Anatomy and Pathology/Oncology

Axial Eye Growth and Refractive Error Development Can Be Modified by Exposing the Peripheral Retina to Relative Myopic or Hyperopic Defocus

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Submitted: April 4, 2014
Accepted: August 25, 2014

Citation: Benavente-Pérez A, Nour A, Troilo D. Axial eye growth and refractive error development can be modified by exposing the peripheral retina to relative myopic or hyperopic defocus. *Invest Ophthalmol Vis Sci*. 2014;55:6765–6773. DOI:10.1167/iovs.14-14524

Purpose. Bifocal contact lenses were used to impose hyperopic and myopic defocus on the peripheral retina of marmosets. Eye growth and refractive state were compared with untreated animals and those treated with single-vision or multizone contact lenses from earlier studies.

Methods. Thirty juvenile marmosets wore one of three experimental annular bifocal contact lens designs on their right eyes and a plano contact lens on the left eye as a control for 10 weeks from 70 days of age (10 marmosets/group). The experimental designs had plano center zones (1.5 or 3 mm) and +5 diopters [D] or −5 D in the periphery (referred to as +5 D/1.5 mm, +5 D/3 mm and −5 D/3 mm). We measured the central and peripheral mean spherical refractive error (MSE), vitreous chamber depth (VC), pupil diameter (PD), calculated eye growth, and myopia progression rates prior to and during treatment. The results were compared with age-matched untreated ($N = 25$), single-vision positive ($N = 19$), negative ($N = 16$), and +5/−5 D multizone lens-reared marmosets ($N = 10$).

Results. At the end of treatment, animals in the −5 D/3 mm group had larger ($P < 0.01$) and more myopic eyes ($P < 0.05$) than animals in the +5 D/1.5 mm group. There was a dose-dependent relationship between the peripheral treatment zone area and the treatment-induced changes in eye growth and refractive state. Pretreatment ocular growth rates and baseline peripheral refraction accounted for 40% of the induced refraction and axial growth rate changes.

Conclusions. Eye growth and refractive state can be manipulated by altering peripheral retinal defocus. Imposing peripheral hyperopic defocus produces axial myopia, whereas peripheral myopic defocus produces axial hyperopia. The effects are smaller than using single-vision contact lenses that impose full-field defocus, but support the use of bifocal or multifocal contact lenses as an effective treatment for myopia control.

Keywords: eye growth, refractive error, peripheral defocus, contact lenses, myopia control

Investigative Ophthalmology & Visual Science

The growth and refractive state of the eye can be manipulated by controlling imposed retinal defocus. Changes in eye growth that lead to compensatory refractive changes occur after imposing hyperopic defocus with negative power lenses or myopic defocus with positive power lenses in several animal models, including primates, and result in larger and more myopic eyes, or shorter and more hyperopic eyes, respectively.[1–6] From other studies with animal models we also know that when hyperopic and myopic defocus is presented simultaneously using spectacles or contact lenses, or when hyperopic defocus is interrupted and replaced by myopic defocus, the eye compensates for the myopic defocus.[7–13] These findings provide a general proof of concept for an optical approach to control refractive error development, and support the possibility of slowing down myopia progression with optical treatments that correct distance vision, while providing simultaneous myopic defocus.[14–17] The use of positive addition lenses such as progressive addition lenses (PALs)[18–21] and bifocal lenses[22] has been shown to slow myopia progression by an average of 0.20 diopters [D]/year,[18–21] increasing to 0.27 D/year when PALs were used in children with high accommodative lags and near esophoria,[19] and up to 0.41 D/year when multifocal lenses were combined with atropine.[23] Data from three recent clinical pilot studies, two of which used multifocal contact lenses instead of spectacle lenses, showed that adding myopic defocus to the distance correction reduced myopia progression by an average of 0.27 D/year after 1 year,[15,16] which is slightly better than the effect seen at 1 year using PALs[18–21] or bifocal lenses.[22] Recent studies of orthokeratology (ortho-k) contact lenses show promise in reducing myopia progression as well by reducing the rate of axial eye growth up to 57% compared with spectacle and soft contact lens wearers.[24–28] The reduction in growth rate may be due to the addition of more myopic defocus to the retinal periphery. Ortho-k lenses have a steeper slope to the secondary peripheral curve compared with the central base curve that results in a thicker peripheral cornea with more positive power compared with a flatter central cornea with less.

Considering the clinical and animal experimental studies together, the reduction in myopia progression observed in the initial clinical studies using soft or ortho-k contact lenses to date, and the likelihood that lens designs and treatment

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procedures have yet to be optimized, optical treatments to reduce myopia progression may be sufficient to decrease the incidence of pathologies associated with myopia.[29]

In our lab, we have previously studied the effects on emmetropization of treating marmoset eyes with single-vision positive or negative power contact lenses[3,30] and with a multizone contact lens design that alternated positive and negative powers.[8] In the alternating multizone lens we found that eyes compensated more for the more myopic defocus.[8] In this current study, we describe the axial growth and refractive changes that occur in the marmoset eye when we use contact lenses of different optical powers that imposed defocus more to the peripheral retina than to the central retina. We used contact lenses for our study instead of spectacle lenses because they provide better lens centration and are less affected by eye movements. We evaluated the role of pupil size and peripheral defocus field size in the compensatory changes observed. We compared the results presented here to results obtained in early studies of animals treated with single-vision negative and positive defocus,[3,30] simultaneous full-field positive and negative defocus,[8] and untreated control animals.

