechanism that the accommodative system appears to use to determine the appropriate response. This method takes into account studies of accommodation showing that the accommodative system optimizes contrast amplitude and gradient (Ciuffreda, 1999). The same sequence of 12 simulated retinal images, including an apodization function to take into account the Stiles-Crawford effect (Burns *et al.*, 1995), was used to implement an algorithm that selected the image that best optimized both contrast amplitude and gradient. In addition retinal images for a rotated E (90° counter clockwise) were computed to more easily account for the biased effect of any residual astigmatism on image quality.

The intensity profile of the pixels from either the vertical or horizontal midline (vertical for the upright E and horizontal for the rotated E) of each image was used to quantify the contrast amplitude and gradient for that defocus level. A value of 0 corresponded to a black pixel and 1 corresponded to a white pixel. The location and values of the 2 maxima (2 white spaces between the “arms” of the E) and 3 minima (the 3 “arms” of the E) were found. A measure to quantify the contrast amplitude was calculated as the average of the difference between the values of the adjacent maxima and minima. A parabolic function was fitted to the location of the 3 minima and the RMS error for each was calculated to quantify the contrast gradient.

The 6 images with the highest values for contrast amplitude for the sequence of upright “E”s and the 6 highest for the rotated “E”s were identified. Only the images that were common to both sets of 6 were used in the next step. For this set of images the 3 images with the highest values for contrast gradient (i.e. lowest error to the fitted function) for both the upright and rotated E were selected. Two different methods were used to determine the “best” image from this subset. The first method gave each image a score of 10, 5, or 3, ranked from lowest error (best) to highest error (worst). The 2 scores for the upright and rotated E were summed, with the best image having the highest score. The second method simply ranked the sum of the fitted errors for the upright and rotated E, the best image having the lowest error sum.

This procedure for the upright E is depicted in Figure 3-2 for the same data shown in Figure 3-1. For both the upright and rotated E, images 5 to 10 had the highest contrast amplitude. Of these, the 3 images with the “best” contrast gradients were 5 to 7 for the upright E, and 6 to 8 for the rotated E. Thus, image 7 scored 20, image 6 scored 8, image 8 scored 5, and image 5 scored 3, indicating that image 7 was the best for the first method (CAG1). The lowest combined

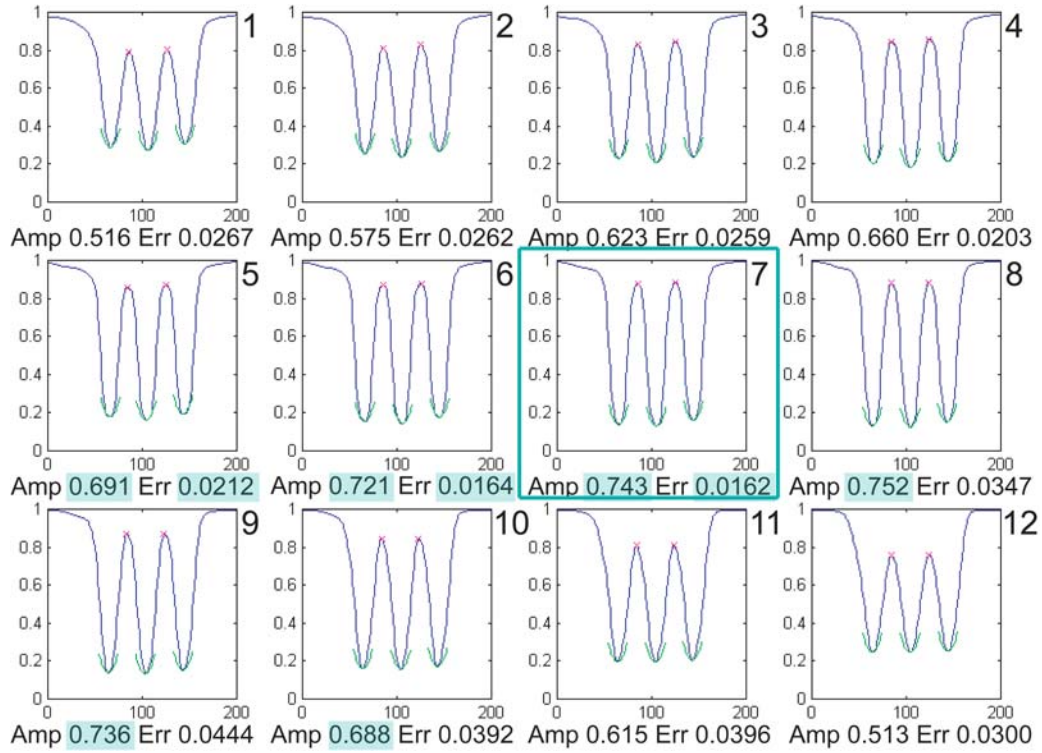


Figure 3-2. An example of the sequence of 12 intensity profiles for the upright E, used by the CAG algorithm. The green arcs show the parabolic functions fitted to the location of the 3 minima. The 6 images with the highest values for contrast amplitude (highlighted in green) were #5 to #10. The 3 images with the lowest RMS errors for the fitted parabola (highlighted in green), corresponding to the highest contrast gradients, were #5 to #7. Image 7 was chosen by the algorithm to best optimize both contrast amplitude and gradient (framed in green).

error was also for image 7, identifying it as the best for the second method (CAG2).

3.2.3.5 Other aberrations

Astigmatism values were converted to diopters, using power vector notation, to allow comparisons of measurements made with different natural pupil sizes (Thibos *et al.*, 1997):

$$J_0 = \frac{c_2^2 2\sqrt{6}}{r^2} \quad (3-3)$$

$$J_{45} = \frac{c_2^{-2} 2\sqrt{6}}{r^2} \quad (3-4)$$

where c_2^2 and c_2^{-2} are the second order Zernike coefficients for astigmatism and r is the pupil radius.

Coma was converted to diopters using the equation for equivalent defocus (Thibos *et al.*, 2002):

$$M_e = \frac{4\sqrt{3}RMSerror}{r^2} \quad (3-5)$$

where the RMS error is measured in microns and the pupil radius is in mm.

3.2.3.6 Excluded data

In subsequent analyses, 4 data sets were excluded: subject 6 (myope) at 2 D, subject 7 (emmetrope) at 2 D, and subject 14 (myope) at 4 and 5 D. In these cases, it was evident from the very reduced accommodative responses that the subjects were inattentive during the measurements. All excluded values were flagged as outliers in the statistical analysis.

3.3 Results

For both refractive error groups, there were leads of accommodation at distance for all metrics (Figure 3-3). For the emmetropes there were lags of accommodation at all near targets for all metrics. For the myopes, however, there were lags of accommodation at all near targets only for Zernike defocus. With the OQMs, the myopes exhibited leads of accommodation for the 2 and 3 D targets, shifting to lags for the 4 and 5 D targets. While with Seidel defocus either no accommodative errors or small leads were seen at all near targets.

For both emmetropes and myopes, the dioptric separation in the accommodative responses calculated by the different metrics for each stimulus vergence appeared to be related to the level of spherical aberration. The spherical aberration shifted from positive to negative for the emmetropes between the 2 and 3 D stimuli (Figure 3-4), which corresponded to the smallest spread in the calculated accommodative responses for the different metrics (Figure 3-3). For the myopes, spherical aberration was closest to zero with the distance target (Figure 3-4), which also corresponded to the smallest spread in calculated accommodative responses for the different metrics (Figure 3-3).

For each refractive error group, a one-way repeated-measures ANOVA was used to compare the differences between the accommodative responses calculated by each metric, for each stimulus level. For the emmetropes at the distance test condition, there was a significant difference in accommodative responses ($p < 0.001$) across metrics. An all-paired comparisons

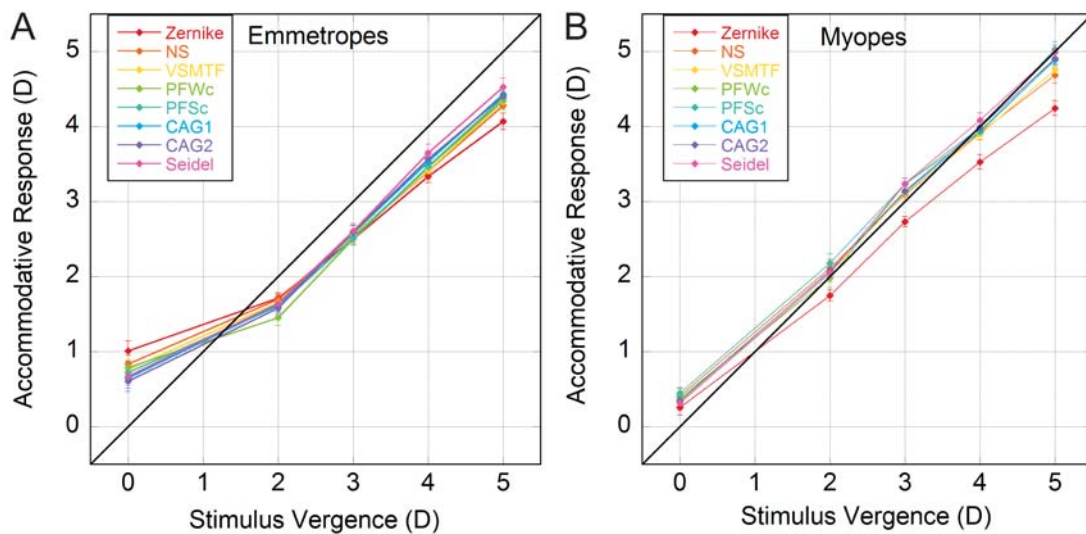


Figure 3-3. Accommodative responses calculated by each metric, for emmetropes (A) and myopes (B). Error bars are \pm SEM.

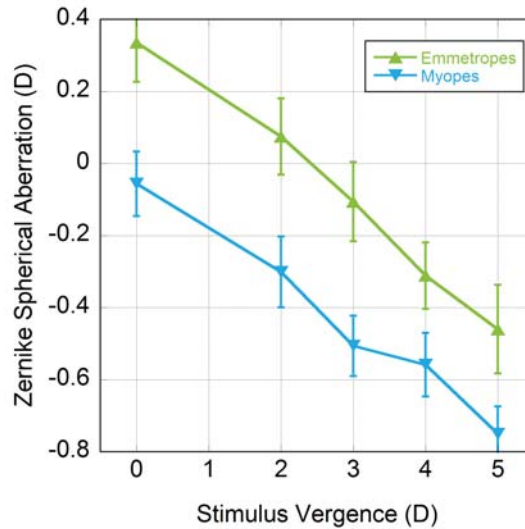


Figure 3-4. Zernike spherical aberration as a function of stimulus vergence for emmetropes and myopes. Differences between refractive error groups were significant ($p < 0.05$) for all stimuli except the 4 D vergence. Error bars are \pm SEM.

test, using the Tukey-Kramer method ($\alpha_{FW} = 0.05$), identified the results for Zernike defocus as significantly different from the results for Seidel defocus, PFSc, CAG1 and CAG2 for the distance target. At the 2 and 3 D stimuli, there were no significant differences in the values calculated by the different metrics. With the 4 and 5 D stimuli, there were significant differences in accommodative responses ($p < 0.001$) across metrics. The all-paired comparisons for the 4 D stimulus found the results for Zernike defocus to be significantly different to the results for Seidel defocus and CAG2, and the results for Seidel defocus also significantly different to the results for NS and VSMTF. The all-paired comparisons for the 5 D stimulus found the results for Zernike defocus to be significantly different to the results for Seidel defocus, PFSc, CAG1 and CAG2.

For the myopes at the distance test condition, there was no significant difference in the values calculated by the different metrics. With all near targets, there was a significant difference in accommodative responses ($p < 0.001$) across metrics. The all paired comparisons, for all near vergences, found the results for Zernike defocus to be significantly different to the results for all other metrics. For the 5 D stimulus, there were also significant differences between the results for NS and the results for both Seidel defocus and PFSc, and between the results for VSMTF and the results for PFSc.

In comparing the difference in accommodative responses between emmetropes and myopes, only the metrics at the two extremes, Zernike and Seidel defocus, were considered. Student's t-tests were used to compare the results for the two groups. For Zernike defocus, myopes had marginally higher accommodative responses than emmetropes, being significantly different only for the 3 D stimulus ($p < 0.05$). For Seidel defocus, myopes again recorded higher accommodative responses; here the differences reached statistical significance for all vergences ($p < 0.05$).

To better illustrate the differences between metrics, accommodative error is plotted in Figure 3-5. The sign convention adopted shows leads of accommodation as positive values and

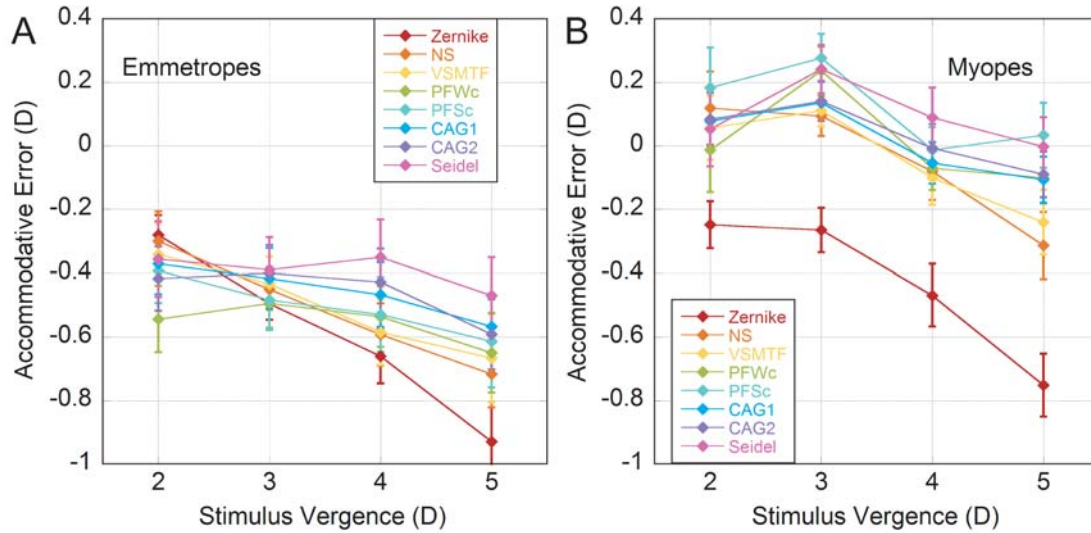


Figure 3-5. Accommodative errors determined by each metric, plotted as a function of stimulus vergence for emmetropes (A) and myopes (B). Leads of accommodation are positive and lags are negative. Error bars are \pm SEM.

lags of accommodation as negative values. When ocular spherical aberration is negative, Seidel and Zernike defocus appear to define the limits of the range of the accommodative error, with Seidel defocus always being higher by an amount equal to the magnitude of the spherical aberration in diopters (Equation 3-2). For both emmetropes and myopes, the trends for the accommodative errors calculated using the OQMs show NS and VSMTF nearer to Zernike defocus, CAG closer to Seidel defocus, with the pupil fraction metrics somewhere in the middle.

Linear regression analyses of the data shown in Figure 3-5, with accommodative error as the dependent variable and stimulus vergence as the independent variable, found the slopes to be significant for Zernike defocus, NS and VSMTF, for both emmetropes and myopes. The slopes for CAG1 and CAG2 were also significant for the myopes. The flattest slope was observed for Seidel defocus for both refractive error groups. These data are summarized in Table 3-2, along with related correlation values.

Table 3-2. Results of linear regression analyses for each metric, with accommodative error as the dependent variable and stimulus vergence as the independent variable. † indicates slopes that are non-zero ($p < 0.05$).

Metric	Slope		Correlation	
	Emmetropes	Myopes	Emmetropes	Myopes
Zernike	-0.211 [†]	-0.171 [†]	-0.657	-0.495
NS	-0.139 [†]	-0.147 [†]	-0.445	-0.406
VSMTF	-0.113 [†]	-0.110 [†]	-0.327	-0.341
PFWc	-0.038	-0.065	-0.135	-0.212
PFSc	-0.071	-0.076	-0.205	-0.218
CAG1	-0.064	-0.074 [†]	-0.208	-0.277
CAG2	-0.055	-0.067 [†]	-0.174	-0.250
Seidel	-0.030	-0.032	-0.085	-0.092

The change in astigmatism and coma with accommodation was examined using Student's t-test. For both emmetropes and myopes, J_{45} , vertical coma and horizontal coma were not significantly different from zero for any stimulus condition. This was also the case for J_0 for the emmetropes, except for the 2 D stimulus, where the average astigmatism increased slightly to 0.12 ± 0.03 D ($p < 0.005$). The myopes showed significant amounts of negative astigmatism (J_0) for all stimulus vergences, ranging from -0.14 ± 0.06 D to -0.21 ± 0.12 D ($p < 0.05$). This was not unexpected as the inclusion criterion for astigmatism allowed up to 1 D, which was not corrected by the spherical soft contact lenses.

