

# The Effect of Spectacle Lenses Containing Peripheral Defocus on Refractive Error and Horizontal Eye Shape in the Guinea Pig

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**PURPOSE.** It has been proposed that the peripheral retina, responding to local optical defocus, contributes to myopia and associated altered eye growth in humans. To test this hypothesis, we measured the changes in central (on-axis) and peripheral ocular dimensions in guinea pigs wearing a concentric bifocal spectacle lens design with power restricted to the periphery.

**METHODS.** Five groups of guinea pigs ( $n = 83$ ) wore either a unifocal (UF) spectacle lens ( $-4$ ,  $0$ , or  $+4$  Diopters [D]), or a peripheral defocus (PF) spectacle lens that had a plano center (diameter of 5 mm) with either  $-4$  or  $+4$  D in the surround ( $-4/0$  or  $+4/0$  D). The overall optical diameter of all lenses was 12 mm. Lenses were worn over one eye from 8 to 18 days of age for negative and plano lenses, or from 8 to 22 days of age for positive lenses. Refractive error was measured centrally and  $30^\circ$  off-axis in the temporal and nasal retina. The shape of the eye was analyzed from images of sectioned eyes.

**RESULTS.** Lenses of  $-4$  D UF induced myopia, reflecting enhanced ocular elongation, which was centered on the optic nerve head and included the surrounding peripapillary zone (PPZ,  $18^\circ$  in diameter). Some ocular expansion, including within the PPZ, also was recorded with  $-4/0$  and  $+4/0$  D PF lenses while the  $+4$  D UF lens inhibited rather than enhanced elongation, centrally and peripherally.

**CONCLUSIONS.** Peripheral defocus-induced ocular expansion encompasses the PPZ, irrespective of the sign of the inducing defocus. Understanding the underlying mechanism potentially has important implications for designing multifocal lenses for controlling myopia in humans and also potentially for understanding the link between myopia and glaucoma.

Keywords: myopia, peripheral hyperopia, guinea pig, eye shape, posterior pole, refractive error

In young animals, form depriving an eye or imposing hyperopic defocus with a negative lens accelerates ocular elongation, with the net result being a myopic shift in refractive error. These effects have been demonstrated in a wide range of animals, including chicks,<sup>1–3</sup> guinea pigs,<sup>4,5</sup> macaques,<sup>6–8</sup> marmosets,<sup>9,10</sup> tree shrews,<sup>11</sup> mice,<sup>12</sup> and fish.<sup>13</sup> However, the induced changes rarely are uniform. In monkeys,<sup>14,15</sup> chicks,<sup>16</sup> and guinea pigs (Zeng G, et al. *IOVS* 2011;52:ARVO E-Abstract 3923), common experimental manipulations typically result in less myopia peripherally (off-axis) compared to centrally (on-axis). Although peripheral refractions generally still are myopic, such regional variation translates into relative peripheral hyperopic shifts off-axis.<sup>17</sup> Human adult myopic eyes also generally exhibit less myopia peripherally than on-axis,<sup>18–22</sup> which has been attributed, at least in part, to the characteristic prolate shape of myopic eyes, that is, on-axis dimensions longer than equatorial dimensions.<sup>23,24</sup> However, optical contributions cannot be ruled out in either case.

A relationship between changes in peripheral refractive error and eye shape has been found in partial visual deprivation experiments in several species (e.g., guinea pigs, Zeng G, et al. *IOVS* 2010;51:ARVO E-Abstract 1736; chicks<sup>25,26</sup>; monkeys<sup>27</sup>). For example, relative myopic defocus imposed on the nasal hemi-field in monkeys induces a corresponding asymmetric eye shape, particularly in the posterior eyecup.<sup>27</sup> Additionally, signals arising from the peripheral retina have been implicated in the development and progression of myopia in animal models. For example, chicks that wear lenses with negative power limited to their periphery show increased ocular elongation on-axis, and refractive changes on-axis as well as peripherally.<sup>16</sup> Likewise, monkey eyes show on-axis myopia when exposed to hyperopic defocus or form deprivation limited to the peripheral retina, and photoablation of the fovea fails to prevent the development of form deprivation myopia.<sup>17</sup>