Materials and Methods

Three custom contact lens designs (Medlens Innovations Inc., Front Royal, VA, USA) were used to impose relative hyperopic or relative myopic defocus on 30 (N = 10/group) juvenile marmosets (*Callithrix jacchus*). All three designs were annular concentric bifocal contact lenses with plano (0 D) center diameters of 1.5 or 3 mm, and +5 or −5 D in the periphery: 1.5 mm center plano with +5 D in the periphery (referred to as +5 D/1.5 mm); 3 mm center plano +5 D in the periphery (referred to as +5 D/3 mm), and 3 mm center plano with −5 D in the periphery (referred to as −5 D/3 mm). All contact lenses had total diameters of 6.0 or 6.5 mm, base curves of 3.6 or 3.8 mm, and were made of methafilcon A (55% water content, oxygen permeability DK: 17).

We fit all contact lenses following our published protocol: 0.10 mm flatter than the flattest keratometry measurement and we assessed the fit using an ophthalmoscope.[8,30,31] No corneal complications were observed in any of the animals treated in this or earlier studies.

We measured the pupil diameters of all our experimental marmosets before and during treatment without cycloplegia at animal room light levels (~700 lux). The average of five images of the pupil were captured using a modified video camera and processed using Image J (National Institutes of Health [NIH], Bethesda, MD, USA). The corresponding central hemifield widths imposed by each lens design for the average pupil size at each time point were calculated from Carkeet[32] and summarized in Table 1. Each hemifield width calculation used the treatment group average anterior chamber depth (ACD) at each time point and a vertex distance of 0 mm.

Marmosets wore the experimental contact lens on the right eye (experimental eye) and a plano control contact lens of same dimensions and material on the fellow eye (control eye) for an average of 9 hours light/15 hours dark cycle following an established protocol for contact lens rearing in marmosets.[8,30,31] Data from earlier studies from age-matched untreated (N = 25), single-vision positive (N = 19, OD: +5 D OS: plano), negative (N = 16, OD: −5 D, OS: plano) and multizone contact lens–reared marmosets (N = 10, OD: simultaneous +5/−5 D, OS: plano) were used for additional comparisons and controls.[8,30] All animal care, treatment, and experimental protocols were reviewed and approved by the SUNY College of Optometry Institutional Animal Care and Use Committee (New York, NY, USA) and conformed to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Ocular biometry and mean spherical refractive error (MSE) were primary outcomes and were measured using our standard protocol for lens treatment.[8] We made two measures during pretreatment (the first one, 3–4 weeks prior to lens rearing, and one immediately before lens rearing) and three during treatment: at 4 (T4), 8 (T8), and 10 weeks (T10) of lens wear. On-axis dimensions of anterior chamber depth (ACD), lens thickness (LT), vitreous chamber depth (VC), choroidal thickness (CT), and retinal thickness (RT) were measured using high frequency A-scan ultrasound (25 MHz; Panametrics, NDT, Ltd., Waltham, MA, USA).[30,33–36] Growth rates were calculated from vitreous chamber measures prior to treatment (pretreatment), and at three time intervals during treatment: early (4–6 weeks into treatment), mid (following 4 weeks into treatment), and late (last 4 weeks of treatment). Refraction, keratometry, and ultrasound biometry were performed at each measure 30 minutes after the instillation of two drops of 1% cyclopentolate and measurements were completed within 2 hours.[30,34,35] On-axis refraction was the average of retinoscopy and Hartinger Coincidence Refractometer (Carl Zeiss, Oberkochen, Germany).[8,30,34,35] Peripheral refraction was measured continuously along the horizontal meridian using infrared (IR) video photorefraction (PowerRefractor; MultiChannel Systems, Tubingen, Germany). Peripheral refractive data was collected from 40° on the temporal retina to 40° on the nasal retina, using a running average of refraction data of approximately 500 refractions across the horizontal meridian. Relative peripheral refractions at 20° and 40° were calculated by subtracting the

Table 1. Average Pupil Diameter (mm) and Anterior Chamber Depth (mm) During Treatment for Each of the Three Annular Designs (Mean ± SE) and the Corresponding Central Hemifields (in deg) Calculated From Carkeet[32]

Treatment Group	Baseline	4 wk	8 wk	10 wk
		Average pupil diameter, mm		
+5 D/3 mm	2.27 ± 0.08	2.59 ± 0.10	2.36 ± 0.06	2.49 ± 0.06
−5 D/3 mm	2.42 ± 0.04	2.42 ± 0.07	2.46 ± 0.07	2.43 ± 0.08
+5 D/1.5 mm	2.27 ± 0.05	2.37 ± 0.04	2.54 ± 0.05	2.54 ± 0.04
		Average ACD, mm		
+5 D/3 mm	1.48 ± 0.01	1.57 ± 0.02	1.66 ± 0.02	1.68 ± 0.02
−5 D/3 mm	1.49 ± 0.01	1.58 ± 0.01	1.67 ± 0.01	1.67 ± 0.02
+5 D/1.5 mm	1.54 ± 0.03	1.60 ± 0.03	1.65 ± 0.02	1.69 ± 0.02
		Corresponding central visual hemifield, deg		
+5 D/3 mm	65.73	65.73	63.40	63.69
−5 D/3 mm	66.22	64.86	63.70	63.42
+5 D/1. 5 mm	57.24	56.91	57.24	56.58