In comparing the emmetropes with the myopes, there was no significant difference in J_{45} and vertical coma for any stimulus vergence. For the 3 D stimulus, there was a small, statistically significant difference in horizontal coma between emmetropes and myopes (0.07 ± 0.03 D, $p < 0.05$). For J_0 there was also a small but significant difference between the two refractive error groups at all stimulus vergences ranging from 0.18 ± 0.07 to 0.31 ± 0.08 D ($p < 0.05$).

Spherical aberration was converted to diopters using the second term of Equation 3-2. Values shifted from positive for emmetropes and approximately zero for myopes at distance, to negative for both groups with increasing levels of accommodation (Figure 3-4). There was a significant difference in spherical aberration between emmetropes and myopes for all stimulus vergences except the 4 D stimulus ($p < 0.05$), with the myopes recording more negative values in all cases.

The myopes tended to have smaller pupil sizes than the emmetropes, by approximately 0.5 mm (Figure 3-6). These differences were significant ($p < 0.05$) for the 2 and 3 D stimuli only.

The neural sharpness (NS) metric was used to estimate the depth-of-focus (DOF) from values calculated using the through-focus algorithm described in the methods over a range of ± 1 D from the peak, in 0.1 D increments. These data points were fitted with a spline and the DOF was defined at the 80% level of the peak (Marcos *et al.*, 1999). The results (Table 3-3) indicate that the myopes had, on average, a slightly larger DOF. Student's t-test was used to compare the DOFs for the two refractive error groups, except for the 2 D stimulus where the Aspin-Welch unequal variance test was used. Differences between the two groups were significant only for the 2 D and 4 D stimuli ($p < 0.05$).

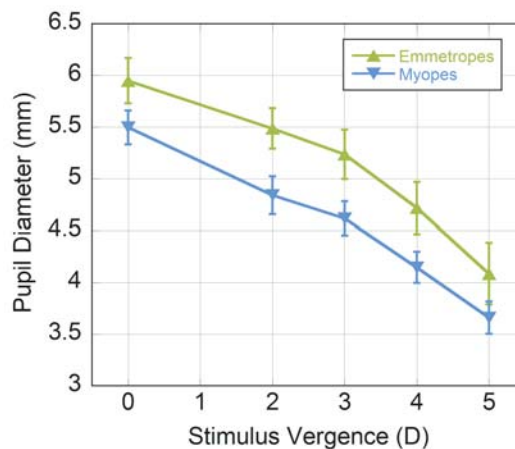


Figure 3-6. Pupil diameter plotted as a function of stimulus vergence for emmetropes and myopes. Differences between refractive error groups were significant for the 2 and 3 D stimuli only ($p < 0.05$). Error bars are \pm SEM.

Table 3-3. Depth of focus (mean \pm SEM) at each stimulus vergence for emmetropes and myopes. † indicates significant differences between the two groups ($p < 0.05$).

Stimulus Vergence (D)	Depth of Focus (D)	
	Emmetropes	Myopes
0	0.63 \pm 0.07	0.74 \pm 0.08
2	0.55 \pm 0.04	0.89 \pm 0.08†
3	0.61 \pm 0.06	0.77 \pm 0.06
4	0.56 \pm 0.05	0.76 \pm 0.05†
5	0.72 \pm 0.05	0.87 \pm 0.06

3.4 Discussion

The main goal of our study was to identify an appropriate method for determining the accommodative response from wavefront aberrations. Whilst it would be more expedient if one of the closed-form solutions, Zernike or Seidel defocus, were found to be suitable, it is not clear that either of these are the ideal method.

The accommodative responses calculated using Zernike defocus resemble data collected with an autorefractor (Tarrant *et al.*, 2008). These results are also in agreement with those of other studies using wavefront sensors to measure accommodation (Buehren and Collins, 2006, Hazel *et al.*, 2003). Identifying results that concur with optometer measurements however, is not the primary goal, as readings from these instruments may also be affected by the presence of HOA (Campbell *et al.*, 1995, Collins, 2001). This leads to the question; what does the Zernike defocus tell us about the accommodative state of the eye?

Zernike defocus is the best fit sphere to the wave aberration and represents the average level of defocus (spherical power) across the pupil. (Note: although the Zernike polynomial for defocus is a parabolic function, over the dimensions of the pupil the difference compared to a sphere is insignificant). As the Zernike polynomials are orthogonal, Zernike defocus is independent of other aberrations, such as spherical aberration, astigmatism, coma, etc., nevertheless, the retinal image quality is highly influenced by the interaction between certain aberrations.

The interaction of most interest for accommodation research is that between Zernike defocus and spherical aberration which has been examined in a number of visual performance studies (Applegate *et al.*, 2003, Chen *et al.*, 2005, Cheng *et al.*, 2004b). These studies demonstrated that specific combinations of negative spherical aberration with negative defocus (hyperopic defocus), and positive spherical aberration with positive defocus (myopic defocus) produced images that were subjectively better focused than those with the same amounts of either spherical aberration or defocus alone. The implication of these results for accommodation is that an “ideal” one-to-one response on the accommodation stimulus-response curve measured with Zernike defocus, is not ideal in terms of image quality. Instead, images will appear less blurred at distance with positive defocus to balance the positive spherical aberration present, and at near with negative defocus to balance the negative spherical aberration resulting from accommodation. Plainis *et al.* (2005), and Buehren and Collins (2006) arrived at similar conclusions in their studies.

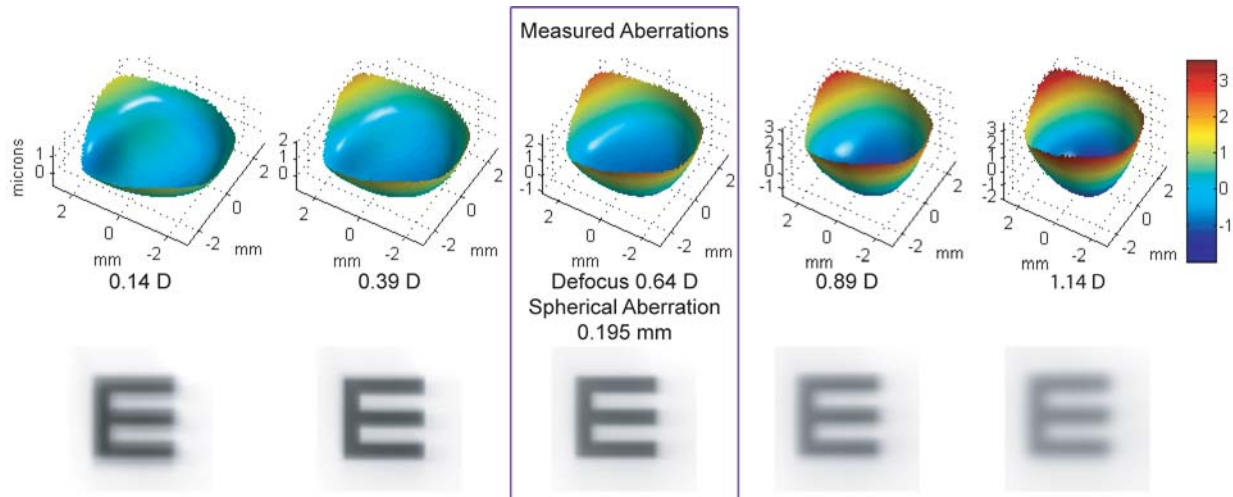


Figure 3-7. This through-focus analysis illustrates the interaction between Zernike spherical aberration and defocus for a myopic subject viewing the distance target. The measured aberrations are framed in violet; to the left are simulations adding negative defocus in 0.25 D increments to the wave aberration, and to the right are simulations adding positive defocus. Below each of the aberration maps is a simulation of the retinal image for a 20/50 Snellen E

The effects of the interaction between Zernike defocus and spherical aberration on the wave aberration and retinal image quality are illustrated for positive spherical aberration and distance viewing in Figure 3-7, and for negative spherical aberration and the 5 D stimulus in Figure 3-8. The measured wave aberration and a simulation of the retinal image are in the center of these figures. To the left are simulations with negative defocus added in 0.25 D increments to the aberration map, and to the right are simulations adding positive defocus.

In Figure 3-7, when there is residual positive spherical aberration (left most image), this produces a flatter contrast gradient, creating blur in the edges of the letter E, despite more “accurate” accommodation (accommodative error: 0.14 D defocus). As positive defocus is added (to the right), the central region of the wave aberration flattens and image quality improves, despite a “worsening” accommodative error (0.64 D defocus). If too much defocus is added (continuing to the right past the measured values), there is an overall loss in contrast amplitude of the retinal image and a reduction in image quality.

In Figure 3-8, showing an accommodating eye, there is residual negative spherical aberration (right most image) and a poor contrast gradient, although only a negligible accommodative error (-0.04 D defocus). As negative defocus is added (to the left), the wave aberration flattens centrally and image quality improves, with a supposed increase in accommodative error (-0.54 D defocus). From these data, it is apparent that Zernike defocus is not a good measure, in terms of defining the plane of best focus, of accommodative error.

Does Seidel defocus provide a better option to Zernike defocus? Seidel defocus represents the curvature of the wavefront at the pupil center (Thibos et al., 2004). It is the paraxial power determined by rays traced through a small central region of the pupil, ignoring rays passing through the pupil periphery (Atchison, 2004). During “accurate” accommodation, the paraxial region of the measured wavefront should match the curvature of the vergence of the near target, thus the wave aberration would be flat at the pupil center. The wave aberration maps

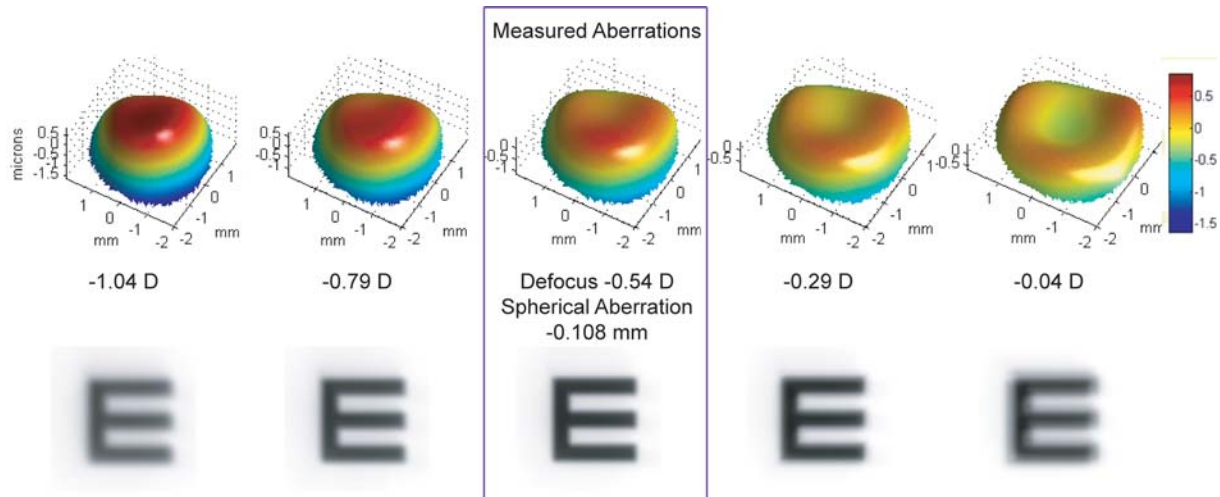


Figure 3-8. This through-focus analysis illustrates the interaction between Zernike spherical aberration and defocus for a myopic subject viewing the 5 D stimulus vergence. The measured aberrations are framed in violet; to the left are simulations adding negative defocus in 0.25 D increments to the wave aberration, and to the right are simulations adding positive defocus. Below each of the aberration maps is a simulation of the retinal image for a 20/50 Snellen E.

in Figures 3-7 and 3-8 appear to meet this criterion. Seidel defocus was 0.0 D for the distance viewing condition (Figure 3-7) and 0.18 D for the 5 D stimulus (Figure 3-8).

From linear regression analyses, the slopes of the Seidel accommodative error were essentially zero for both refractive error groups, and there was no significant correlation between accommodative error and stimulus vergence. These results indicate that the accommodative error was approximately constant across all stimulus vergences, the average being 0.10 D for the myopes and -0.39 D for the emmetropes. Thus paraxial rays were focused quite accurately for the myopes, but not so for the emmetropes, who recorded significantly lower accommodative responses compared to the myopes for all near target distances.

Two possible explanations are offered for the negative shift in Seidel accommodative error for the emmetropes compared to that of the myopes; either, it is only the Seidel error that is more negative, or the complete set of accommodative errors (Seidel + through-focus metrics + Zernike) are all shifted in the negative direction. For the Zernike response, based on the interaction between spherical aberration and defocus, a larger accommodative error would be expected for conditions where the spherical aberration is more negative. This is the situation for each refractive error group; as spherical aberration becomes more negative with increasing stimulus vergence, the Zernike accommodative error also becomes larger. The emmetropes however, exhibited smaller amounts of negative spherical aberration for all near targets compared to the myopes (Figure 3-4), therefore their Zernike responses should have been correspondingly higher. Nevertheless, there was no significant difference in Zernike defocus between emmetropes and myopes, except for the 2 D stimulus vergence, with the myopes' response being higher.

These results suggested that the set of accommodative errors for all metrics was shifted in the negative direction for the emmetropes. Therefore we considered whether there were any optical explanations, such as differences in other aberrations, pupil sizes, DOF, etc., that could explain this offset. There was no significant difference in horizontal or vertical coma and oblique

astigmatism (J_{45}) between emmetropes and myopes. The myopes had, on average, significantly larger amounts of astigmatism (J_0) compared to the emmetropes, although in magnitude this difference was very small. Myopes also had smaller pupil sizes (Figure 3-6) compared to emmetropes, significantly different for the 2 and 3 D stimulus conditions. Both of these findings imply that the myopes should have a larger DOF compared to the emmetropes, which was supported by the results of the DOF estimates from the neural sharpness metric (Table 3-3).

While the idea that differences in DOF could explain differences in accommodative accuracy seems reasonable, 3 recent adaptive optics (AO) studies of accommodation illustrate that the relationship between DOF and accommodation is not simple (Chen *et al.*, 2006, Chin *et al.*, 2009, Fernandez and Artal, 2005). One common premise investigated by these studies was that correcting HOA should decrease the DOF and therefore improve the accommodative accuracy. However, Fernandez and Artal (2005) found that correcting astigmatism, coma and trefoil had no effect on the accommodative response amplitudes of their 2 subjects. Chen *et al.* (2006) investigated the effect of removing astigmatism and HOA with AO. Of the 4 subjects who were able to accommodate with HOA corrected none showed a significant difference in response gain with corrected aberrations. Similar results were reported by Chin *et al.* (2009), specifically, correction of astigmatism and HOA did not significantly affect the accommodative response gain of their 4 subjects.

With no apparent optical reason to account for the negative shift in accommodative error found with the emmetropes, an alternative possibility may relate to the stability of our subjects' refractive error. Accommodative lag has been shown to be highly correlated with myopia progression for both myopes and non-myopes (Allen and O'Leary, 2006), with larger lags associated with the development of myopic shifts in refractive error. A plausible, albeit highly unlikely, scenario is that a large proportion of our emmetropes were undergoing myopic shifts in their refractive errors while an equivalent number of our myopes had stable refractive errors.

An interesting feature of the Seidel accommodative error data was that there was no increase in lag of accommodation with increasing stimulus vergence. Changes in accommodative error associated with changes in DOF have been well documented (Ciuffreda, 1999). An increase in lag would be expected with higher accommodative stimuli, due to the increase in DOF that results from pupillary miosis, image degradation with increasing negative spherical aberration, and a reduction in visual acuity (Heath, 1956, Tucker and Charman, 1975, Ward and Charman, 1985). The finding that paraxial focus predicts a fairly constant accommodative error was also reported by Hazel *et al.* (2003), although the data from Plainis *et al.* (2005) does not show the same effect. This departure from the classical stimulus-response curve as determined with Seidel defocus suggests that it also may not be a good measure of the true accommodative error.

Furthermore, in the presence of aberrations, the best image plane of an optical system is not necessarily the paraxial image plane (Welford, 1986). It is also important to keep in mind that determining the best image plane is not the same as choosing the best geometric focus (i.e. circle of least confusion). For an optical system with spherical aberration, the best geometric focus (described by ray tracing) is located $\frac{3}{4}$ of the way between the paraxial and marginal foci, whereas including the effects of diffraction, the best focus (determined by the PSF) is halfway between the two. There is no evidence that the accommodative system chooses the best geometric focus, on the contrary it may choose the best diffraction focus or one closer to the paraxial focus (Mouroulis, 1999).