These results suggest that optical treatment strategies that aim to alter the defocus experience of the peripheral retina may be useful in controlling myopia progression. Indeed, new

spectacle and contact lenses designed to alter peripheral retinal defocus have been tested with encouraging results as myopia control treatments.<sup>28,29</sup> Specifically, spectacle lenses designed to reduce peripheral hyperopia attenuated the rate of myopia progression in children with parental myopia only (although it should be noted these lenses failed to reduce progression rates in children without a parental history of myopia).<sup>28</sup> Encouraging results also have been reported with soft concentric multifocal lens designs, with reductions in progression by as much as approximately 50% reported.<sup>30,31</sup> In a recent network meta-analysis, Huang et al.<sup>32</sup> compared the efficacy of a number of interventions for myopia control. They reported that peripheral defocus modifying contact lenses were moderately effective at controlling myopia progression in children, achieving an average reduction in axial elongation of 0.11 mm/y, relative to single vision lens treatments. These contact lens designs also generally were more effective at controlling myopia development than tested spectacle lens designs, such as progressive addition lenses, although not significantly so, but were less effective than atropine eye drops. With improved understanding of the mechanism(s) underlying these peripheral defocus treatment outcomes it should be possible to refine lens designs to further improve them.

Although a major contributor to myopic refractions is axial (eye) length, there is limited information regarding the changes in eye shape during the development of myopia and the effect of peripheral defocus on eye shape. Therefore, we determined the changes in eye shape in guinea pigs in response to wearing spectacle lenses with either negative or positive power in their periphery and plano in their center. Some of these data been reported previously (Bowrey HE, et al. *IOVS* 2013;54:ARVO E-Abstract 5176).

## METHODS

### Animals and Housing

A total of 83 pigmented guinea pigs (*Cavia porcellus*) from the University of Newcastle were housed with their mothers and littermates, as described previously,<sup>33</sup> in opaque plastic boxes (65 × 45 × 20 cm) with stainless wire tops. Overhead incandescent lamps (12 × 40 W) were evenly diffused through a translucent Perspex barrier located 200 mm above the boxes (luminance was 400 lux at the center of each box). Lights were on a 12-hour day/12-hour night cycle. Animals were provided with food and water ad libitum. All procedures were approved by the University of Newcastle under Australian legislative requirements and were in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

### Procedures

From 8 days of age, 83 animals wore one of five lens designs over one eye: three unifocal (UF; -4 diopters [D],  $n = 18$ ; 0 D [plano],  $n = 14$ ; and +4 D,  $n = 18$ ) and two peripheral defocus (PF; -4/0 D,  $n = 19$  and +4/0 D,  $n = 14$ ). Group allocation was random and was mixed within litters. Fellow eyes served as matched controls. The duration of lens wear was 10 days for negative lenses and 14 days for positive lenses, to allow a similar degree of compensation, measured in terms of induced interocular differences relative to plano controls (McFadden SA, et al. *IOVS* 2008;49:ARVO E-Abstract 3713).<sup>34</sup> A flow chart showing the order of procedures used to characterize treatment effects is shown in Supplementary Figure S1. In brief, at 18 or 22 days of age, cycloplegia was induced in both eyes and on-axis refractive errors were measured as described