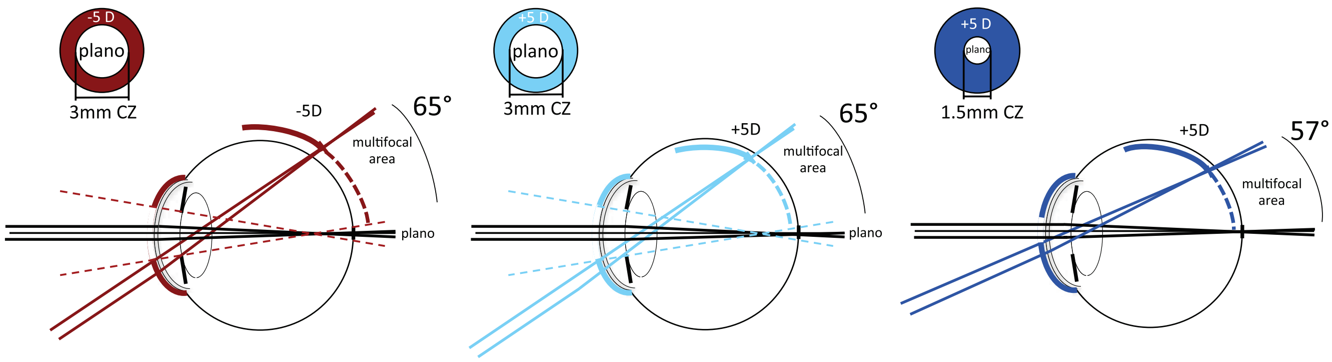

FIGURE 1. Diagrams of each contact lens design describing the peripheral zones of hyperopic or myopic imposed defocus, and the retinal zones with simultaneous plano and defocused vision based on calculations from Carkeet.[32] The diagrams are for illustration only and not drawn to scale. The −5 D/3 mm lens (*red*) is shown to the *left*, the +5 D/3 mm (*light blue*) is show in the *middle*, and the + 5D/1.5 mm (*dark blue*) is shown to the *right*. In lenses with 3 mm central plano zones there was approximately 1° of clear vision on the optic axis for the average pupil diameter.

refraction on the nasal and temporal peripheral retina from the central refraction.

Statistics

Stata (College Station, TX, USA) was used to perform statistical analysis. We used one-way ANOVA and post hoc analysis using Tukey tests to examine the differences between treatment groups. Repeated measures ANOVA was used to examine treatment effects over time within each group. Pearson's linear correlation was used to explore the relationship between the effective peripheral refraction and the compensatory changes in refraction and eye growth. Multiregression models were developed to evaluate whether pupil size, eye growth rate prior to treatment, central and peripheral refraction at baseline, or effective peripheral refraction at baseline would interact to predict the induced changes in growth rate after 4 to 6 weeks of treatment.

RESULTS

We treated marmosets with custom designed contact lenses that we calculated would impose defocus mainly to the retinal periphery. Average pupil diameters throughout treatment ranged from 2.27 mm at baseline to 2.54 mm at the end of treatment (Table 1). We used these pupil diameters and their anterior segment dimensions to estimate the average peripheral hemifield of lens imposed defocused vision.[32,37] In animals treated with 3 mm central plano zones, the field of peripheral single vision defocus on the retina was greater than 65° away from the optic axis and greater than 57° in those treated with 1.5 mm central plano zones. Within these angles the retina received simultaneous defocus from the lens power and clear vision from the central plano zone. For lenses with 3 mm central zones, which were slightly larger than the entrance pupil, there was a small central retinal area of clear vision (±0.47° on average). For lenses with the 1.5 mm central zone, which was smaller than the pupil diameter, the entire retina subtending the central ±57° received simultaneous defocus and clear vision. Figure 1 shows schematic representations of the effects of the different lens designs used.

ANOVA showed significant differences between the effects of the different lenses in terms of the normalized interocular differences in VC ($P < 0.01$) and refractive state ($P < 0.05$). Post hoc analysis at the end of treatment showed that −5 D/3 mm contact lenses created significantly larger experimental eyes compared with +5 D/1.5 mm (experimental–control [exp-con] VC, mean ± SE, +0.08 ± 0.04 mm, −0.07 ± 0.02 mm, $P < 0.05$) and more myopia compared with +5 D/1.5 mm lenses (exp-con MSE, mean ± SE, −1.28 ± 0.37 D, +0.94 ± 0.65 D, $P < 0.05$). In Figure 2 and Table 2, we show the average VC and refractive state for the experimental and control eyes in each experimental group. Table 2 shows the actual data and Figure 2 shows the data normalized to baseline. Experimental and control eyes were significantly different at the end of treatment in animals treated with −5 D/3 mm for refractive error (MSE at T10 mean ± SE, exp: −4.66 ± 0.39 D, con: −3.38 ± 0.62 D, $P < 0.01$) and in animals treated with +5 D/1.5 mm for VC depth at T8 and T10 (VC at T8 mean ± SE, exp: 0.41 ± 0.03 mm, con: 0.50 ± 0.04 mm, $P < 0.01$; VC at T10 mean ± SE, exp: 0.53 ± 0.03 mm, con: 0.60 ± 0.03 mm, $P < 0.01$).

Figure 3 shows three plots describing the development of interocular differences in ocular growth and refractive state induced by each of the three contact lens designs during the treatment period. Each graph shows the relationship between interocular differences (exp-con) in refraction (*y*-axis) and VC (*x*-axis). Each arrow represents the data from an individual animal over the treatment period where the tail is the baseline measure at the onset of lens wear, and the head is the last measure at the end of lens wear. The grey zone represents the 95% confidence interval (CI) of the interocular VC and refraction differences for the age-matched untreated data. Individual data outside of the 95% CI indicate significant changes. Data in the top left quadrant of each graph indicate treated eyes that are smaller and more hyperopic than their contralateral control eyes. Data in the bottom right quadrant indicates that they are larger and more myopic.