The idea that the eye alters its accommodative state to bring into focus the best image plane instead of the paraxial image plane has been proposed in previous studies (Cui *et al.*, 1993). It is also consistent with research determining objective refractions from wavefront aberrations (Cheng *et al.*, 2004b, Guirao and Williams, 2003, Thibos *et al.*, 2004), in which the optimum focus was found to lie somewhere between the paraxial focus (Seidel defocus) and the least squares solution (Zernike defocus). Therefore, metrics that identify the best image plane, and define accommodative error relative to this plane rather than the paraxial plane, should provide a more valid measure of the true accommodative response.

This was the basis of the through-focus procedure which attempts to determine the optimum spherical power needed to maximize the optical or visual quality of the eye. The biggest challenge with this technique was to find a suitable OQM that quantifies image quality using the same criteria as the accommodative system. Of the metrics evaluated, the pupil fraction metrics were unsuitable for reasons already outlined; however both NS and VSMTF appear to be reasonable choices. NS captures the effectiveness of a PSF for stimulating the neural portion of the visual system (Chen *et al.*, 2005). The VSMTF weights the MTF by the neural CSF, and thus the modulation near the peak of the CSF (e.g., 6 cpd) is weighted maximally (Thibos *et al.*, 2004). The CAG algorithm which endeavors to optimize both contrast amplitude and gradient of the retinal image, to mimic the mechanism used by the accommodative system (Ciuffreda, 1999), also warrants further investigation.

The striking difference in the stimulus-response curves between the emmetropes and the myopes raises the question of which curve represents the “expected” response? Based on the typical appearance of this curve (Ciuffreda and Kenyon, 1983), it appears that the emmetropes are accommodating “as expected”, however this may not be the case. The above discussion suggests that the myopes’ accommodative response curve is what should be expected. If the best image plane lies somewhere between Seidel and Zernike defocus, then during accommodation when the eye has negative spherical aberration, the former would overestimate and the latter would underestimate the accommodative response.

Another consideration is the introduction of a systematic bias in our data analyses due to the wavelength selected to calculate the accommodative responses from the wave aberration data. Our choice was an estimate of which wavelength would be best focused on the retina over the range of stimulus vergences presented based on published data. Millodot and Sivak (1973) found that with white light illumination, the wavelength focused on the retina changed from red for distant objects to blue for near objects, and to green for target vergences approximating the resting state of accommodation. Rather than complicating the analyses further by using a different reference wavelength for each stimulus vergence, we chose 550 nm based on experimental evidence that demonstrated that the response curves in white and green illumination are very similar (Charman and Tucker, 1978). Also, 550 nm is midway between the peaks of the photopigment absorption spectra for the long wavelength sensitive cones (L-cones) and the middle wavelength sensitive cones (M-cones) at 565 nm and 535 nm respectively.

The effect of changing the reference wavelength is illustrated in Figure 3-9 using the measured aberrations for the same myopic subject and stimulus vergence (5 D) shown in Figure 3-8. When 550 nm light is in focus on the retina the Zernike defocus is -0.54 D (Figure 3-8), however for 535 nm this shifts to -0.40 D, and for 565 nm to -0.68 D (Figure 3-9) with the wave aberration becoming slightly more concave and convex, respectively.

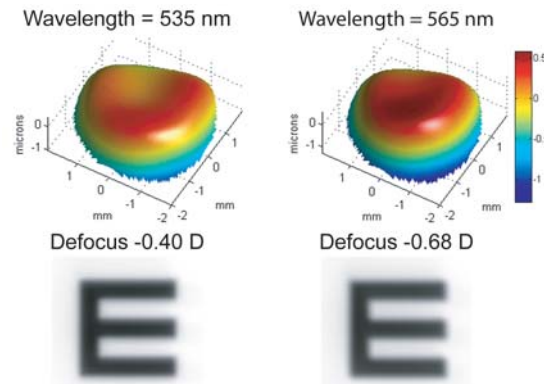


Figure 3-9. The effect of changing the reference wavelength; the wave aberration, Zernike defocus and simulated retinal image for a myopic subject viewing the 5 D stimulus vergence, calculated for 535 nm (left images) and 565 nm (right images).

The use of a single wavelength in our analyses also ignores an additional consequence of longitudinal chromatic aberration, that the 3 cone types effectively sample the retinal image in 3 different focal planes. Recent research supports the idea that the ratio of the L-cone contrast to the M-cone contrast influences the accommodative response (Rucker and Kruger, 2004a), with a further role for short wavelength sensitive cones (S-cones) (Rucker and Kruger, 2004b). Based on the results from these studies it was theorized that the habitual lag of accommodation may represent a balance between the S-cone contrast and the LM-cone contrast.

The implication of these results is that differences in accommodative responses between emmetropes and myopes could be associated with differences in sensitivities to L- and M-cone contrasts. One study reported an increased sensitivity to L-cone contrast relative to M-cone contrast with increasing myopia, and a corresponding increase in mean accommodation level (Rucker and Kruger, 2006). While there appear to be no quantitative differences in chromatic aberration between emmetropes and myopes (Wildsoet *et al.*, 1993), a shift in relative L:M-cone sensitivity could result from cone pigment polymorphism (Wagner-Schuman *et al.*, 2008) or differences in the relative numbers of L- and M-cones, perhaps accounting for differences between the emmetropic and myopic subjects reported here. However, it should be noted that all 3 chromatic aberration studies of accommodation did not consider monochromatic aberrations. A model that considers both monochromatic and chromatic aberrations is likely to yield the most robust predictions.

3.5 Conclusions

When determining the accommodative response from wavefront aberrations, it appears that neither of the closed-form solutions, Zernike nor Seidel defocus, are the best method. When the eye has negative spherical aberration, which is typical during accommodation, Zernike defocus tends to underestimate the accommodative response, leading to the prediction of a larger lag of accommodation than is evident from the retinal image quality. Seidel defocus, on the other hand, tends to overestimate the accommodative response, resulting in either a smaller lag of accommodation, or even a lead of accommodation relative to the best image plane.

The data presented here suggests that a better approach to quantifying the accommodative response is to first determine the best image plane using a suitable OQM, and then calculate the

accommodative error relative to this plane. Any metric chosen will provide a biased estimate of the best image plane depending on the specific feature of image quality optimized. Different metrics will therefore result in different values for the accommodative response; however they should be in agreement to within a range comparable with the variability expected from the measurement and analysis procedures. Both NS and VSMTF meet these criteria and the CAG algorithm also shows promise.

In situations where a computational method requiring multiple iterations to determine the best image plane is not viable, a reasonable alternative could be simply to use the average of the Zernike and Seidel defocus as a measure of the accommodative response. This would provide a numeric value similar to that obtained with one of the OQMs, however without the insight gained from an analysis that also quantifies retinal image quality.

Chapter 4

The Effects of Multifocal Soft Contact Lenses on the Accommodative Response of Young Adults

Abstract

Monocular accommodative responses were measured using a wavefront sensor in young adult emmetropes and myopes for distance and 4 near target vergences: 2, 3, 4 and 5 D. Data were collected from 30 subjects wearing each of 6 soft contact lenses, a single vision distance lens (SVD), a single vision near lens (SVN) incorporating a +1.50 D add, as well as center-distance (MFD) and center-near (MFN) multifocal lenses with both +1.50 and +2.00 D adds. The effects of multifocal contact lenses on accommodative responses were evaluated using 4 different optical quality metrics. For large pupils (> 5 mm), accommodative responses calculated using a neural sharpness metric increased with MFD lenses, which added positive spherical aberration, compared to that with the SVD lens, and decreased with MFN lenses, which added negative spherical aberration, compared to that with the SVN lens, although responses were larger than that with the SVD lens. Assuming accommodative lags exacerbate myopia progression, these effects on accommodation responses are consistent with reported slowing of myopia progression with MFD lenses and predict a similar benefit from MFN lenses as well.

4.1 Introduction

Interest in controlling the progression of myopia has increased in recent years, along with the rising prevalence figures for myopia world-wide. Results from intervention trials using progressive addition lenses (PALs) were included in a recent review of treatment options for slowing the progression of myopia (Gwiazda, 2009). While the small and relatively short-lived treatment effects observed with PALs have led to questions about their clinical utility, the larger treatment effects seen with certain subgroups of myopes provided the motivation for at least some of the more recent trials of contact lenses for myopia control (Aller and Wildsoet, 2008, Aller and Wildsoet, 2006). The latter studies provided the motivation for the current study and to provide context, we briefly summarize the results of the best designed of relevant clinical trials.

Two studies involving PALs report clinically significant treatment effects in those with accommodative abnormalities. In the US-based COMET study (Gwiazda *et al.*, 2003), the average reduction in myopia progression was only small and deemed clinically insignificant (0.20 D) in the PAL group compared to the control group wearing single vision lenses (SVL) over a 3-year follow-up period. However, subgroup analyses revealed significantly larger treatment effects, ranging between 0.44 and 0.64 D on average, for children exhibiting either shorter reading distances, lower baseline myopia, or near esophoria and larger accommodative lags (Gwiazda *et al.*, 2004). A 3-year cross-over trial involving SVLs and PALs conducted in Japan yielded similar results (Hasebe *et al.*, 2008), with mean myopia progression in the PAL group reduced by 0.31 D compared to that of the SVL group over the first 18-month period, although there was minimal slowing of progression over the second 18-month period. Subgroup analyses revealed larger initial treatment effects in children with larger lags of accommodation (0.61 D) and more esophoria (0.55 D).

Interpretation of the results from the PAL studies is problematic because of the difficulty in ensuring that the children used the near additions appropriately. For example, the downward deviation of the spectacles observed with some children in the Japanese study would have reduced the time spent looking through the near additions and so any therapeutic effect of the PALs (Hasebe *et al.*, 2005). Also because children have high accommodative amplitudes, there is limited incentive for children to maintain the appropriate posture required to access the near addition during close work. The likely exceptions are those children with binocular vision and accommodative anomalies for which use of the near addition would provide symptomatic relief.

Bifocal (BF) and multifocal (MF) soft contact lenses (SCL) have been explored as an alternative that avoids the above compliance issues for PALs (Aller and Wildsoet, 2008, Howell, 2008, Rodgin, 2001, Aller and Wildsoet, 2006). Most lens designs involve simultaneous vision in which concentric distance and near optical zones are projected onto the pupil (Ares *et al.*, 2005, Chateau and Baude, 1997). As the lenses are designed for presbyopes who generally have smaller pupils than children and teenagers (Schafer and Weale, 1970), the latter groups are likely to receive consistent benefit from the near addition during reading with these contact lens designs.

The most convincing data supporting the use of BF SCLs for myopia control comes from a small masked clinical trial in which the average myopia progression was reduced by 0.56 D in the BF SCL treatment group compared to the single vision SCL control group over 2 years (Aller and Wildsoet, 2006). A second study comparing MF SCLs to MF spectacles reported a mean decrease in myopia progression by 0.38 D with MF SCLs over 12 months (Howell, 2008). However, because the contact lens treatment followed the spectacle lens treatment, it is

impossible to rule out natural age-related slowing of myopia progression as a contributing factor to the latter result. A similar problem of interpretation is encountered in a series of 53 case studies (Rodgin, 2001), in which average myopia progression was found to be negligible after switching to BF SCL.

A unifying hypothesis that links data from the above clinical trials and experimental animal studies is that hyperopic defocus drives myopia development and progression. The most direct support for this hypothesis comes from animal studies in which hyperopic defocus imposed with spectacle lenses is observed to increase ocular elongation and induce myopia (Wildsoet, 1997). Accommodative lags also introduce hyperopic defocus and although a causal link between accommodative lags and myopia remains a subject of debate (Mutti *et al.*, 2006), larger lags of accommodation have been linked to the development of myopia in some studies (Goss, 1991, Gwiazda *et al.*, 2005, Drobe and de Saint-Andre, 1995), and also implicated as a risk factor in the progression of myopia (Abbott *et al.*, 1998, Allen and O'Leary, 2006, Gwiazda *et al.*, 1995, Mutti *et al.*, 2006).

Because use of the near addition in BF and MF SCLs does not require specific head and eye postures, its more consistent use and thus correction of accommodative lags may explain the apparent effectiveness of such lenses in controlling myopia progression. However, there may be alternative explanations. In a previous study (Tarrant *et al.*, 2008), we reported leads of accommodation with BF SCLs for both myopes and emmetropes over a range of test distances, while only emmetropes showed this behavior for the single vision near lenses. These lens design-dependent differences in accommodative responses implied some influence other than the near addition on accommodation and we hypothesized that the observed changes in accommodation were due to changes in ocular spherical aberration induced with the BF SCLs. A limitation of our study was its dependence on measured consensual accommodative responses as we were unable to obtain valid refractometer readings through the BF SCLs because of the discontinuities in power across the lens.

The study described here involved measurements with a wavefront analyzer of young adult emmetropes and myopes wearing either single vision or MF SCLs for a range of vergences. The selected MF lens design, which has a continuous power profile across the lens, used in combination with an aberrometer, allowed direct measurements of accommodative responses through the lenses. Our study had 2 purposes, firstly to verify that the metrics for calculating accommodative responses from wavefront aberrations would provide valid results when applied to data collected with the MF SCLs, and secondly to investigate the effects of MF SCLs on the ocular aberrations and accommodative responses of emmetropes and myopes.

4.2 Methods

4.2.1 Subjects

Thirty young adults participated in the study. Their age profile (mean \pm SD) was 23.5 ± 2.9 years (range: 19 to 31 years) and included 13 emmetropes (spherical equivalent refractive error (S_E): 0.21 ± 0.20 D, range: plano to +0.50 D) and 17 myopes (S_E : -3.47 ± 1.47 D, range: -1.25 to -5.75 D). Astigmatism was limited to ≤ 1.00 D and anisometropia to < 2.00 D. All participants had corrected visual acuity of 20/20 or better, no binocular vision anomalies, and binocular accommodative amplitudes and facility were assessed to be within normal range based on age.

The study protocol conformed to the provisions of the Declaration of Helsinki and was approved by the University of California, Berkeley institutional review board. Informed consent was obtained from the participants after the nature and possible complications of the study were explained in writing.

4.2.2 Contact lenses

The same brand of commercially available soft hydrogel contact lenses was used throughout the study (CooperVision Frequency 55). Each subject was tested with two single vision (SV) lenses, one with their S_E distance prescription (SVD) and one with a near prescription generated by adding +1.50 D to their distance prescription (SVN). The emmetropes with plano distance prescriptions wore +0.25 D SVD lenses. Four multifocal (MF) lenses were tested. They included center-distance (MFD) and center-near (MFN) designs, combined with +1.50 and +2.00 D near additions, hereafter referred to by the following codes, MF15D, MF2D, MF15N and MF2N. The MFD design had a 2.3 mm diameter central distance zone, surrounded by a 5 mm wide zone of progressively increasing power to the full near addition. The MFN design had a 1.7 mm diameter central near zone surrounded by a 5 mm wide zone of progressively decreasing power to the distance prescription.

4.2.3 Accommodation measurements

Monochromatic wavefront aberrations were measured using a COAS wavefront analyzer (Abbott Medical Optics, Albuquerque, NM). Measurements were made of the dominant eye viewing a distance target and 4 near target vergences: 2, 3, 4 and 5 D. The near target was an external letter chart, viewed monocularly through a beam splitter, and positioned at the appropriate distance for each target vergence. It consisted of 4 lines, each made up of 5 high contrast letters and decreasing in size such that at each of the 4 near viewing distances, one line had an angular subtense of 12.5 minutes of arc. Participants were instructed to look at the middle letter of the appropriate line of letters and to keep the letters as clear as possible. The test sequence for the contact lenses was randomized, as was the presentation sequence for the near targets. Measurements were taken in the dark with a small LED providing the illumination for the near target. For each test condition 20 measurements were obtained from continuous recordings at a sample rate of approximately 10 Hz.

4.2.4 Data analyses

The wavefront data were fit with a sixth order Zernike expansion calculated for a wavelength of 550 nm and natural pupil sizes. Accommodative responses for each test condition were calculated from exported Zernike coefficients using the following 4 metrics:

- i. least-squares fitting (Zernike defocus) (Thibos et al., 2004),
- ii. paraxial curvature matching (Seidel defocus) (Thibos et al., 2004),
- iii. maximizing optical quality using the neural sharpness (NS) metric (Chen *et al.*, 2005, Thibos *et al.*, 2004),
- iv. maximizing optical quality using an algorithm that optimizes both the contrast amplitude and gradient of the retinal image (CAG) (Tarrant et al., 2010).

The equations for Zernike and Seidel defocus, and the through-focus procedure for maximizing optical quality used by the NS metric and CAG algorithm, were described in detail

in a previous paper (Tarrant et al., 2010). In that study we evaluated the suitability for calculating accommodative responses of 7 metrics proven successful in determining objective refractions from wave aberrations. We found that during accommodation when the eye has negative spherical aberration, Zernike defocus tends to underestimate, whereas Seidel defocus tends to overestimate accommodative responses; they were included for verification purposes in the current study. A better approach was to use the through-focus procedure which determines the best image plane using a suitable OQM and then calculates the accommodative error relative to this plane.