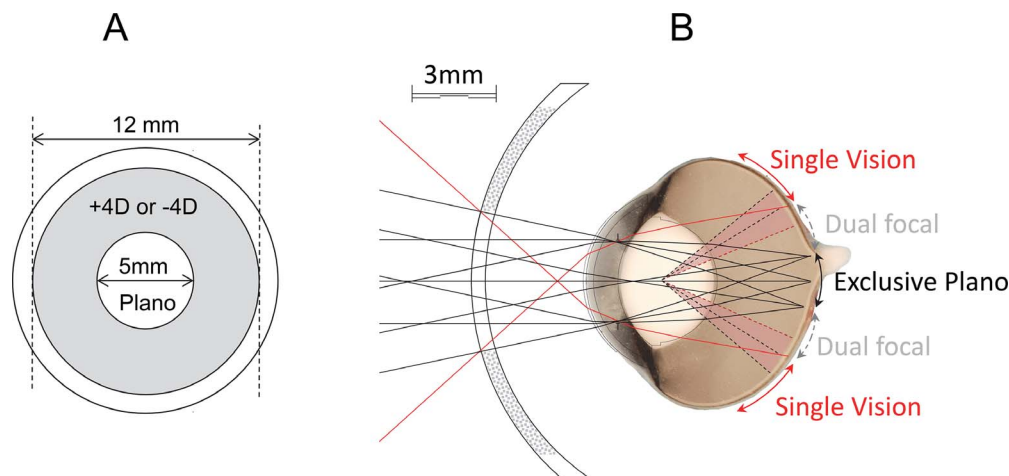
previously.<sup>35</sup> On and off-axis refractive errors also were measured in a randomly selected subset of animals (-4 D,  $n = 13$ ; 0 D,  $n = 5$ ; -4/0 D,  $n = 13$ ; +4 D,  $n = 9$ ; +4/0 D,  $n = 11$ ). Immediately after the refractive error measurements, animals were anesthetized and axial ocular components measured using high frequency A-scan ultrasonography (in all animals). Immediately afterwards, while still anesthetized, animals were euthanized with sodium pentobarbitone (0.5 ml/g; intracardiac; Virbac Laboratories, Peakhurst, Australia) and their eyes enucleated within 3 minutes of death. Horizontal eye shape parameters were obtained from digital images of sectioned eyes from a random subset of animals (-4 D,  $n = 7$ ; 0 D,  $n = 8$ ; -4/0 D,  $n = 7$ ; +4 D,  $n = 11$ ; +4/0 D,  $n = 6$ ). An additional group from our published data that wore no lens<sup>36</sup> is included in Supplementary Figure S3 for comparison.

**Lens Treatments.** The lens designs tested were either unifocal (UF, 3 types) or contained peripheral defocus (PF, 2 types). UF lenses contained either positive, negative, or plano power (+4, -4, or 0 D, respectively) and were made from polymethylmethacrylate (PMMA) with an overall diameter of 14 mm and an overall optical zone of 12 mm (Gelfex, Perth, Australia). The two concentric PF lenses were identical in physical dimensions to the UF lenses, but had a central 5 mm diameter plano (0 D) zone, surrounded by a zone of either positive (+4 D) or negative (-4 D) power (referred to as +4/0 D and -4/0 D PF, respectively, Fig. 1A). Lenses were mounted onto fiber washers backed with hoop fastener attached to mating arcs made from loop fastener (Velcro Australia, Hallem, Australia), which were affixed above and below the eye as described previously.<sup>33,37</sup> The distance of the lens apex to the cornea was 3.6 mm, giving an effective power at the cornea of -3.95 D for the -4 D UF lens and +4.06 D for the +4 D UF lens.<sup>33</sup>

To estimate the horizontal defocus profile imposed on the retina by the above PF lens design, ray tracing (OSLO Premium v.6.4.5; Lambda Research Corporation, Littleton, MA, USA) was performed using a schematic eye model for a 13-day-old guinea pig as described previously.<sup>38</sup> A 3 mm pupil diameter was used as this approximates that measured in animals of this age within their rearing environment. Modelling located the approximate boundaries of dual and single vision zones (Fig. 1B). Eye movements, which in the guinea pig are largely limited to small horizontal saccades (~7°), also were taken into account.<sup>39</sup> The predicted profile includes a dual focus transition zone of approximately 15° (shaded region in Fig. 1B), bridging central and more peripheral single vision zones. A small central zone, which included the optic nerve head, viewed the plano lens zone exclusively.