The top graph of Figure 3 (data in red) shows the effects of the −5 D/3 mm lenses, which imposed hyperopic defocus in the periphery. After normalizing the treatment effects to baseline, we found that at the end of treatment the experimental eyes were, on average, longer and more myopic than the control eyes but did not reach statistical significance (exp-con, mean VC ± SE, +0.07 ± 0.04 mm, repeated ANOVA $P = 0.07$; mean MSE ± SE, −1.28 ± 0.37 D, repeated ANOVA $P = 0.12$). We saw evidence of a response to the lens during the first 4 weeks of treatment; 7 of 10 treated eyes developed more myopia compared with their contralateral eyes (exp-con, mean MSE ± SE, −1.49 ± 0.45 D), five of which also grew more (exp-con, mean VC ± SE, +0.07 ± 0.02 mm). During the middle 4 weeks of treatment eight treated eyes developed more myopia compared with their contralateral eyes (exp-con, mean MSE ± SE, −1.44 ± 0.42 D), seven of which also grew more (exp-con, mean VC ± SE +0.10 ± 0.02 mm).

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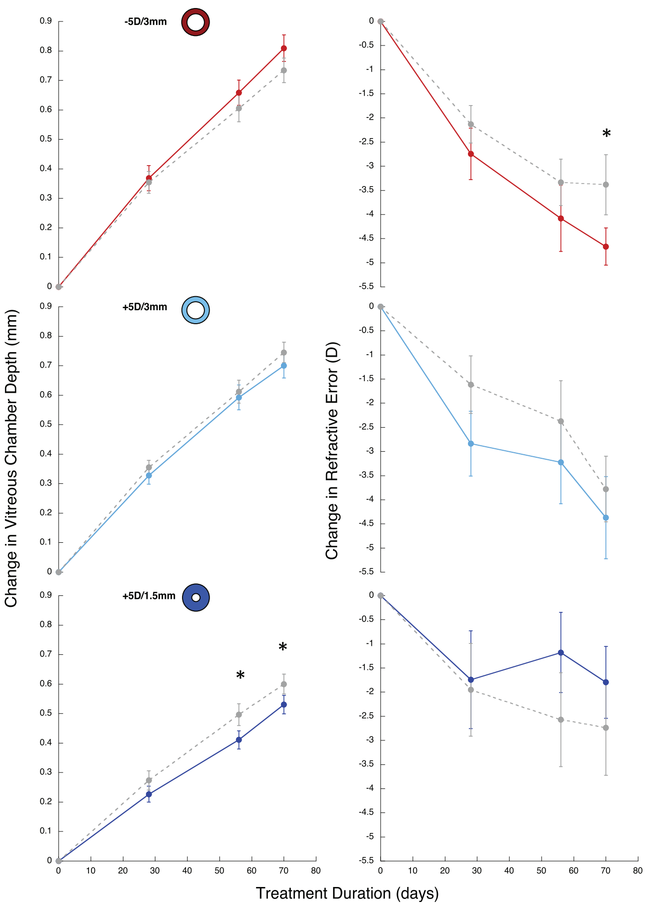

Figure 2. Average VC and refractive state for the experimental and control eyes in each experimental group, normalized to baseline. The –5 D/3 mm lens (*red*) is shown at the *top*, the +5 D/3 mm (*light blue*) is show in the *middle*, and the +5 D/1.5 mm (*dark blue*) is shown at the *bottom*. *Asterisk* indicates statistical significance $P < 0.05$.

The effects of treatment with +5 D/3 mm lenses are shown in the middle graph in Figure 3 (data in light blue). After normalizing these data, we did not find significant changes in mean vitreous chamber or refractive differences (exp-con, mean VC ± SE, –0.04 ± 0.02 repeated ANOVA $P = 0.20$; mean MSE ± SE, –0.06 ± 0.01, repeated ANOVA $P = 0.18$), however four of the subjects showed changes outside of the 95% CI that are consistent with the expected response to the lens. During the first 4 weeks of treatment, 7 of 10 animals developed smaller VCs in the treated compared with their contralateral eyes (exp-con, mean VC ± SE, –0.04 ± 0.01 mm), but only one of which also became relatively more hyperopic (exp-con, MSE, +1.83 D). After 8 weeks of treatment, five animals had smaller treated eye VCs (exp-con, mean VC ± SE, –0.09 ± 0.01 mm), four of which developed relatively more hyperopia (exp-con, mean MSE ± SE, +1.37 ± 0.65 D).

Data from the marmosets treated with +5 D/1.5 mm lenses are shown in the bottom graph of Figure 3 (data in dark blue). After normalizing to baseline, the experimental eyes as a group were significantly shorter and tended to be more hyperopic than the control eyes at the end of treatment (exp-con, mean VC ± SE, –0.07 ± 0.02, repeated ANOVA $P < 0.01$; mean MSE ± SE, +0.94 ± 0.65 repeated ANOVA $P = 0.08$). By 4 weeks of treatment, 8 of 10 animals developed shorter VCs (exp-con, mean VC ± SE, –0.07 ± 0.01 mm), three of which were relatively more hyperopic (exp-con, mean MSE ± SE, +1.99 ± 1.39 D). After 8 weeks of treatment, the effects increased and all 10 animals had shorter vitreous chambers in the experimental eye (exp-con, mean VC ± SE, –0.08 ± 0.01 mm), seven of which were also more hyperopic in their treated eyes (exp-con, mean MSE ± SE, +2.17 ± 0.89 D).