The second part of the study assessed the effects of the MF SCLs on ocular aberrations and accommodative responses. The lenses were divided into 2 groups, depending on whether they were expected to add positive or negative spherical aberration to ocular aberrations. The MFD lenses were predicted to add positive spherical aberration; their results were compared to those with the SVD lens. The MFN lenses were expected to add negative spherical aberration; their results were compared to those with the SVN lens. Zernike spherical aberration was converted to diopters using the second term of the equation for Seidel defocus to remove the dependence on pupil size and so allow use of natural pupil sizes in comparative analyses.

Because aberrations can influence depth-of-focus (DOF), the NS metric was used to estimate the DOF for each lens from values calculated using the through-focus procedure (Tarrant et al., 2010). Defocus was added to the measured wave aberration in 0.1 D increments over a range of ± 1.5 D from the maximum metric value. These data points were fitted with a spline and the DOF defined as the width of the function at the 80% level of the maximum value (Marcos et al., 1999).

4.2.5 Statistical analyses

One-way repeated measures ANOVAs using the Tukey-Kramer method for multiple comparisons ($\alpha_{FW} < 0.05$) were used in the following analyses. First, to verify the validity of the results calculated by the optical quality metrics, ANOVAs were used to compare the differences between the accommodative responses calculated by each metric, for each refractive error group and stimulus vergence. Second, to assess the effects of the MF SCLs on ocular aberrations and accommodative responses for each refractive error group and each stimulus vergence ANOVAs were used to compare the differences in each of the following measurements: spherical aberration, accommodative responses calculated by the NS metric and Seidel defocus, pupil diameter and DOF, for the positive spherical aberration lens series (SVD, MF15D and MF2D lenses) and for the negative spherical aberration lens series (SVN, MF15N and MF2N lenses). Student's t-tests were used to compare the differences in spherical aberration and pupil diameter between emmetropes and myopes for individual lenses.

Two of the measurement sets for the SVD, SVN, MF15N and MF2N lenses and 1 of the measurement sets for the MF15D and MF2D lenses were excluded from reported statistical analyses. In these cases it was evident from the very reduced accommodative responses that the subjects were inattentive during the measurements. All excluded data were flagged as outliers in initial statistical analyses.

4.3 Results

4.3.1 Lens-induced changes in ocular spherical aberration

The MFD lenses added positive spherical aberration to the ocular aberrations relative to the SVD lens (Figure 4-1A). For the emmetropes, the differences in spherical aberration measured with both MF15D and MF2D lenses compared to that with the SVD lens were statistically significant for all vergences. The values for the MF2D lens were larger than those for the MF15D lens although the differences were statistically significant for the 4 D stimulus vergence only. For the myopes, the differences in spherical aberration measured with both MF15D and MF2D lenses compared to that with the SVD lens were statistically significant in all cases except for the MF15D lens compared to the SVD lens at the 5 D stimulus vergence. The differences between the results for the MF15D and MF2D lenses were significant for the 3, 4 and 5 D stimulus vergences. The measured spherical aberration for the myopes was on average more negative than the emmetropes with all 3 lenses. These intergroup differences were significant in all cases except for the 4 D stimulus vergence with the SVD lens and the 5 D stimulus vergence with the MF2D lens.

The MFN lenses added negative spherical aberration relative to the SVN lens (Figure 4-1B). For the emmetropes, the differences in spherical aberration with the MF15N and MF2N lenses compared to the SVN lens were all statistically significant except for the 5 D stimulus vergence and MF15N lens. The values for the MF2N lens were generally larger than those with the MF15N lens although they were not statistically significant except for the 2 D stimulus vergence. For myopes, the differences in spherical aberration with both the MF15N and the MF2N lenses compared to the SVN lens were statistically significant for all stimuli, although there was no significant difference in the results for the MF15N and MF2N lenses. The myopes again recorded more negative values for spherical aberration than the emmetropes with all 3 lenses. These intergroup differences were significant for the SVN lens at all vergences except the 5 D stimulus and for the MF15N lens and the distance target.

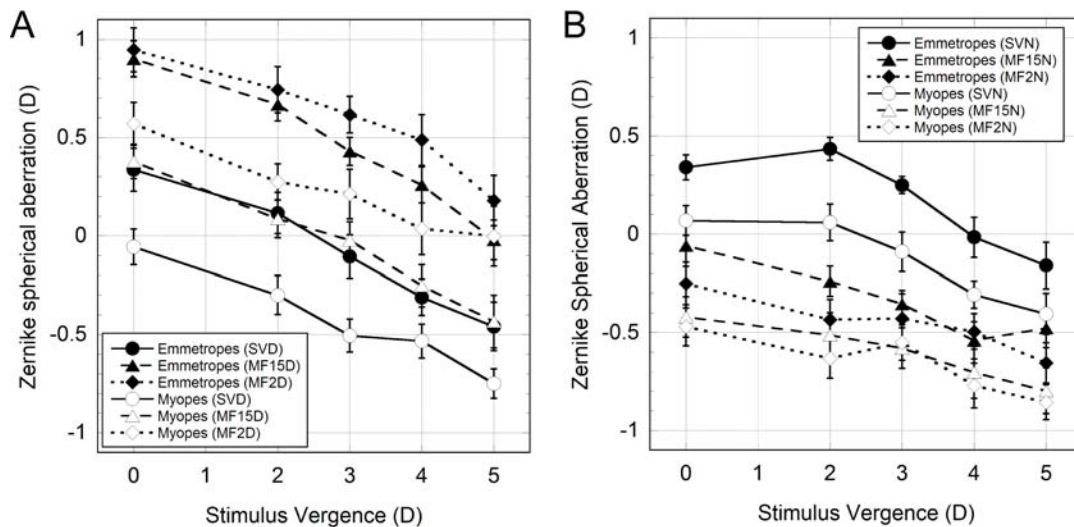


Figure 4-1. Zernike spherical aberration as a function of stimulus vergence for emmetropes and myopes, for (A) the SVD and MFD lenses with +1.50 D (MF15D) and +2.00 D (MF2D) add powers, and (B) the SVN and MFN lenses with +1.50 D (MF15N) and +2.00 D (MF2N) add powers. Error bars are \pm SEM.

4.3.2 Verification of the optical quality metrics

For both emmetropes and myopes, the dioptric separation in the accommodative responses calculated by the 4 different metrics for each stimulus vergence was related to the amount of spherical aberration. Results for the positive spherical aberration lens series (SVD, MF15D, MF2D) and negative spherical aberration lens series (SVN, MF15N, MF2N) are shown in Figures 4-2 and 4-3 respectively. For emmetropes, results for each of the metrics converged to similar values for the SVD lens between the 2 and 3 D stimulus vergences, and for the MF15D lens at the 5 D stimulus vergence (Figure 4-2A), corresponding in both cases to the vergences for which spherical aberration was approximately zero (Figure 4-1). For myopes, results for each of the metrics converged at the distance target for the SVD lens, at the 3 D stimulus vergence for the MF15D lens and at the 5 D stimulus vergence for the MF2D lens (Figure 4-2B), again corresponding to the vergences for which spherical aberration was approximately zero (Figure 4-1). The smallest spread in the calculated accommodative responses for the different metrics occurred for the SVN lens at the 4 D stimulus vergence, and for the MF15N lens at the distance target for emmetropes (Figure 4-3A), and for the SVN lens between the 2 and 3 D stimulus vergences for myopes (Figure 4-3B). Again these test conditions corresponded to the vergences for which the spherical aberration was approximately zero (Figure 4-1).

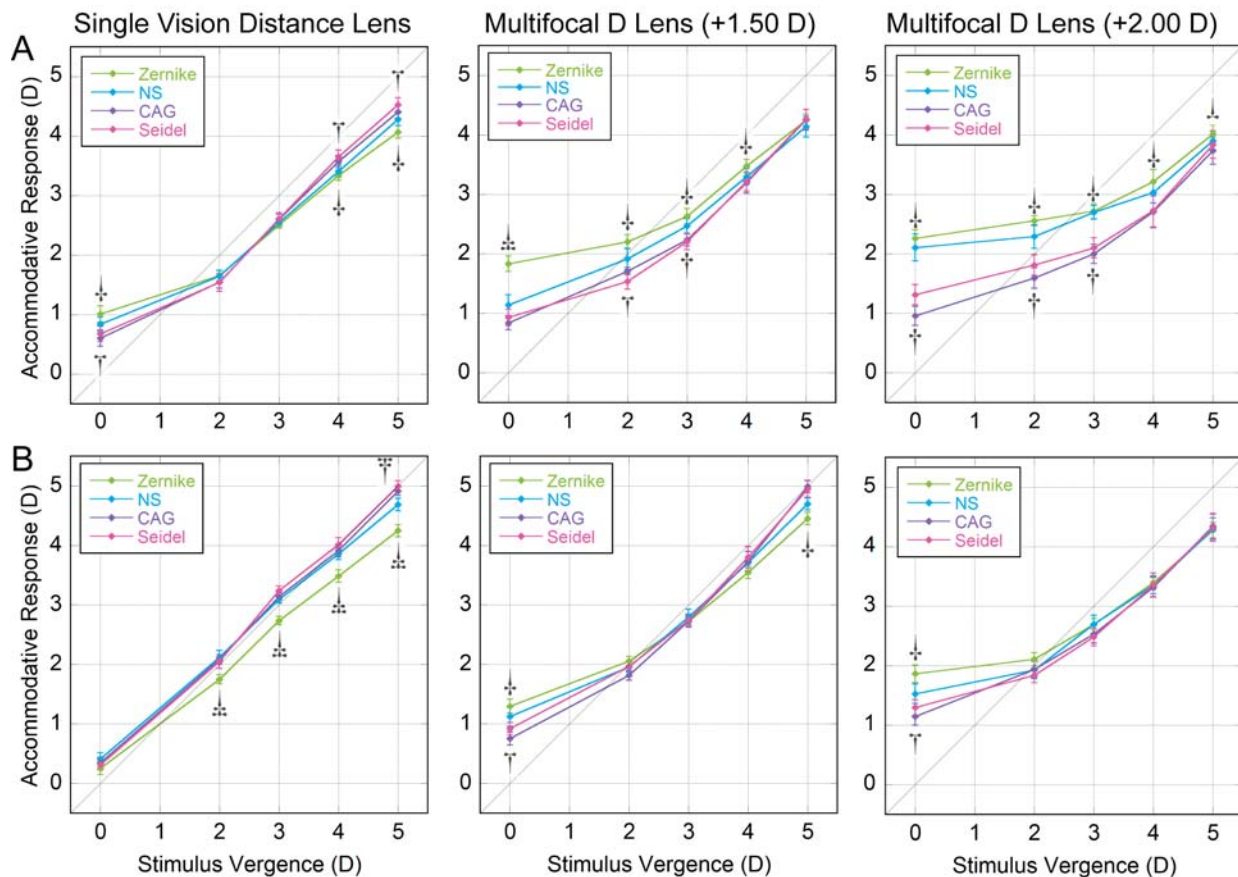


Figure 4-2. Accommodative responses calculated using each of 4 metrics for (A) emmetropes and (B) myopes for the SVD lens (left panel) and the MFD lenses with +1.50 D (center panel) and +2.00 D (right panel) add powers. Error bars are \pm SEM. Symbols indicate significant differences and are defined in Table 4-1

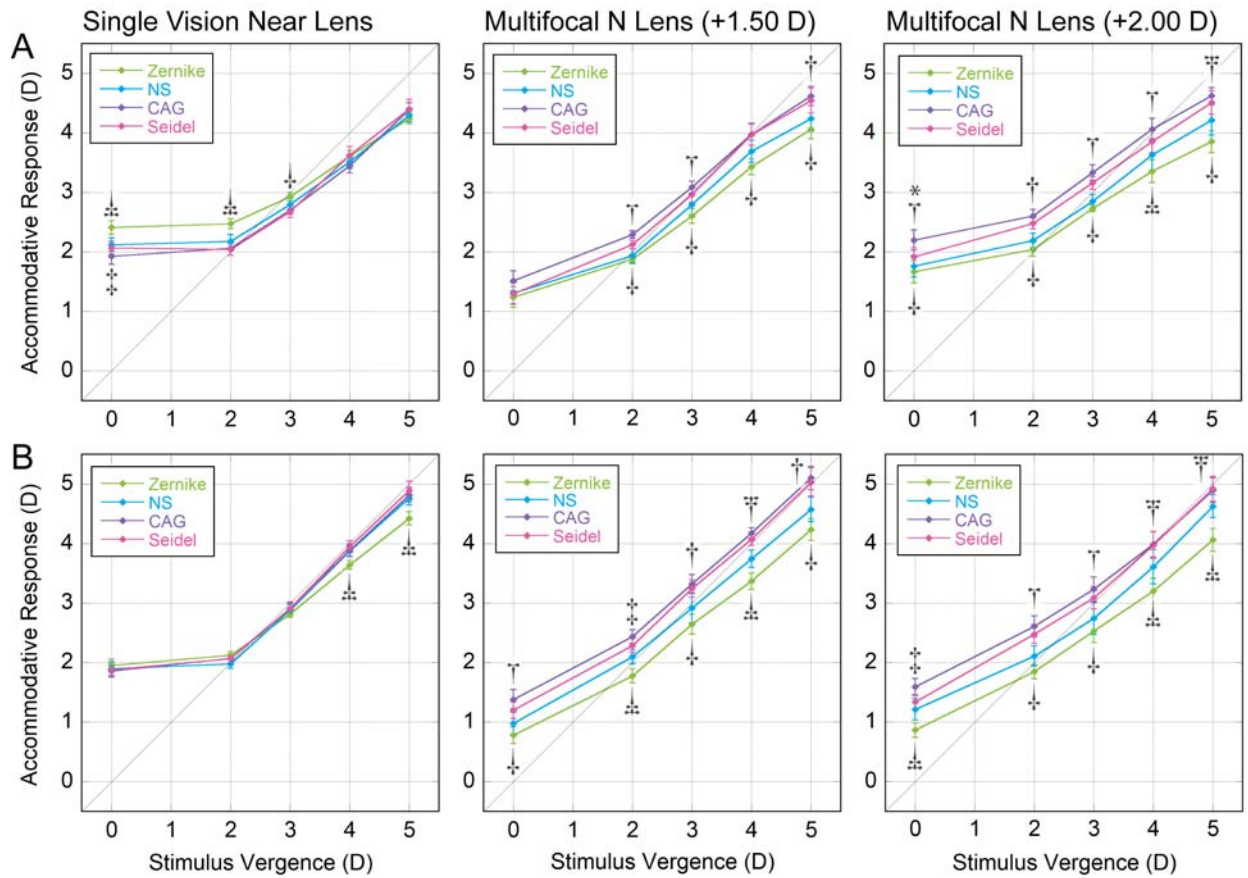


Figure 4-3. Accommodative responses calculated using each of 4 metrics for (A) emmetropes and (B) myopes for the SVN lens (left panel) and the MFN lenses with +1.50 D (center panel) and +2.00 D (right panel) add powers. Error bars are \pm SEM. Symbols indicate significant differences and are defined in Table 4-1.

Table 4-1. Definitions for symbols used in Figures 4-2 and 4-3 to indicate statistically significant differences ($\alpha_{FW} < 0.05$) in accommodative responses calculated using the different metrics.

Symbol & compared accommodative responses	
⚡ Zernike vs. NS, CAG & Seidel	⚡ NS vs. Zernike, CAG & Seidel
⚡ Zernike vs. CAG & Seidel	⚡ NS vs. CAG & Seidel
⚡ Zernike vs. CAG	⚡ NS vs. either CAG or Seidel
* Seidel vs. CAG	⚡ NS vs. Zernike & CAG

4.3.3 Accommodative responses with multifocal lenses

Different accommodative response patterns were observed with the MF lenses depending on whether the lenses added positive or negative spherical aberration. Because the best method to determine accommodative responses from wavefront aberrations is to use the through-focus procedure with an OQM to define the best image plane, we are mainly interested in the results determined using the NS metric, although the responses calculated with respect to the paraxial image plane (Seidel defocus) are included for comparative purposes (Figure 4-4). With the MFD lenses the general trend was for accommodative responses calculated by the NS metric to be larger compared to those with the SVD lens at low stimulus vergences and to be smaller at high stimulus vergences. The MFN lenses showed the opposite effect, responses calculated by the NS metric tended to be smaller compared to those with the SVN lens at low stimulus vergences and to be larger at high stimulus vergences. In contrast, accommodative responses calculated by Seidel defocus tended to be smaller with the MFD compared to those with the SVD lens for all near vergences and the responses tended to be larger with the MFN compared to SVN lenses also for all near vergences. The statistically significant outcomes are summarized in Table 4-2.

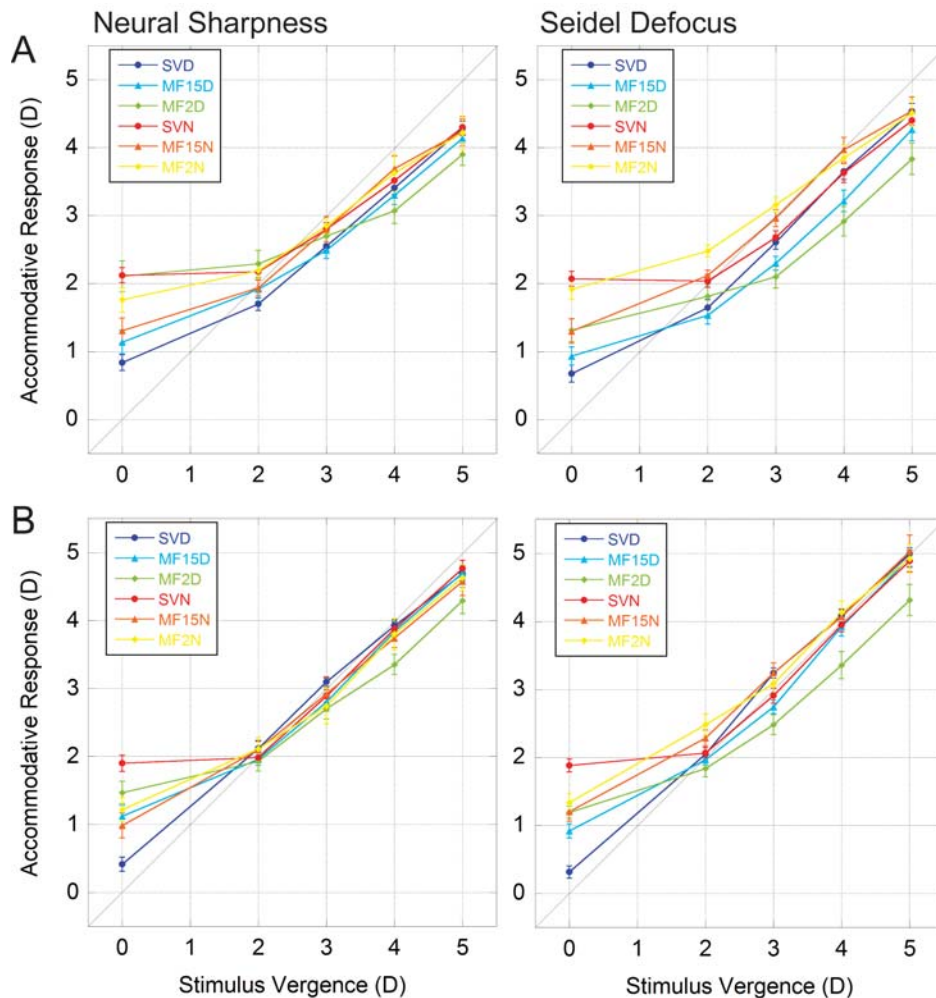


Figure 4-4. Accommodative responses with all contact lenses for (A) emmetropes and (B) myopes calculated for the neural sharpness metric (left panel) and Seidel defocus (right panel). Error bars are \pm SEM.

Table 4-2. For emmetropes and myopes, a summary of statistically significant differences between accommodative responses calculated using both the NS metric and Seidel defocus for multifocal D (MFD) lenses compared to the SVD lens, for the MF2D lens compared to the MF15D lens, for multifocal N (MFN) lenses compared to the SVN lens and for the MF2N lens compared to the MF15N lenses.

	Emmetropes					Myopes				
Baseline lens	Stimulus vergence (D)									
	0	2	3	4	5	0	2	3	4	5
	NS metric									
SVD	MF2D↑	MF2D↑				MF15D↑			MF2D↓	
MF15D	MF2D↑								MF2D↓	
SVN	MF15N↓					MF15N↓				
MF15N	MF2N↓									
	Seidel defocus									
SVD	MF2D↑		MF15D↓	MF15D↓	MF15D↓	MF15D↑		MF15D↓	MF2D↓	MF2D↓
MF15D	MF2D↑		MF2D↓	MF2D↓	MF2D↓	MF2D↑		MF2D↓		MF2D↓
SVN	MF15N↓	MF2N↑	MF2N↑			MF15N↓	MF2N↑			
MF15N	MF2N↑	MF2N↑								

Pupil diameter was not affected by lens design but did vary with refractive error (Figure 4-5). For both emmetropes and myopes, pupil diameters recorded with the positive spherical aberration lens series and with the negative spherical aberration lens series were not significantly different. However, myopes tended to have smaller pupils than emmetropes under all conditions, with these differences being statistically significant for the SVD lens and 2 and 3 D stimulus vergences, for the MF15N lens and the 0 and 2 D stimulus vergences, and for the MF2N lens and

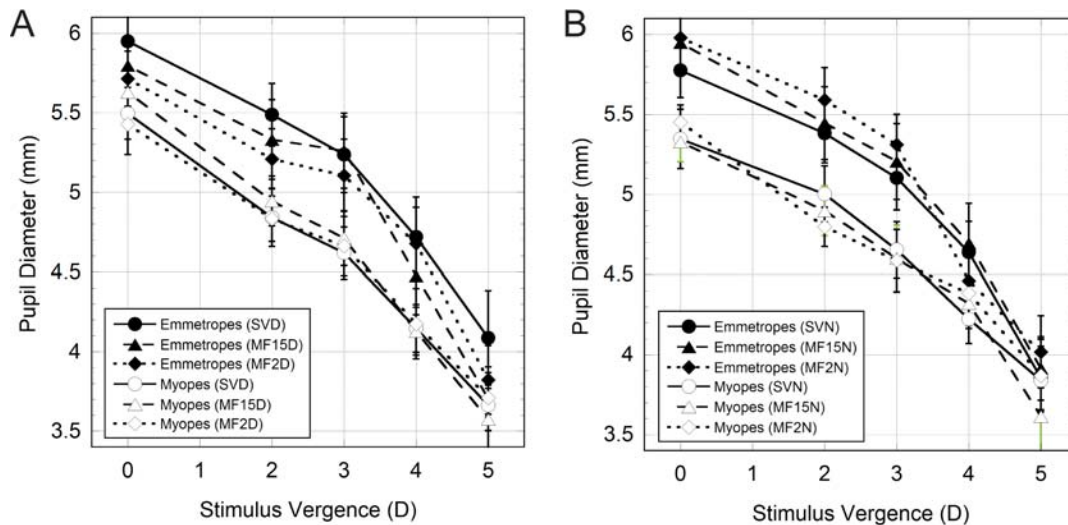


Figure 4-5. Pupil diameter as a function of stimulus vergence for emmetropes and myopes, for (A) the SVD and MFD lenses with +1.50 D (MF15D) and +2.00 D (MF2D) add powers, and (B) the SVN and MFN lenses with +1.50 D (MF15N) and +2.00 D (MF2N) add powers. Error bars are \pm SEM

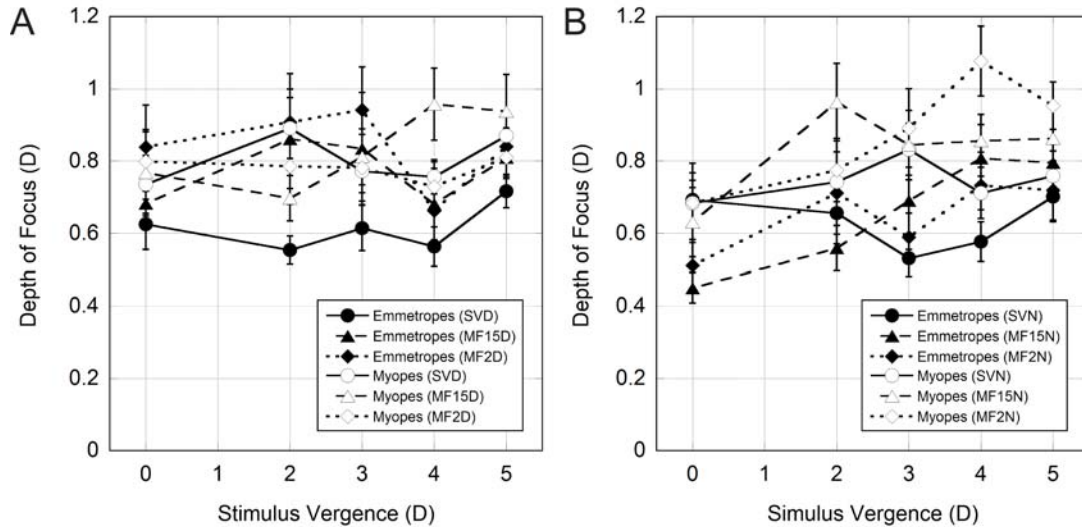


Figure 4-6. DOF as a function of stimulus vergence for emmetropes and myopes, for (A) the SVD and MFD lenses with +1.50 D (MF15D) and +2.00 D (MF2D) add powers, and (B) the SVN and MFN lenses with +1.50 D (MF15N) and +2.00 D (MF2N) add powers. Error bars are \pm SEM.

the 0, 2 and 3 D stimulus vergences ($p < 0.05$).

Lens design had little effect on DOF (Figure 4-6), with statistically significant differences being recorded for only 2 test conditions. For the emmetropes, the DOF with the MF15N lens was significantly less than that with the SVN lens for the distance target. For the myopes, the DOF with the SVN lens was significantly less than that with the MF2N lens for the 4 D stimulus vergence.

4.4 Discussion

4.4.1 Verification of the optical quality metrics

The first aim of our study was to assess whether the OQMs would produce acceptable results with measurements from the MF contact lenses given the possibility that this data may have higher aberration levels compared to the single vision lens data. The OQMs were originally designed to evaluate visual performance in controlled experiments in which the wave aberration was purposely kept low ($RMS \leq 0.25 \mu\text{m}$ over a 6 mm pupil, a dioptric equivalent of ≤ 0.19 D) (Marsack et al., 2004), however there was no expectation that such metrics would predict approximately the same best focus for higher aberration levels (Mouroulis, 1999). By observation it is clear that the calculated accommodative responses with the MF lenses appear consistent with those with the single vision lenses (Figures 4-2 and 4-3). Specifically, when the eye has negative spherical aberration, which is typical during accommodation, Zernike defocus produced the lowest accommodative response and Seidel defocus the highest response. The same pattern was consistently seen with the MFN lens series (Figure 4-3), with which negative spherical aberration was recorded for all test conditions (Figure 4-1). When the eye has positive spherical aberration, as was the case with the MFD lens series (Figures 4-1 and 4-2) and the SVN lens for the emmetropes (Figures 4-1 and 4-3), the opposite pattern was observed, with Zernike defocus producing the highest accommodative response and Seidel defocus the lowest. The NS

metric for all lenses consistently predicted the accommodative response to be between Zernike and Seidel defocus.

The CAG algorithm produced similar results to Seidel defocus for all test conditions except one (MF2N lens at distance). This algorithm was designed to optimize both the contrast amplitude and gradient of the retinal image determined from the point spread function (PSF), including an apodization function to take into account the Stiles-Crawford effect. Comparison of results obtained with the CAG algorithm and the NS metric, which includes a neural weighting function, may provide insight into the differences between retinal image quality and visual image quality (neuro-optical quality). Therefore the CAG algorithm has potential merit for studies in which retinal image quality rather than visual image quality is of interest, such as ocular growth regulation in which local retinal processing appears to play a key role (Wildsoet, 2003).

4.4.2 Accommodative responses with multifocal lenses

The effects of the MF lenses on accommodative responses can be explained in terms of the induced changes in spherical aberration and differences in pupil diameters across both test conditions and refractive error groups. For the MFD lenses, which added positive spherical aberration relative to the SVD lens, increases in the accommodative response calculated by the NS metric were found when the pupil was greater than approximately 5 mm and decreases for smaller pupils. The opposite trends were found with the MFN lenses, which added negative spherical aberration relative to the SVN lens, with decreases in the accommodative response for larger pupils and increases with smaller pupil diameters.

The responses for the larger pupil diameters are related to the results of visual performance studies examining the interaction between Zernike spherical aberration and defocus for pupil diameters in the 5 to 6 mm range (Applegate *et al.*, 2003, Chen *et al.*, 2005, Cheng *et al.*, 2004b). These studies demonstrated that specific combinations of negative spherical aberration with negative (hyperopic) defocus, and positive spherical aberration with positive (myopic) defocus produced images that were subjectively better focused than those corresponding to the same amounts of either spherical aberration or defocus alone. These results predict for accommodation, that adding positive spherical aberration will result in an increased accommodative response determined by Zernike defocus while adding negative spherical aberration will have the opposite effect.

Accommodative responses calculated using the NS metric for smaller pupil diameters were similar to responses calculated using Seidel defocus because pupil constriction limits the analysis to paraxial rays. However, while the overall direction of the shifts in the accommodative responses with the MF lenses was similar for both metrics, the range was smaller with responses calculated by the NS metric. This difference probably reflects the effect of the bivariate-Gaussian neural weighting function in reducing the extent of the PSF for the NS metric.

The accommodative responses calculated by the NS metric for smaller pupil diameters and those from Seidel defocus can be compared to the results from accommodation studies using autorefractors which typically restrict measurements to the paraxial region of the pupil (Seidel defocus) (Collins *et al.*, 1997, Theagarayan *et al.*, 2009). Both studies found that adding positive spherical aberration produced a decrease in the accommodative response whereas adding negative spherical aberration resulted in an increased response. The same trends were observed with an adaptive optics system used to induce both positive and negative spherical aberration,

where the accommodative response was determined using paraxial curvature matching (Seidel defocus) (Gambra *et al.*, 2009).

The pupil size dependency of the effect of spherical aberration on accommodative responses observed with our data should not be surprising as both are known to influence optimum focus. Specifically, spherical aberration shifts optimum focus away from the paraxial focus towards the marginal focus (Charman and Jennings, 1976), and in the presence of positive spherical aberration optimum focus becomes more myopic as pupil size increases (Meeteren van, 1974, Jansonius and Kooijman, 1998, Nio *et al.*, 2002). Spherical aberration also makes optimum focus dependant on the target spatial frequency, being more myopic for low spatial frequencies (Charman and Jennings, 1976, Green and Campbell, 1965, Jansonius and Kooijman, 1998, Meeteren van, 1974, Nio *et al.*, 2002). Nonetheless, these results do not imply that accommodative responses to more complex multifrequency targets such as Snellen letters can be predicted simply by knowing the frequency spectrum of the target and the responses to the individual spatial frequencies (Charman and Tucker, 1977).

Because MF lens designs utilizing simultaneous vision are known to influence DOF (Ares *et al.*, 2005), we considered whether changes in DOF could explain the differences between SV and MF lenses in accommodative responses. However, for both emmetropes and myopes there were no consistent trends for either MFD or MFN lenses and only 2 of the differences were statistically significant.

4.4.3 Refractive error-related differences in aberrations, accommodation and pupil size

The myopic subjects in our study recorded relatively negative spherical aberration with the SVD lens at all vergences compared to their emmetropic counterparts. Similar trends have been reported in previous studies (Carkeet *et al.*, 2002, Collins *et al.*, 1995, Kwan *et al.*, 2009) and also in comparisons of myopes with hyperopes (Llorente *et al.*, 2004), although other studies have reported the opposite trends (He *et al.*, 2002) or no association between spherical aberration and refractive error (Cheng *et al.*, 2003, Atchison *et al.*, 2006b, Marcos *et al.*, 2002). Inter-study differences in the age range of their subjects and the confounding effect of age-related changes in lenticular spherical aberration (Artal *et al.*, 2002, Glasser and Campbell, 1998, McLellan *et al.*, 2001, Radhakrishnan and Charman, 2007a) may partly account for these differences in study outcomes.

In our previous study (Tarrant *et al.*, 2010) we could not explain the difference in accommodative responses with the SVD lens between the emmetropes and the myopes. Fortuitously, with the MF15D lens the myopes had similar levels of spherical aberration to the emmetropes with the SVD lens at all vergences (Figure 4-1), and in these cases their accommodative responses were also similar (compare Figure 4-2B center panel with Figure 4-2A left panel). Likewise, the spherical aberration levels of the emmetropes with the SVN lens (Figure 4-1B) were close to those of the myopes with the MF2D lens (Figure 4-1A) and their accommodative responses were also comparable (Figure 4-3A left panel & Figure 4-2B right panel respectively). From these data it seems reasonable to conclude that differences in accommodative responses between emmetropes and myopes could be attributed to differences in spherical aberration and pupil diameters.