To compare the effects that the different contact lenses had on ocular growth, we plotted interocular differences in vitreous chamber growth rates for each group during the first 4 to 6 weeks of treatment (early-treatment period), the following 4 weeks of treatment (mid-treatment period), and the last 4 weeks of treatment (late-treatment period) after adjusting for baseline differences between groups (Fig. 4). We found significant differences between the groups during the early- and mid-treatment periods (ANOVA $P < 0.05$). Analysis of interocular differences in growth rates between the groups over time revealed that during the early treatment period, the average interocular growth rate in animals treated with +5 D/1.5 mm contact lenses (right most blue bar) was significantly smaller compared with animals treated with positive single-vision lenses (dark blue bar) and negative single-vision lenses (dark red bar). This difference remained mid-way through treatment ($P < 0.01$) and disappeared by the end of treatment. During the mid-treatment period, the average interocular difference in interocular growth rates in +5 D/1.5 mm animals (right most blue bar) was significantly smaller than the other treatment groups (all $P < 0.05$). This effect was not apparent at the end of treatment, when growth rates in animals treated

Table 2. Mean Refractive Error (D) and VD (mm) of the Individual Eyes During Treatment for Each of the Three Annular Designs (Mean ± SD)

Treatment Group	Baseline	4 wk	8 wk	10 wk
Refractive error (D)				
−5 D/3 mm treated eye	+1.04 ± 2.66	−1.70 ± 2.92	−3.04 ± 3.38	−3.62 ± 2.61
−5 D/3 mm control eye	+0.17 ± 2.34	−1.96 ± 2.50	−3.16 ± 2.62	−3.21 ± 2.57
+5 D/3 mm treated eye	+1.61 ± 2.68	−1.22 ± 2.59	−1.61 ± 2.92	−2.76 ± 2.59
+5 D/3 mm control eye	+0.58 ± 2.97	−1.03 ± 2.85	−1.78 ± 2.30	−3.19 ± 2.55
+5 D/1.5mm treated eye	−0.03 ± 2.15	−1.77 ± 2.54	−1.21 ± 1.90	−1.83 ± 2.20
+5 D/1.5mm control eye	−0.17 ± 1.53	−2.11 ± 2.71	−2.74 ± 2.47	−2.90 ± 2.46
VD (mm)				
−5 D/3 mm treated eye	5.76 ± 0.24	6.13 ± 0.29	6.42 ± 0.22	6.57 ± 0.27
−5 D/3 mm control eye	5.75 ± 0.25	6.11 ± 0.28	6.36 ± 0.19	6.49 ± 0.25
+5 D/3 mm treated eye	5.87 ± 0.19	6.20 ± 0.23	6.47 ± 0.34	6.58 ± 0.25
+5 D/3 mm control eye	5.86 ± 0.20	6.22 ± 0.23	6.52 ± 0.29	6.61 ± 0.23
+5 D/1.5mm treated eye	5.95 ± 0.21	6.18 ± 0.23	6.36 ± 0.25	6.48 ± 0.25
+5 D/1.5mm control eye	5.94 ± 0.18	6.21 ± 0.24	6.43 ± 0.26	6.54 ± 0.25

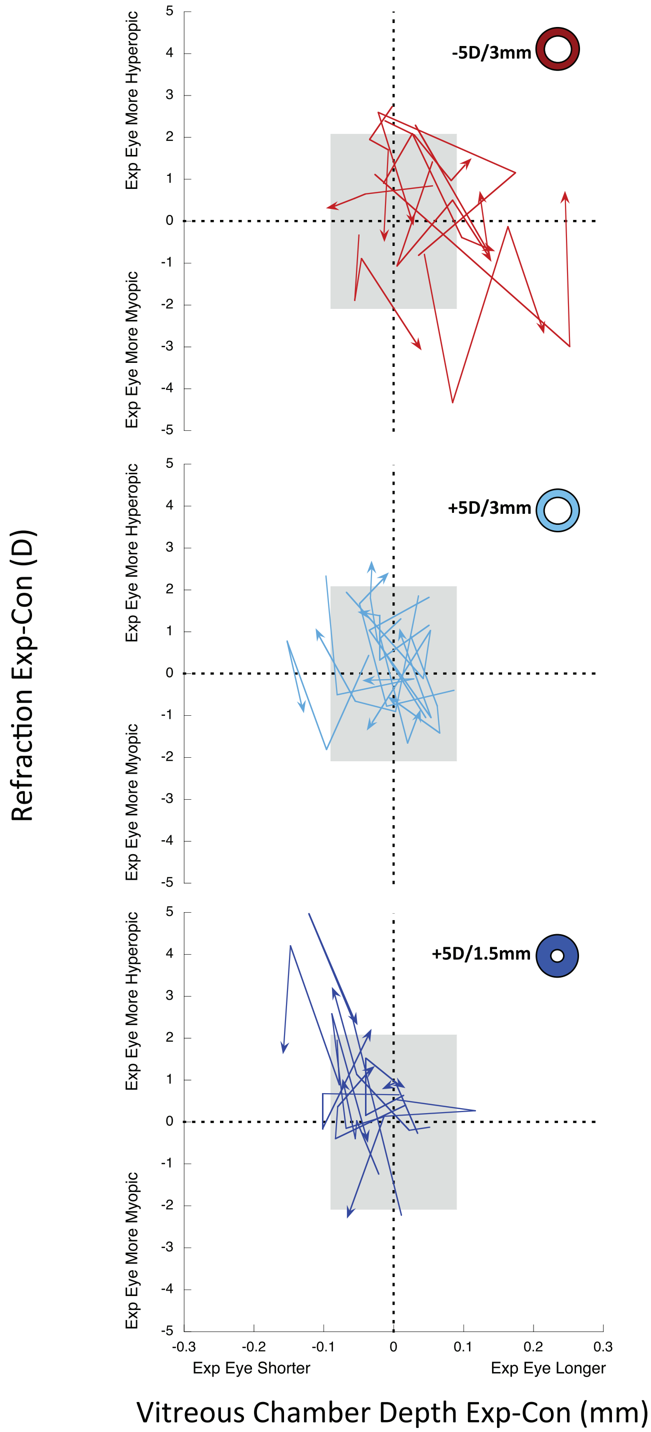

FIGURE 3. Quadrant plots describing the relation between interocular differences (exp-con) in VC (x axis), and mean spherical refraction (y axis). Each plot shows data from an experimental lens design. The *top graph* (*red*) corresponds to animals treated with −5 D/3 mm lenses, the *middle graph* (*light blue*) corresponds to animals treated with +5 D/3 mm lenses, and the *bottom graph* (*dark blue*) corresponds to animals treated with +5 D/1.5 mm lenses. The interocular differences in VC depth or mean spherical refraction are shown for each animal as an individual *arrow*. Baseline measures are indicated by the tails of the *arrows*. The final experimental measurement is indicated at the arrowhead. The *grey rectangle* represents the 95% CI of age-matched untreated marmosets. *Lines* outside of the 95% CI indicate significant interocular differences. Data points in the *top left quadrant* indicate that the experimental eyes are smaller and more hyperopic than contralateral control eyes; points in the *top right quadrant* indicate eyes that are larger but more hyperopic; points in the *bottom left quadrant* show eyes that are smaller but more myopic than contralateral controls, and points in the *bottom right quadrant* show eyes that are larger and more myopic.