Our myopic subjects tended to have smaller entrance pupils than the emmetropes for all lenses and vergences and because the myopes were corrected with contact lenses, spectacle

magnification cannot explain this observation. Either the opposite trend, or no refractive error-related differences in pupil size have been reported in other studies. Hirsch and Weymouth (1949) reported a small, significant negative correlation between pupil size and refractive error in college-aged subjects with myopes having larger pupils. Chaidaroon and Juwattanasomran (2002) also found myopes had larger pupils than emmetropes across an age range of 18 to 54 years, although these data were not adjusted for age. Studies that found no significant refractive error-related difference in age-adjusted pupil size included an accommodative study of 18 to 35 year-old emmetropes and myopes (Charman and Radhakrishnan, 2009) and two studies encompassing wider age ranges (17 - 83 years (Winn *et al.*, 1994) and 20 - 73 years (Netto *et al.*, 2004). Similar results were found for non age-adjusted data, in an accommodative study comparing myopes to emmetropes aged 20 to 30 years (Subbaram and Bullimore, 2002), and a study involving young 18 to 26 year old emmetropes and myopes (Jones, 1990). Variations across studies in measurement techniques, illumination, method and degree of accommodation control and the ages of subjects are likely contributing factors to these different study outcomes.

4.4.4 Multifocal lenses and myopia progression

For multifocal lenses to be an effective means of controlling myopia progression they need to significantly reduce the hyperopic focus resulting from lags of accommodation, assuming the validity of this treatment paradigm. The MFD lenses achieve this by adding positive spherical aberration to the ocular aberrations, which shifts the best image plane in the myopic direction. Even if these lenses had no effect on accommodation, this myopic shift in optimum focus should have the desired effect of reducing the hyperopic defocus signal driving eye growth. However, the data from our study suggests that there is additional benefit for pupil sizes greater than approximately 5 mm, in the form of increased accommodative responses, which will reduce lags of accommodation compared to those seen with the SVD lens.

In considering the MFN lenses, it is known that a reading addition (such as that incorporated in the SVN lenses) decreases the accommodative demand for near objects and as a consequence also decreases the lag of accommodation compared to that with SVD lenses (Tarrant *et al.*, 2008). Obviously binocular wear of SVN lenses is not an option because of the detrimental effect on distance visual acuity and monovision (SVD lens for the dominant eye, SVN lens for the non-dominant eye) is also unacceptable because slowed myopia progression would be limited to the SVN-treated eye and lead to anisometropia (Phillips, 2005). MFN lenses provide an alternative method of reducing the accommodative demand with less compromise to distance vision, although the effective add is less than that of the corresponding SVN lens, due to the added negative spherical aberration in the MFN lens. Even though the MFN lenses induced more negative levels of spherical aberration compared to the SVN lenses and also compared to the SVD lenses, for larger pupils the accommodative responses for the MFN lenses were higher compared to the SVD lenses due to the near addition shifting the best image plane in the myopic direction (Figure 4-4), for this reason it is plausible that the MFN lens design could be as effective as the MFD lens design for myopia control.

For both the SVN and MFN lenses, the near addition shifts the best image plane in the myopic direction in 2 ways. Firstly, simply as a consequence of adding myopic defocus with the near addition and secondly by moving the zero spherical aberration condition to higher stimulus vergences. For example, for the emmetropes the position of zero spherical aberration shifts from between the 2 and 3 D stimulus vergences with the SVD lens (Figure 4-2A) to the 4 D stimulus

vergence with the SVN lens (Figure 4-3A), and for the myopes, it shifts from the distance target with the SVD lens (Figure 4-2B) to between the 2 and 3 D stimulus vergences with the SVN lens (Figure 4-3B). In both cases this has the effect of changing the original zero spherical aberration condition (with the SVD lens) to positive spherical aberration (with the SVN lens) and consequently for larger pupils shifting the best image plane of the SVN lens in the myopic direction compared to the SVD lens (Figure 4-4).

The near pupillary response is an important factor because of the pupil size dependency of the effect of spherical aberration on the accommodative response. Although it is generally accepted that increases in accommodation are accompanied by increases in pupillary constriction, there was considerable inter-subject variation in pupil constriction with accommodation, with some subjects showing negligible changes in pupil diameter with increased accommodative responses. Data from some recent studies also show similar variability in the near pupillary response (Gislen *et al.*, 2008, Radhakrishnan and Charman, 2007b, Schaeffel *et al.*, 1993).

Our subjects were slightly older compared to the age range typically targeted for myopia control therapy (children and teenagers) therefore changes in pupil sizes and the near pupillary response with age need to be taken into account. For subjects in the age range of 20 to 40 years, some studies have reported no systematic change in accommodative miosis with age although older individuals tend to have smaller pupils than younger individuals (Kasthurirangan and Glasser, 2006, Radhakrishnan and Charman, 2007b, Schafer and Weale, 1970) Conversely, other studies found increases in the pupillary near response with age and a negligible response for children younger than 10 years old (Schaeffel *et al.*, 1993, Wilhelm *et al.*, 1993). In the most recent study (Gislen *et al.*, 2008), children (9 to 10 years) were observed to have larger pupils and weaker accommodative pupil responses compared to adults (22 to 26 years). These trends of larger pupils and a reduced pupillary near response in children compared to adults therefore predict similar effects of the MF lenses on accommodative responses as described for pupils larger than 5 mm in the preceding discussion.

Although the myopes in our study had, on average, pupil diameters less than 5 mm for the near vergence conditions, such small pupil sizes do not appear to be characteristic of younger myopes. It seems reasonable to expect that myopes with pupils larger than 5 mm will experience similar changes in accommodative responses with MF lenses to emmetropes with pupils larger than 5 mm, given that for similar levels of spherical aberration, myopes show similar accommodative responses to emmetropes (Figure 4-2). Given also that the accommodative responses calculated using the NS metric for the emmetropes are very similar for the MF15N and MF15D lenses (Figure 4-4), either of these lenses should have the desired effect of reducing accommodative lags compared to the SVD lens.

In our previous, related study, we used a refractometer to measure the consensual accommodative responses of young adult emmetropes and myopes when wearing BF soft contact lenses and reported leads of accommodation at all test distances for all subjects (Tarrant *et al.*, 2008). However these results were based on the assumption that the BF lenses provided the full effective near addition prescribed, yet there was no way to verify this assumption and thus the presumed accommodative leads. To explain the latter, we hypothesized that the increased accommodative responses compared to those observed with the SVD lenses resulted from an interaction between defocus and spherical aberration induced by an increase in positive spherical aberration with the BF lenses. The results from the current study suggest that the effect of MF lenses on accommodative responses is more complicated, with added positive spherical

aberration producing increased responses for larger pupil sizes but decreased responses for smaller pupil sizes.

4.5 Conclusions

We have confirmed that OQMs can be used to determine accommodative responses from wavefront sensor data when wearing MF lenses. The accommodative responses calculated using Seidel defocus were similar to the results from previous studies in that paraxial rays became more hyperopic with added positive spherical aberration and more myopic with added negative spherical aberration. However, in the presence of spherical aberration the best image plane of an optical system is not the paraxial image plane, therefore metrics such as NS provide a better measure of the accommodative response. The influence of MF lenses on accommodation was affected independently by both spherical aberration and pupil size. For pupil diameters larger than approximately 5 mm, accommodative responses calculated with the NS metric became more myopic with added positive spherical aberration and more hyperopic with added negative spherical aberration. Both MFD and MFN lenses are predicted to have a therapeutic benefit in controlling myopia progression, although the optical basis for their effects on accommodative lags, the presumed stimulus for progression, is different.

Chapter 5

Long-term Effects of Orthokeratology on Accommodative and Pupillary Responses

Abstract

Purpose: To measure the changes in ocular aberrations induced by orthokeratology and to assess their long-term effect on the accommodative response.

Methods: Ocular aberrations were measured in 28 young myopic adults when viewing distance and 4 near vergences: 2, 3, 4 and 5 D. Measurements were made prior to and 4 weeks, 6 months and 1 year after being fit with orthokeratology (ortho-k) lenses. Paraxial curvature matching (Seidel defocus) and a neural sharpness (NS) optical quality metric were used to calculate the accommodative response.

Results: There was a significant increase in positive spherical aberration after ortho-k for all vergences and follow-ups. The accommodative response calculated by the NS metric increased significantly after ortho-k for the distance target at all follow-ups and for the 2 and 3 D stimulus vergences at 1 year. The accommodative response calculated by Seidel defocus decreased significantly after ortho-k for the 2 and 3 D stimulus vergences at all follow-ups and for the 4 D stimulus vergence at 4 weeks. After ortho-k the pupil diameter decreased significantly for the distance target at 4 weeks then increased significantly for all stimulus vergences at 1 year.

Conclusions: The positive spherical aberration induced by ortho-k produced a myopic shift in the best image plane defined by the NS metric and therefore increased accommodative responses for distance and near vergences, more so at 1 year due to the dramatic increase in pupil diameter. Increases in pupil sizes were hypothesized to be due to changes in both the pupillary light and near reflexes.

5.1 Introduction

Orthokeratology (ortho-k) is a clinical technique that uses reverse geometry rigid gas permeable contact lenses to remodel the anterior corneal surface to temporarily reduce myopic refractive errors (Mountford *et al.*, 2004, Swarbrick, 2006). Two recent studies, both involving myopic children, also suggest that ortho-k may slow myopia progression (Cho *et al.*, 2005, Walline *et al.*, 2009). In one of these studies involving 7-12 year old children, the mean increase in vitreous chamber depth over a 24 month period was approximately halved by ortho-k compared to spectacle lens wear (0.23 vs. 0.48 mm) (Cho *et al.*, 2005). In the other study involving similarly aged children, the mean change in vitreous chamber depth over a 2 year period was 0.11 mm less in those undergoing ortho-k compared to those wearing soft contact lenses (Walline *et al.*, 2009).

One theory offered in explanation for the slowing of myopia progression with ortho-k is the conversion of relative peripheral hyperopia to relative peripheral myopia, a consequence of treatment-induced changes in corneal shape (Charman *et al.*, 2006). Lending support to this theory, several studies have reported differences in peripheral refractive errors between myopes, emmetropes and hyperopes across the horizontal meridian, with myopes typically showing relative hyperopia in the periphery, and emmetropes and hyperopes showing relative peripheral myopia (Atchison *et al.*, 2006a, Atchison *et al.*, 2005, Millodot, 1981, Mutti *et al.*, 2000, Schmid, 2003, Seidemann *et al.*, 2002). These studies followed on from an earlier study in which hyperopic peripheral refractions were found to predominate in hyperopic and emmetropic adults who later became myopic (Hoogerheide *et al.*, 1971), and a later related study in which children who became myopic were found to have more hyperopic relative peripheral refractive errors before the onset of myopia (Mutti *et al.*, 2007). These various findings, along with parallel findings in animal studies showing influences of peripheral retinal defocus on eye growth regulation (Smith *et al.*, 2009), have been interpreted as evidence for a role of peripheral hyperopic defocus in the development of myopia (Wallman and Winawer, 2004).

The change in corneal shape associated with ortho-k also produces increased ocular aberrations (Berntsen *et al.*, 2005, Hiraoka *et al.*, 2005, Joslin *et al.*, 2003, Hiraoka *et al.*, 2008, Hiraoka *et al.*, 2007, Stillitano *et al.*, 2008). The largest increase was found with spherical aberration for all studies while some also found significant increases in horizontal coma related to decentration of the treatment zone (Hiraoka *et al.*, 2005, Joslin *et al.*, 2003). The overall increases in ocular aberrations likely account for reported reductions in low contrast visual acuity (VA) (Berntsen *et al.*, 2005, Hiraoka *et al.*, 2007) and contrast sensitivity (Hiraoka *et al.*, 2008, Hiraoka *et al.*, 2007), although some studies report no effect on either VA or contrast sensitivity after ortho-k (Johnson *et al.*, 2007, Stillitano *et al.*, 2008).

Of particular interest to the current study is the consistent finding across all studies that spherical aberration is most affected as it is also known to affect accommodation. For example, adding positive spherical aberration, either using specially designed soft contact lenses or through adaptive optics, results in a decrease in accommodation and vice versa (Collins *et al.*, 1997, Theagarayan *et al.*, 2009, Gamba *et al.*, 2009). It is not known whether the reported increases in spherical aberration with ortho-k affect accommodation.

The purpose of this study was to measure the changes in ocular aberrations induced by ortho-k and to assess the effect of the changes on accommodation. Because of reports of perceptual adaptation to one's own ocular aberrations (Artal *et al.*, 2004), measurements were

made at various time intervals after the initiation of therapy out to 1 year, to characterize the time course of any induced changes.

5.2 Methods

5.2.1 Subjects

Twenty-eight young myopic adults between 18 to 30 years (mean \pm SD: 22 \pm 3 years) participated in the study. Inclusion criteria for refractive error were between -1.00 and -5.00 D of myopia, astigmatism \leq 1.00 D and anisometropia $<$ 2.00 D. Previous rigid gas permeable contact lens wearers were not eligible. All participants had normal corrected VA (20/20 or better) and no ocular health or binocular vision anomalies, with binocular accommodative amplitudes and facilities also being within normal parameters based on age.

The study protocol conformed to the provisions of the Declaration of Helsinki and was approved by the University of California, Berkeley institutional review board. Informed consent was obtained from the participants after the nature and possible complications of the study were explained in writing.

5.2.2 Contact lens fitting

Prior to commencing ortho-k, participants underwent a initial baseline examination including manifest subjective refraction, best corrected Snellen VA, slit lamp evaluation, corneal topography, wavefront aberrations (see below), and ocular axial lengths (measured with an IOL Master (average of 5 readings; Carl Zeiss Meditec Inc., Dublin, CA)). Participants were fit with Paragon CRT lenses following the manufacturer's fitting guidelines, and made in Paragon HDS 100 material (Paragon Vision Sciences, Mesa, Arizona). They were instructed to wear their CRT lenses overnight for at least 7 hours every night while sleeping. Approximately 4 weeks after initiating ortho-k treatment the trial lens fitting parameters were finalized and the contact lenses worn for the remainder of the study were ordered. Follow-up examinations were conducted after the lens parameters were finalized and at approximately 6 months and 1 year after commencing ortho-k. Axial length measurements were repeated at the 1 year follow-up.

5.2.3 Accommodation measurements

Monochromatic wavefront aberrations were measured using a COAS wavefront sensor, (Abbott Medical Optics, Albuquerque, NM). Measurements were made of the dominant eye viewing a distance target and 4 near target vergences of 2, 3, 4 and 5 D. The near target was an external letter chart, viewed monocularly through a beam splitter, and positioned at the appropriate distance for each target vergence. It consisted of 4 lines each made up of 5 high contrast letters, and decreasing in size such that at each of the 4 near viewing distances, one line had an angular subtense of 12.5 minutes of arc. Participants were instructed to look at the middle letter of the appropriate line of letters and to keep the letters as clear as possible. The presentation sequence for the near targets was randomized. For each test condition 20 measurements were recorded continuously at a sample rate of approximately 10 Hz. Measurements were taken in the dark, with a small LED providing the illumination for the near target.

For the pre-treatment measurements participants wore soft hydrogel single vision distance contact lenses with their spherical equivalent distance prescription. Aberration measurements were repeated at 4 weeks, 6 months and 1 year after starting ortho-k.

5.2.4 Data analyses

The wavefront data were fit with a sixth order Zernike expansion calculated for a wavelength of 550 nm and natural pupil sizes. Accommodative responses for each test condition were calculated from the exported Zernike coefficients using 2 metrics: paraxial curvature matching (Seidel defocus) and maximizing optical quality using a neural sharpness (NS) metric (Chen *et al.*, 2005, Thibos *et al.*, 2004). The equation for Seidel defocus and the through-focus procedure used by the NS metric are described in detail in a previous paper (Tarrant *et al.*, 2010). To allow for comparisons of measurements made with different natural pupil sizes aberrations were converted to diopters; spherical aberration using the second term in the equation for Seidel defocus (Tarrant *et al.*, 2010), astigmatism using power vector notation (Thibos *et al.*, 1997), and coma using the equation for equivalent defocus (Thibos *et al.*, 2002).

For each stimulus vergence, the differences between post- and pre-treatment values were assessed for each follow-up using a one-way repeated measures ANOVA with Dunnett's two-sided multiple comparison test (pre-treatment values served as the reference ($\alpha_{FW} < 0.05$)). The effects of ortho-k on the following parameters were assessed: spherical aberration, astigmatism (J_0 and J_{45}), horizontal and vertical coma, accommodative responses calculated by the NS metric and Seidel defocus and pupil diameter. We found unanticipated changes in pupil diameters and consequently spherical aberration at 1 year compared to 4 weeks and 6 months of treatment, and further analyzed these differences using Scheffe's post-hoc procedure ($\alpha_{FW} < 0.05$).

The change in pupil diameter per diopter change in accommodative response was examined by plotting the pupil data against both the NS and Seidel accommodative responses. A linear regression was fitted to each individual's response and a one-way repeated measures ANOVA using Dunnett's two-sided multiple comparison test was used to assess differences between post- and pre-treatment values in the intercepts and slopes ($\alpha_{FW} < 0.05$). Scheffe's procedure ($\alpha_{FW} < 0.05$) was used to compare post-treatment intercepts and slopes derived from regression analyses.

5.3 Results

Twenty-three of the initial 28 participants completed the 6 month follow-up and 21 of them completed the 1 year follow-up. Reasons for discontinuing ortho-k included poor uncorrected VA ($n = 3$), lens discomfort ($n = 2$), personal concerns ($n = 1$) and moved from the area ($n = 1$). The mean (\pm SD) spherical equivalent (S_E) refractive error of the measured eye was -2.61 ± 1.07 D before ortho-k, -0.02 ± 0.17 D at 4 weeks, -0.14 ± 0.15 D at 6 months and -0.05 ± 0.19 D at 1 year. The mean axial lengths (\pm SD) were 24.72 ± 0.84 mm OD and 24.67 ± 0.71 mm OS before ortho-k and 24.65 ± 0.79 mm OD and 24.64 ± 0.69 mm OS after 1 year of treatment.

Uncorrected VAs at 4 weeks were 20/25 or better, with 79% achieving 20/20 or better. At 6 months uncorrected VAs were 20/25 or better for all except one subject (20/30) with 65% achieving 20/20 or better. The subject with reduced acuity was not fully corrected by the ortho-k procedure; their manifest refractive error was -0.50 DS OU. At 1 year uncorrected VAs were 20/20 or better for all participants, including the one subject with reduced VA at 6 months.

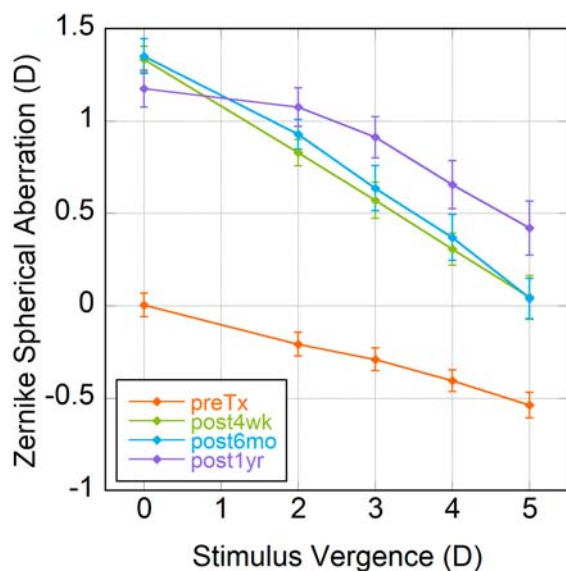


Figure 5-1. Zernike spherical aberration as a function of stimulus vergence for pre-treatment, and post-4 week, 6 month and 1 year follow-ups. Error bars are \pm SEM.

There were no significant changes in either astigmatism (J_0 and J_{45}) or coma (horizontal and vertical) associated with ortho-k over the duration of the study. There was a significant shift in spherical aberration in the positive direction after ortho-k for all stimulus vergences and follow-ups (Figure 5-1). In comparing spherical aberration at 4 weeks, 6 months and 1 year, it was significantly higher only at 1 year compared to 4 weeks for the 3 and 4 D stimulus vergences.

There were significant increases in accommodative responses calculated using the NS

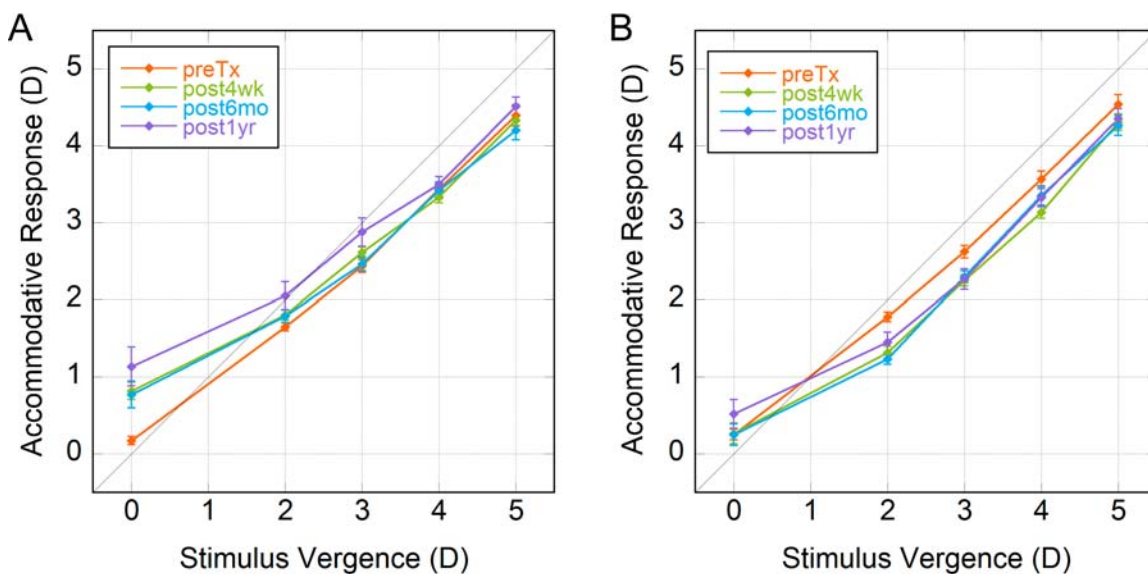


Figure 5-2. Accommodative responses calculated using (A) the NS metric and (B) Seidel defocus for pre-treatment, and post-4 week, 6 month and 1 year follow-ups. Error bars are \pm SEM.

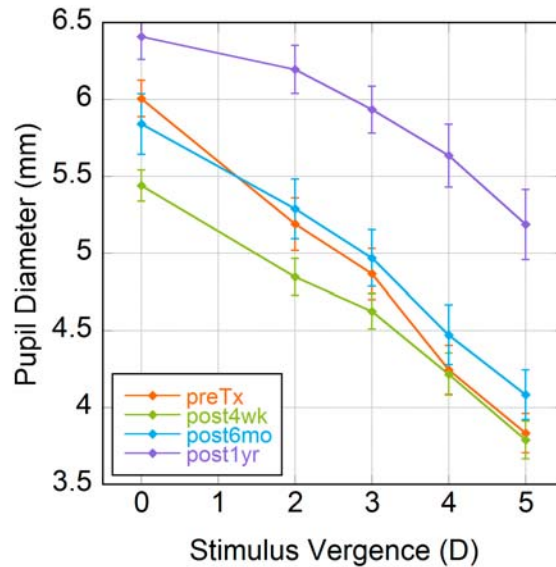


Figure 5-3. Pupil diameter as a function of stimulus vergence for pre-treatment, and post- 4 week, 6 month and 1 year follow-ups. Error bars are \pm SEM.

metric for the 2 and 3 D stimulus vergences after 1 year of ortho-k, and the distance target at all follow-ups (Figure 5-2A). In contrast, there were significant decreases in accommodative responses calculated using Seidel defocus after ortho-k for the 2 and 3 D stimulus vergences at all follow-ups, and for the 4 D stimulus vergence at 4 weeks (Figure 5-2B). Note that the residual uncorrected refractive errors are less than the post-treatment increases in the lead of accommodation for the 0 D (distance) stimulus, calculated using the NS metric, and thus can not account for them.

The pupil diameter decreased significantly for the distance target at 4 weeks after ortho-k and increased significantly for all stimulus vergences at 1 year (Figure 5-3). In comparing pupil diameters at 4 weeks, 6 months and 1 year, they were significantly larger at 1 year compared to both 4 weeks and 6 months for all stimulus vergences, and larger at 6 months compared to 4 weeks only for the distance target. The results of linear regression analyses of pupil diameter versus calculated accommodative responses for the NS metric and Seidel defocus reflect the above trends; the intercept is smaller at 4 weeks and larger at 1 year compared to pre-treatment

Table 5-1. Results of linear regression analyses (\pm SEM) with pupil diameter as the independent variable and accommodative response as the dependent variable.

	NS accommodative response		Seidel accommodative response	
	Intercept (mm)	Slope (mm.D ⁻¹)	Intercept (mm)	Slope (mm.D ⁻¹)
Pre-treatment	6.04 \pm 0.16	-0.50 \pm 0.04	6.10 \pm 0.17	-0.49 \pm 0.04
Post 4 week	5.81 \pm 0.15 [‡]	-0.47 \pm 0.05	5.54 \pm 0.13 ^{†‡}	-0.41 \pm 0.04
Post 6 month	6.21 \pm 0.25 [‡]	-0.50 \pm 0.05	5.90 \pm 0.21 [‡]	-0.42 \pm 0.03
Post 1 year	6.97 \pm 0.25 [†]	-0.38 \pm 0.07	6.64 \pm 0.18 [†]	-0.32 \pm 0.05 [†]

([†] indicates significant differences compared to pre-treatment, [‡] indicates significant differences compared to 1 year follow-up)

data (Table 5-1). The slopes of the regression lines derived from the 1 year data also tended to flatten compared to those derived from pretreatment data, although only the slopes derived from Seidel defocus data were significantly different.

5.4 Discussion

As expected and consistent with results from previous ortho-k studies, we observed significant increases in spherical aberration with ortho-k (Berntsen *et al.*, 2005, Hiraoka *et al.*, 2005, Hiraoka *et al.*, 2008, Hiraoka *et al.*, 2007, Joslin *et al.*, 2003, Stillitano *et al.*, 2008). However, unanticipated was the long term increase in spherical aberration, which was reflected in the difference in spherical aberration after 1 year compared to 4 weeks and 6 months of treatment. The latter effect was also not reported in two previous long-term ortho-k studies (Hiraoka *et al.*, 2008, Stillitano *et al.*, 2008), both found an initial increase in spherical aberration but no further change over the 1 year study duration. This discrepancy between our study outcomes is likely a product of differences in wavefront data analysis, specifically our use of natural instead of fixed pupil diameters as in the two other studies. Thus for our subjects, the positive shift in spherical aberration recorded at 1 year compared to 4 weeks and 6 months for all near targets reflected the significantly larger pupil diameters at 1 year. This difference in study outcomes highlights the potential risk of introducing artifacts through the use of fixed pupil sizes in such analyses. Interestingly for the distance target, spherical aberration was slightly more negative at 1 year compared to 4 weeks and 6 months, despite the pupil diameter being significantly larger, raising the possibility that participants were accommodating more at 1 year. Accommodative responses calculated using the NS metric for the distance target appear to support this conclusion.

Our subjects did not show significant changes in either horizontal or vertical coma similar to the findings of Berntsen *et al.* (2005), although others have reported significant changes in either or both horizontal and vertical coma which were attributed to lens decentration (Hiraoka *et al.*, 2005, Hiraoka *et al.*, 2008, Hiraoka *et al.*, 2007, Joslin *et al.*, 2003, Stillitano *et al.*, 2008). For one of two long-term studies, Hiraoka *et al.* (2008) reported no significant fluctuations in third-order (coma-like) high-order aberrations (HOA), while the other, Stillitano *et al.* (2008) reported that coma (horizontal + vertical terms) increased over the first 90 days and then stabilized. No significant changes in either horizontal and vertical astigmatism (J_{180}) or oblique astigmatism (J_{45}) were observed over the course of our study. This observation was similar to that of Stillitano *et al.* (2008) who reported no significant change in astigmatism ($J_{180} + J_{45}$) from baseline over the course of their study.

The accommodative responses calculated by the NS metric indicate that the shift in positive spherical aberration induced by ortho-k results in an increased response at lower stimulus vergences, more so at 1 year due to the dramatic increase in pupil sizes. These increased responses can be explained in terms of the effect of spherical aberration on the best image plane. Spherical aberration changes the optimum focus causing it to shift away from the paraxial focus towards the marginal focus (Charman and Jennings, 1976), and with positive spherical aberration the optimum focus becomes more myopic as the pupil size increases (Meeteren van, 1974).

The interdependence between spherical aberration, optimum focus and accommodative responses is illustrated in Figure 5-4 for positive spherical aberration, which was the average finding for our study subjects for all near targets after ortho-k. Figure 5-4A shows the best geometric focus (disc of least confusion, described by ray tracing) located three quarters of the

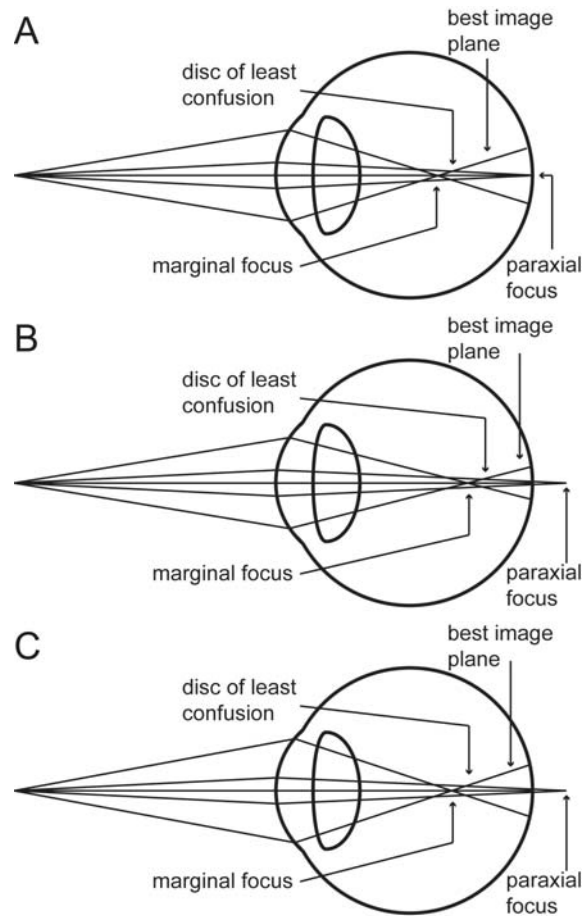


Figure 5-4. (A) The effect of positive spherical aberration on the best geometric focus (disc of least confusion) and the best image plane (determined by the PSF). (B) Adding negative defocus shifts the paraxial focus and the best image plane in the hyperopic direction. (C) Relaxing accommodation shifts the paraxial focus in the hyperopic direction, however the best image plane may shift in the myopic direction as positive spherical aberration increases.

way between the paraxial and marginal foci, whereas the best image plane (determined by the point spread function (PSF)) is halfway between the two (Mouroulis, 1999). For the eye to alter its accommodative state to bring into focus the best image plane instead of the paraxial image plane defocus would shift in the hyperopic direction (Figure 5-4B), however as accommodation relaxes, spherical aberration shifts in the positive direction and the pupil diameter increases also producing an increase in positive spherical aberration (Figure 5-4C). The net effect of the increase in positive spherical aberration will be a shift in the best image plane in the myopic direction relative to the paraxial image plane.

In the previous chapter we found a pupil size dependency for the effect of spherical aberration on the accommodative responses calculated by the NS metric. The same trend can be observed in the data reported here. For pupil diameters larger than approximately 5 mm, increases in positive spherical aberration resulted in increased accommodative responses. Results for the distance target and the 2 D stimulus vergence at 4 weeks and 6 months and all stimulus vergences at 1 year illustrate this point. However, as the pupil diameter became smaller with increasing stimulus vergence the opposite effect was observed. Increases in positive spherical

aberration resulted in decreased accommodative responses, for example the 5 D stimulus vergence at 4 weeks and 6 months. The latter result is similar to the results calculated by Seidel defocus because the analysis for the NS metric has been reduced to the paraxial region.

The accommodative responses calculated using Seidel defocus are comparable with results from accommodation studies using autorefractors, which typically restrict measurements to the paraxial region of the pupil (Collins *et al.*, 1997, Theagarayan *et al.*, 2009). Both studies found that added positive spherical aberration produced a decrease in the accommodative response. The same trend was observed with an adaptive optics system used to add positive spherical aberration, where the accommodative response was determined using paraxial curvature matching (Seidel defocus) (Gambra *et al.*, 2009).

While Allen and O'Leary (2006) found that binocular accommodative lag was highly correlated with myopia progression for both early-onset and late-onset myopes, the changes in accommodative responses in our subjects cannot be attributed to changes in refractive error over the 1 year duration. Our subjects exhibited a small reduction in axial length over the course of the study indicating that their refractive errors were stable.