with multizone and +5 D/3 mm contact lenses became significantly smaller compared with those in untreated animals ($P < 0.05$) as well.

Although contralateral effects in monocular paradigms have been reported in several studies[38,39] and require further investigation (Rucker FJ, et al. *IOVS* 2009;50:ARVO E-Abstract 3931), we did not see strong evidence of such effects in our contact lens rearing paradigm. In an earlier study[30] using the same contact lens-rearing paradigm as in this study, we did not observe a significant difference between the plano-wearing control eyes of marmosets wearing either positive or negative power experimental lenses over the contralateral eye. We further examined the eyes wearing plano contact lenses in this study by comparing the VC depth and axial growth rates in untreated animals to the contralateral control eyes of marmosets treated with annular contact lenses at each time point (T4, T8, and T10). There were no statistically significant differences in either VC depth or axial growth rates between untreated eyes and eyes treated with plano contact lenses at any time point (ANOVA, all $P > 0.5$).

The lens treatment effects on axial eye growth and refraction at the end of treatment were correlated with the size and power of the treatment zone in the contact lens (growth $R = 0.91$ $P < 0.01$; refraction $R = 0.89$ $P < 0.05$; Fig. 5). Eyes got larger and more myopic with larger treatment zones of negative defocus, and smaller and more hyperopic with larger treatment zones of myopic defocus.

We also measured the effects the lenses had on ACD, LT, CT, and RT experienced during treatment, and found that refraction changes at the end of treatment correlated with small, but significant interocular changes in LT ($R = -0.18$, $P < 0.01$) and CT ($R = -0.14$, $P < 0.05$).

We used multiple regression analysis to assess whether the lens induced changes in vitreous chamber growth and refractive state could be explained by interactions of pupil size, baseline growth, and axial and peripheral refractive state. We found that pretreatment growth rates and baseline relative peripheral refraction at 20° nasal retina were the best predictors for the growth rate changes after 4 to 6 weeks of treatment, such that faster growth rates and more relative myopia nasally before starting treatment correlated with slower growth after treatment ($y = -0.0121 - 0.2734$ [pretreatment growth rate] $+ 0.0036$ [baseline refraction at 20° nasal], $R = 0.40$, $P < 0.05$).

DISCUSSION

This study provides evidence from an experimental nonhuman primate model that the peripheral retina can signal compensatory eye growth for defocus imposed by specially designed bifocal contact lenses. We used contact lenses instead of spectacle lenses, as used in other experimental models, because they provide better control over the effects of eye movement and lens centration on the amount of retinal defocus delivered to the periphery.[8] We found that the power in the periphery of the contact lenses is effective at modulating the development of

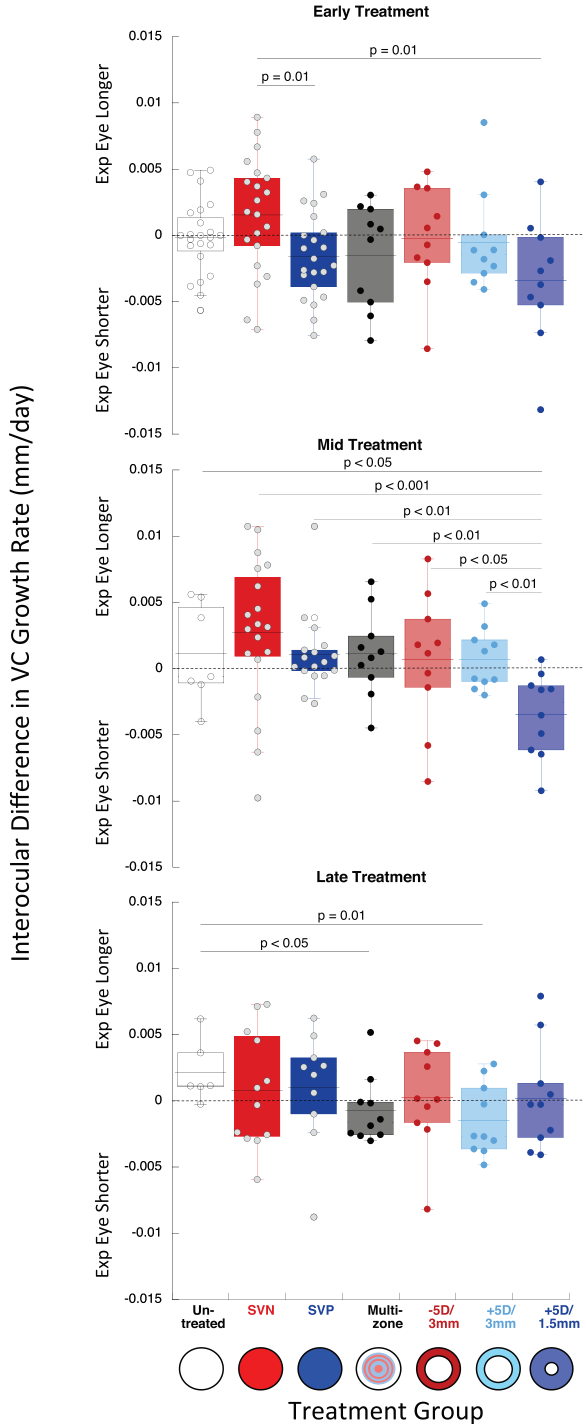

FIGURE 4. *Box plots* representing the interocular differences in ocular growth rate (exp-con) during the early (4–6 weeks into treatment), middle- (following four weeks of treatment) and late-periods (last four weeks into treatment) of treatment for the different treatment groups: untreated controls (*white*), single-vision −5D (*dark red*), single-vision +5D (*dark blue*), multizone +5/−5 D (*black*), −5 D/3 mm (*light red*), +5 D/3 mm (*blue*), and +5 D/1.5 mm (*light blue*). The data shown are means ± SE.

axial eye growth and refractive state, such that imposing relative hyperopic defocus mainly to the periphery resulted in relatively larger and more myopic eyes, whereas imposing relative myopic defocus induced relatively smaller and more hyperopic eyes. The absolute degree of myopia that resulted from treating marmosets using contact lenses with negative power in the periphery was greater than the amount of hyperopia induced using contact lenses with positive power on the periphery. However, eyes treated with the positive power in the periphery grew significantly less than untreated eyes and eyes treated with multizone contact lenses that imposed both negative and positive power simultaneously. The changes in eye growth and refractive state were smaller and more transient when the defocus was limited to the periphery compared with those observed with full-field, single-vision defocus. This was true except when the myopic defocus from lenses with positive power was mixed with negative power or clear vision over a large region of the retina (multizone +5/−5 D and +5 D/1.5 mm contact lenses, respectively). In those cases the growth changes were slightly smaller, but lasted longer, than when myopic defocus from single vision positive lenses was imposed across the entire retina.

We could not assess the exact relationship between contact lens centration and corneal apex in our animals. However, because of the ocular globe and eyelid anatomy in the marmosets, the fit of all these contact lenses resembles that of a scleral fit. In a previously published paper, we assessed contact lens centration quantitatively by measuring the refractive changes induced by plano contact lenses on the temporal and nasal periphery, and we found that plano contact lenses induced a significant increase in effective myopia only at 40° on the temporal retina (nasal visual field, mean change ± SE, +1.22 ± 0.33 D). At this time, we assessed whether the small change in peripheral refraction induced by plano contact lenses would induce any compensatory changes in eye growth, and therefore biasing the compensatory ocular growth changes. We compared the average VC changes throughout treatment in the contralateral eyes treated with plano contact lenses to those from untreated marmosets but did not find any differences in growth changes between plano-treated eyes and untreated eyes. We speculate that the relative myopia on the temporal retina induced by plano contact lenses may be attributable to a positive tear meniscus created by the interaction of eye gaze and lens decentration when we measure peripheral refraction by turning the marmoset's head.[8]

The existence of paracentral zones of simultaneous defocus and clear vision are the result of the interaction between lens optics, centration, pupil size, and vertex distance, and have been described in chicks wearing bifocal spectacle lenses.[11] Such an interaction between contact lens fit, centration, and tear film has also been described in human eyes,[40] and emphasizes the need to measure the effective peripheral defocus imposed by soft bifocal contact lenses accurately into the periphery when fitting lenses for myopia control.[40]

Our data show that axial eye growth and refractive state in marmosets can be changed by imposed defocus that is weighted to the periphery, and is similar, but less, than what has been reported for the same powers when imposed across the entire retina.[5,30,31,41] The visual control of eye growth and refractive state using imposed peripheral defocus has been demonstrated in several experimental studies of local visual control of eye growth.[42–45] Given the existence of local visual control of eye growth,[42–45] how defocus imposed in the periphery affects axial growth needs explanation. We speculate that the 360° design of our lenses (compared with hemifield or partial field manipulations) and the large spread of peripheral defocus across the retina sufficiently integrates a large enough growth signal and local response to override a different signal coming from the central retina. The differences in the magnitudes of the responses to our different lens designs supports this view, but additional investigation is required.

Even though the absolute changes in eye growth and refractive state from imposing myopic defocus with positive lenses are smaller than those from imposing hyperopic defocus with negative lenses in primates,[3,30,46–48] the results presented in this paper support the use of positive addition to distance correction for myopia in humans to control progression rates. In our experiments with marmosets, unlike what happens in chick eyes,[1,11,38,49–51] the magnitude of the response to imposed full-field, single-vision hyperopic defocus is greater than that to full-field, single-vision myopic defocus. From the results of this study, it appears that this is also the case for peripheral defocus. This may be due to differences in the strength of the response to myopic versus hyperopic defocus, but also to the fact that the marmosets refraction at baseline is slightly hyperopic. However, when positive and negative defocus compete simultaneously, the response to myopic defocus dominates over hyperopic defocus in both chick[9,11,13] and marmoset eyes[8] supporting the therapeutic potential of positive addition for myopia control.

The duration of imposed retinal defocus is an important factor to consider for controlling the eye growth and the development of refractive state. Differences in the response to imposed myopic and hyperopic defocus were also observed in studies examining the temporal integration of defocus.[50,52–54] Alternating positive and negative defocus at higher temporal frequencies in chick eyes lead to relatively more compensatory hyperopia for the positive lenses than when alternating at lower frequencies.[50] In yet another study, only a few minutes of exposure to myopic defocus each day was effective in preventing the response to hours of hyperopic defocus, which produces axial elongation and myopia.[55] We also considered the effect of the duration of bifocal lenses wear by examining growth rate changes throughout treatment (Fig. 4) and noticed that the effects were stronger at the beginning than at the end of treatment in all treatment groups. We found this in response to our concentric multizone lenses as well[8] and we speculate that it might be related to the reduction in total defocus imposed over time as the eye changes its growth and refractive state. This could be confirmed by additional experiments that increase the peripheral power of the contact lenses over the treatment period.