Adaptation to image blur has been shown to lead to increased accommodation in myopes when a reduction in contrast was introduced using Bangerter Foils (Vera-Diaz *et al.*, 2004), raising the question of whether blur adaptation could have contributed to the changes in accommodative responses reported here. Although the added spherical aberration induced by ortho-k, considered in isolation, would produce blur in the retinal image, because of the interaction between defocus and spherical aberration and the resultant improvement in image quality that can be achieved through their appropriate combination (Applegate *et al.*, 2003, Chen *et al.*, 2005, Cheng *et al.*, 2004b), optimization of image quality rather than adaptation to image blur would seem a more plausible explanation for observed changes in accommodation after ortho-k. Note also that when blur is induced with positive defocus rather than with diffusing filters, blur adaptation had no effect on steady-state accommodative responses or the accommodative stimulus-response curve gradient (Cufflin *et al.*, 2007, George and Rosenfield, 2002).

The effect of ortho-k on pupil size varied with treatment duration, with the increases observed after long term treatment being both unexpected and intriguing. At 4 weeks pupil diameters were markedly reduced for the distance target and the 2 and 3 D stimulus vergences. At 6 months recorded pupil sizes had returned approximately to their pre-ortho-k values for all stimulus vergences, while accommodative responses calculated for both the NS metric and Seidel defocus remained unchanged compared to 4 week values. At 1 year pupil diameters were significantly larger compared to values recorded at both 4 weeks and 6 months for all stimulus vergences, even though accommodative responses calculated using Seidel defocus were not significantly altered, and responses calculated using the NS metric were increased. Thus at both 6 month and 1 year follow-ups, relative pupillary dilation was observed in the absence of any reduction in accommodative response.

A plausible explanation for the initial decrease in pupil size is accommodative miosis, assuming that subjects increased their accommodative responses after ortho-k. However, accommodative responses determined by Seidel defocus showed no change for the distance target and reduced responses for the 2 and 3 D stimulus vergences after ortho-k. Furthermore, accommodative responses calculated by the NS metric were higher after ortho-k because the increase in positive spherical aberration shifted the best image plane in the myopic direction and

not necessarily because accommodative effort was increased. This seemingly contradictory observation of pupillary constriction in conjunction with minimal change or reduced accommodation implies that the pupil responses are not tightly coupled to accommodative responses. This apparent independence of the pupillary near response was explained by Loewenfeld (1993) as a co-movement elicited together with accommodation and convergence but not brought about by either. One qualification to the above discussion relates to the assumption that a hyperopic shift in Seidel defocus is always associated with a reduction in accommodation; this may be an oversimplification as the paraxial image plane is also influenced by spherical aberration.

The linear regression analyses showed changes in both the intercept and slope of the pupillary responses. Changes in the intercept may arise due to changes in the pupillary light response whereas changes in the slope may be due to changes in the pupillary near response. It is also evident that changes induced by ortho-k occurred at different rates for accommodative responses compared to pupillary responses. Specifically, accommodative responses did not change significantly after 4 weeks whereas pupillary responses continued to change over the entire treatment period.

While it is possible that the illumination conditions under which measurements were made may have changed slightly over the study duration, such changes are expected to be small and so unlikely to explain the increases in pupil size observed at the 1 year follow-up. The ambient room lighting was scotopic for all measurements and thus not subject to variation over time. The small LED illuminating the near target remained at a fairly constant level to ensure participants could see the target clearly and it is doubtful that light reflected off of the target would have significantly affected pupil size. The only other light source was the super luminescent diode (SLD) used by the COAS for the aberration measurements, however as its radiant intensity was not measured during the study it is unknown whether this may have changed.

To assess whether any changes in SLD intensity could have an effect on pupil diameter, a secondary study measured accommodative responses for the 2 and 3 D stimulus vergences with variable SLD power settings. As the power setting was increased from the lowest to the highest setting pupil diameter (\pm SD) decreased from 4.90 ± 0.04 mm to 4.34 ± 0.09 mm for the 2 D stimulus vergence but increased from 4.05 ± 0.08 mm to 4.20 ± 0.07 mm for the 3 D stimulus vergence. These results argue against dimming of the SLD over the course of the study, as an explanation for the long-term increase in pupil size of our subjects. Furthermore, because the process of recruiting, screening and fitting contact lenses extended over a year, the 1 year follow-ups for some subjects were conducted around the same time as the 4 week and 6 month follow-ups for other subjects, likely diluting any effect of a reduction in SLD intensity.

As the reshaping of the cornea and resultant increase in spherical aberration with ortho-k are similar to that produced by refractive surgery for myopia (Marcos *et al.*, 2001, Moreno-Barriuso *et al.*, 2001) it is possible that similar changes in pupil sizes may have been reported with these patients. The single study which reported pre- and post-treatment pupil diameters 3 months after surgery for myopic and hyperopic refractive corrections combined found no significant difference in pupil sizes (Spadea *et al.*, 2005). However, relative mydriasis was observed after unilateral photorefractive keratectomy (PRK) in all treated eyes in a small study with a longer follow-up period (21.8 ± 12.6 months) (Geerling *et al.*, 2000). The amount of anisocoria did not correlate with the applied laser energy, ablation depth, or refractive change, but showed a negative correlation with increasing time after PRK.

Nevertheless the reasons for our subjects significantly larger pupils at 1 year are not simple to explain. While the larger pupils at 1 year result in more spherical aberration compared to that recorded at 4 weeks and it is doubtful that retinal image quality would improve by any quantifiable measure, image quality may not have become significantly worse. For example, Strang *et al.* (1999) demonstrated that the contrast sensitivity function (CSF) did not necessarily deteriorate with increasing pupil size, a reflection of the complex interactions between individual aberrations, defocus and pupil size. In the latter study, the subject with the largest spherical aberration exhibited the least variation in CSF with pupil size while the subject with the least spherical aberration exhibited the greatest variation in CSF with pupil size. In another study of relevance, Woodhouse (1975) found that the pupil size which gave the highest resolution was close to the size of the natural pupil for all light levels, the implication being that the pupillary light response serves to optimize VA. Specifically for the case of an 8 mm pupil, there was no loss of resolution at low luminance levels and only a small (< 19 %) loss of resolution at high luminances, while for a 2 mm pupil, there was no loss of resolution at high luminance levels but up to a 57% loss of resolution at low luminances.

It is possible that neural adaptation to optical aberrations may play a role in the observed changes in pupil sizes. Previous studies indicate that the neural visual system was adapted to the unique pattern of ocular monochromatic aberrations to which it was exposed (Artal *et al.*, 2004) and that the best subjective image quality occurred when some of these aberrations were left uncorrected (Chen *et al.*, 2007). However it was not clear from either of these studies what was the nature of the visual improvement produced by the neural adaptation, nor the rate at which the visual system could adapt to changes in aberrations. Refractive surgery studies reporting on the time course of post-operative night vision complaints could provide some clues as to the time frame required for neural adaptation. It has been demonstrated that most visual disturbances decrease with time (Fan-Paul *et al.*, 2002, Pop and Payette, 2004, Schallhorn *et al.*, 2003) with only a small percentage of patients experiencing significant difficulties 12 months after surgery. While this improvement in quality of vision with time has been attributed in part to neural adaptation it also results from physical-optical improvement with decreased corneal scarring and corneal remodeling (Fan-Paul *et al.*, 2002). There are also reports of rapid adaptation to simulated optical blur, within minutes (Webster *et al.*, 2002), leaving open the question of whether there may be more than one adaptation process involved.

In terms of controlling myopia progression shifting the best image plane in the myopic direction for distance and near vision should be beneficial, assuming that the fovea provides some input to the emmetropization process. Given that emmetropization is a visually guided process, it should also be influenced more by optimum focus than paraxial focus. The increased pupil sizes with ortho-k over the 1 year treatment period also should be advantageous as this produced increased myopic shifts in the best image plane and despite the accompanying increase in spherical aberration did not adversely affect VA. Results from the LORIC study, involving the use of ortho-k to control myopia in children, also confirm that higher levels of spherical aberration appear favorable in that they found the change in vitreous chamber depth was lowest for participants with the most myopic refractive error at baseline (Cho *et al.*, 2005), and spherical aberration has been shown to be correlated with the amount of myopic correction (Hiraoka *et al.*, 2005, Hiraoka *et al.*, 2007).

In summary, the positive spherical aberration induced by ortho-k produced a myopic shift in the best image plane defined by the NS metric and therefore increased accommodative responses for distance and near targets, more so at 1 year due to the dramatic increase in pupil

diameter. The increased pupil sizes appear to be due to changes in both the pupillary light and near reflexes as evidenced by observed changes over the treatment period in both the slopes and intercepts of the pupil diameter versus accommodative response function.

Chapter 6

Dissertation Summary and Discussion

6.1 Major Findings of the Dissertation

The relative success of orthokeratology in slowing myopic eye growth compared to alternative methods such as bifocal spectacles and PALS has heralded a resurgence of interest in optical treatments for the control of myopia progression. Because ortho-k does not involve the use of a reading addition, it is presumed that this treatment has no effect on the accommodative response. However, the fact that the aberration profile induced by ortho-k is similar to that induced by a center-distance multifocal contact lens, together with the comparative success of MF SCL in slowing myopia progression, suggest that these two treatments may influence eye growth by similar mechanisms. What is lacking are comprehensive studies of the optical effects of these treatments, beyond simple ray tracing models, and their effects on accommodation. This dissertation work, which includes 4 main studies, represents efforts to characterize the effects of MF SCL and ortho-k, on the ocular aberrations and accommodative responses of young adult emmetropes and myopes.

The monocular accommodative responses of young adults wearing BF SCL were measured in a preliminary study using a refractometer. Because the discontinuities in power across the BF lens precluded taking readings through the lenses with this instrument, consensual accommodative responses, recorded under monocular conditions were used as a measure of their effects on accommodation. The assumption that consensual accommodative responses adequately represent accommodative behavior through the lenses was a limitation of this study. Interpretation of the results was also based on the assumption that subjects accessed the full near addition prescribed; however there was no way to verify this assumption and thus the calculated accommodative leads. Nevertheless, the results from this study suggested that the effect of BF SCLs on the accommodative responses of young subjects was more complex than could be predicted from the presence of a reading addition.

Study design refinements that eliminated the need to rely on consensual accommodation measurements included the selection of a MF SCL design that had a continuous power profile across the lens and the use of a wavefront sensor that allowed readings to be taken through the lenses. However, there remained the problem of interpretation of these results as there was no standard method for determining the accommodative response from wavefront aberrations; instead it had been assumed that methods for calculating objective refractions were also applicable to accommodation. To address this assumption some of the latter methods were evaluated to determine their applicability for accommodation research. Accommodative responses were calculated using each of the following techniques: least squares fitting (Zernike defocus), paraxial curvature matching (Seidel defocus) and a through-focus procedure which selected the best image quality determined by each of 6 optical quality metrics (PFWc, PFSc, PFCc, NS, VSMTF, and CAG). During accommodation, when the eye has negative spherical aberration, Zernike defocus tended to underestimate whereas Seidel defocus tended to overestimate the accommodative response. A better approach was to determine the best image plane using a suitable metric, such as NS or VSMTF, with the accommodative error then being calculated with reference to this plane.

The above findings were applied in the analysis of the data obtained from young adult myopes and emmetropes wearing center-distance (MFD) and center-near (MFN) MF SCLs. The purpose of this study was to investigate the effects of MF lenses on the ocular aberrations and accommodative responses and compare the responses of emmetropes and myopes. Monochromatic wavefront aberrations were measured for a distance target and 4 near target vergences. Four MF lenses were tested, including MFD and MFN designs, both with +1.50 D and +2.00 D near additions. The results from the MFD lenses were compared to those from a single vision distance lens (SVD), and the results from the MFN lenses were compared to the results from a single vision near lens (SVN). The MFD lenses added positive spherical aberration relative to the SVD lens and the MFN lenses added negative spherical aberration relative to the SVN lens. The accommodative responses were determined using 4 different metrics with emphasis given to the results obtained with the NS metric. For pupils larger than approximately 5 mm, accommodative responses determined by the NS metric increased with the MFD lenses compared to that with the SVD lens and decreased for the MFN lenses compared to that with the SVN lens. Differences in accommodative responses between emmetropes and myopes could be accounted for by differences in spherical aberration and pupil sizes.

The final study measured the change in ocular aberrations induced by ortho-k and assessed the long-term effect of this treatment on accommodative responses. Measurements were made prior to and 4 weeks, 6 months and 1 year after commencing ortho-k. Similar to the MFD lenses, ortho-k added positive spherical aberration to the ocular aberrations, resulting in increased accommodative responses for the 0, 2 and 3 D stimulus vergences at 1 year compared to pre-treatment measurements. An unexpected result was the significant increase in pupillary diameter for all stimulus vergences at 1 year compared to pre-treatment values. This effect appeared to be due to changes in both the pupillary light and near reflexes, as evidenced by both an increase in overall pupil diameter and a flattening of the slope of the individual pupil diameter versus accommodative response functions.

6.2 Discussion

The major findings of this dissertation contribute considerably to understanding the effects of MF SCLs and ortho-k, two novel myopia control treatments, on accommodation and thus foveal vision. Furthermore, emmetropization, being a visually guided process, is likely to be influenced more by optimum focus than paraxial focus, when there is discrepancy between the two. Specifically in terms of controlling myopia progression, shifting the best image plane in the myopic direction for distance and near vision should be beneficial.

Both MFD and MFN lenses produce myopic shifts in the best image plane, the former by adding positive spherical aberration and the latter by added positive power via the center near addition. For pupils larger than approximately 5 mm, both lenses resulted in increased accommodative responses determined by the NS metric compared with the SVD lens. Assuming hyperopic defocus from accommodative lags is a driving factor in myopic eye growth, these effects on accommodative responses are consistent with the reported slowing of myopia progression with MFD lenses and predict a similar benefit from MFN lenses.

As with the MFD lenses, the spherical aberration induced by ortho-k shifts the best image plane in the myopic direction for both distance and near vergences. The dramatic increase in pupil sizes over the 1 year treatment period were also advantageous in terms of controlling myopia progression, due to the associated increase in spherical aberration and accompanying

increase in accommodative responses. Importantly visual acuity was not adversely affected. This apparent benefit of increased levels of spherical aberration is consistent with reported better treatment effects for individuals with higher refractive errors at baseline and consequently greater ortho-k induced spherical aberration.

Improved understanding of the complex interactions between spherical aberration, pupil size and accommodative responses represents one of the major contributions of this dissertation to the scientific literature. Results reported herein also highlight the inherent limitations of conclusions about the performance of optical treatments based on theoretical models, which can not account for the many unknown variables associated with the optics of individual eyes; instead *in vivo* longitudinal measurements of ocular parameters are essential to fully understand such treatment effects. The results from this dissertation also provide directions for developing new optical treatments for the control of myopia progression and also guidance for designing clinical studies directed at understanding such treatment effects and the origin of inter-subject differences in treatment efficacy.

6.3 Future Work

Further investigation involving long-term studies of the contact lens treatments targeted in this dissertation research should be conducted to expand upon the findings reported herein, to confirm the findings of related small-scale clinical trials of the same, and to address as yet unresolved questions. Key issues are listed below.

- i. Effectiveness of MFD versus MFN lenses in controlling myopia progression: Such a study would aid in assessing whether the treatment effect is primarily a product of altered foveal defocus or whether peripheral retinal defocus is also implicated, given that MFN lenses have different optical effects on the peripheral retina compared to MFD lenses. Specifically, the defocus imposed on the peripheral retina will be relatively more myopic with MFD compared to MFN lenses.
- ii. Relationship between the magnitude of spherical aberration and the treatment effectiveness: Because of inter-subject differences in spherical aberration, changes in spherical aberration with accommodation, pupil sizes and pupillary near responses, the MF lenses will not necessarily induce the same amount of spherical aberration in different individuals. For any optical device under consideration as an anti-myopia treatment, it will be important to quantify both the added spherical aberration imposed by the treatment and the resultant induced spherical aberration, as the relationship between these two quantities is not predictable and may be non-linear.
- iii. Relationship between pupil sizes and the treatment effectiveness: Studies need to be undertaken to address the question of whether there is a minimum pupil size for achieving myopia control with MF SCLs and ortho-k. The questions of whether MFD lenses have the same effects on pupillary responses as ortho-k and whether MFN lenses affect pupillary responses also need to be addressed.
- iv. Relationship between individual aberration patterns and treatment effectiveness: Accommodative responses determined by the NS metric were on average midway between Seidel and Zernike defocus, however because of differences in individual aberrations other than spherical aberration, individual responses varied from being close to Seidel defocus (i.e. higher) to below Zernike defocus (i.e. lower) for eyes with negative spherical aberration during accommodation. A study to correlate the pattern of

individual aberrations associated with these shifts in the accommodative response to higher or lower values would identify other aberrations that may be important in determining the success of manipulating the accommodative response by inducing changes in spherical aberration alone. For example, with optical treatments that create positive spherical aberration during accommodation, if the accommodative response is closer to Seidel defocus (i.e. lower), the question of whether these participants experience less effective myopia control compared with those with accommodative responses closer to Zernike defocus (i.e. higher) needs to be addressed.

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