Similar to findings in chick eyes,[10,11] the final refractive state in our marmosets was largely dependent on the sign and the size of the peripheral treatment zone used (Fig. 5). This dose-effect has been observed in several other experimental studies[10,11,38] and suggests a larger compensatory effect to contact lenses of larger peripheral treatment zones. However, as shown in Figures 4 and 5, changes in eye growth and refraction experienced by those marmosets wearing the +5 D/1.5 mm contact lenses were not only greater, they appeared to last longer, than those experienced by animals wearing other lenses with positive power. We need to explore this further, but we consider that it might be related to results described by Liu and Wildsoet[11] in chicks, which showed that exposing the peripheral chick retina to positive defocus triggered greater growth changes than exposing an area on the central retina of equivalent size. In their study, they suggested an interaction between the higher order aberrations of the contact lens with those of the eye to explain their results, but argued that such explanation would not justify the large effect that they also obtained with their +5 D center zone lenses. We hypothesize that fluctuations in pupil size might be an added element that might explain these results and requires further examination.

The lens effects on eye growth and refractive state reported in this paper in a nonhuman primate support several recent human studies and may help understand how different lens designs for myopia control might work in humans. Pilot clinical trials with aspheric and concentric multifocal contact lenses that impose 1 to 2.5 D of myopic defocus, while correcting distance vision have shown the potential to reduce myopia

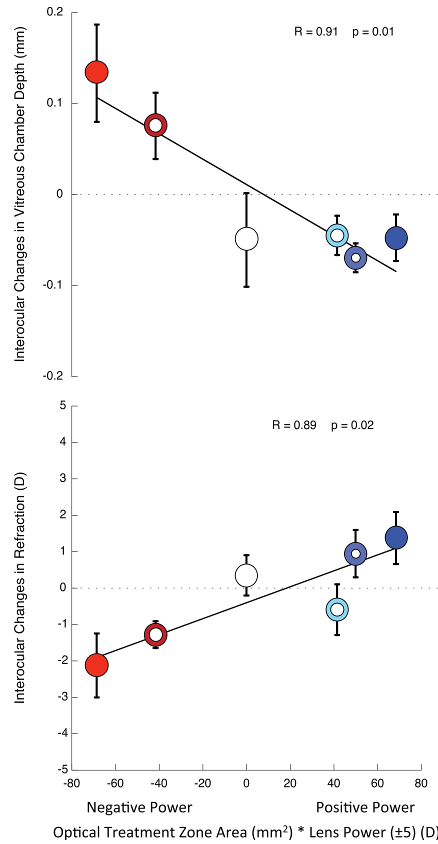

Figure 5. Scatter plots showing the correlations between changes (post baseline) in the interocular differences of VC (mm, *top graph*) or refraction (D, *bottom graph*) as a function of the contact lens area treatment zone (mm^2) multiplied by the power of the treatment zone (D).

progression rates.[15–17] The results obtained after 12, 20, and 24 months of treatment showed reduced progression rates by an average of 0.25 to 0.30 D/y, which corresponds to on average 35% to 46% reduction in refractive error between the treated and control groups. Lam and colleagues[17] also reported a relationship between wearing time and treatment effect, and described that 5 hours/day was the minimum wearing time showing a statistical effect on myopia control. It is possible that these effects may be improved through modifications to the lens design, better understanding of the spatial and temporal integration of visual signals for controlling eye growth, and the selection of patients with greater potential for successful responses to treatment. Understanding the complex interaction of eye shape, peripheral optics, and the effects of different visual environments, as well as visual behavior in it, may be particularly important in this regard.[29,56]

We examined a number of variables measured pretreatment, including peripheral refraction, nasal-temporal asymmetry, and ocular growth rates, to determine whether they predicted the observed responses to the lenses. Based on our multiple regression models we found that pretreatment eye growth rates and baseline relative peripheral refraction at 20° nasal taken together predicted 40% of the refractive and growth changes observed in this study. The eyes of animals that grew less during treatment had grown more prior to treatment and showed relatively more myopia on the nasal retina at baseline. Factors such as these may be important considerations to refine future optical treatment strategies for myopia control in humans. Given the variability seen in the eye shape and peripheral refraction of myopes,[29,56–60] more clinically meaningful results may be obtained by customizing the size and power of the peripheral treatment zone based on the patient's pre-existing rate of eye growth and peripheral refractive state at baseline.

In summary, the results from this study confirm that eye growth and the development of axial refractive state can be controlled using bifocal contact lenses that provide more of their power to the retinal periphery. The treatment effect correlated with the size of the peripheral treatment zone, as well as with the peripheral refractive state and eye growth rate before treatment started. These findings support the use of optical treatments such as multifocal contact lenses for myopia control in children. These findings also indicate the need for more experimental and clinical studies to define optimal lens parameters and any specific ocular or visual measures that might be used to determine which patients will most likely benefit from particular contact designs. Nevertheless, any reduction in myopia progression rate will help reduce the vision threatening complications associated with myopia[29] and the development of effective new lens designs and their application is an important breakthrough in myopia control treatments.

Acknowledgments

The authors thank Keisha Roden, Luying Yan, Geoffrey Chu, and Julie Tse for their help on lens insertion and removal.

Supported by the National Institutes of Health (NIH R01 EY11228; Bethesda, MD, USA).

Disclosure: **A. Benavente-Perez**, Johnson and Johnson Vision Care, Inc. (F); **A. Nour**, Johnson and Johnson Vision Care, Inc. (F); **D. Troilo**, Johnson and Johnson Vision Care, Inc. (F, C)

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