**Measurement of Refractive Error.** Refractive error was measured in both eyes using streak retinoscopy approximately 1.25 hours after the induction of cycloplegia. Cycloplegia was induced with a drop of topical cyclopentolate (Cyclogyl 1%; Alcon, Fort Worth, TX, USA) bathed on the cornea for several minutes. On-axis measures were taken in the center of the pupil. For the off-axis measures, two readings were taken at approximately 30° from the optic axis, nasally and temporally, as described previously.<sup>36</sup> At each of the three locations, the results for the two principal meridians were averaged to estimate the spherical equivalent refractive error.

**Measurement of Ocular Length (OL) In Vivo.** To determine the effect of lens-wear on axial ocular dimensions in live animals, data were extracted from ultrasonography records from anesthetized animals (1.5% isoflurane in oxygen), obtained using a high frequency A-scan (20 MHz) system as described previously.<sup>33</sup> OL, the primary parameter used to assess treatment effects, was defined as the distance between the front of the cornea to the retinal/choroidal interface. We also measured the vitreous chamber depth (defined as the



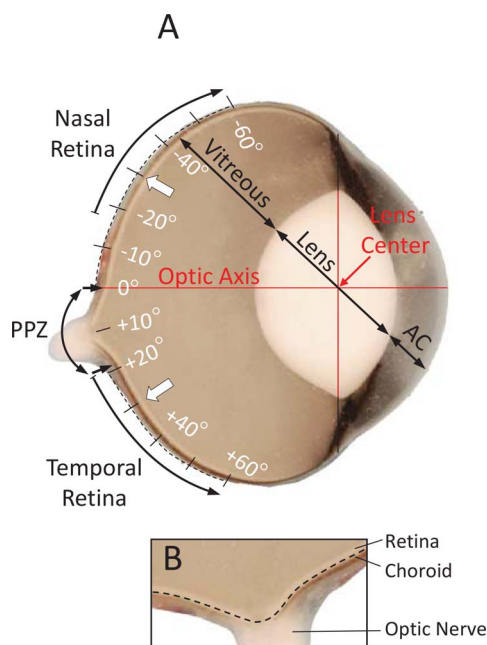
**FIGURE 1.** Bifocal lens parameters. **(A)** Lens dimensions. *Gray area* shows the extent of the powered zone. The central plano zone contained no power. **(B)** Modelling of the retinal defocus profile imposed by a  $-4$  D/0 D lens on a 13 day-old guinea pig eye in the horizontal plane containing the optic nerve. At this age, eyes show peripheral hyperopia, of approximately  $+2.6$  D at  $30^\circ$ , which is further increased by  $-4$  D spectacle lenses. The *red peripheral rays* demarcate the central limit of zones experiencing defocus with the PF lenses, located at  $\pm 35^\circ$ , were there no eye movements. The central area that exclusively experiences rays through the plano region of the lens also is shown. Dual focus zones are indicated by the *dashed arrows*, and would experience plano and peripheral power, as a product of the lens and pupil apertures. The regions shaded in *pink* (each  $\pm 7.5^\circ$ ) show the possible extent of saccadic eye movements.

distance between the posterior lens and the vitreous/retinal boundary), anterior chamber depth (includes the thickness of the cornea), and crystalline lens thickness (from the front surface to the back surface on axis).

**Determination of Horizontal Eye Shape.** To determine the effect of lens-wear on eye shape *ex vivo*, distance information was extracted from digital images corresponding to the mid horizontal plane of sectioned eyes as described previously.<sup>36</sup> Following enucleation (left and right in random order), eyes were positioned on the stage of a customized, freezing microtome (Zeiss HM 430; Carl Zeiss Meditec, Jena, Germany), covered in embedding medium (Tissue-Tek optimal cutting temperature compound) and then frozen to  $-35^\circ\text{C}$  over 45 seconds. Consecutive  $50\ \mu\text{m}$  sections were cut, and high-resolution images (250 pixel/mm) taken of the remaining block face using a digital camera (10 MP D7000 with a Nikkor AF-S DX 55-300 mm lens; Nikon, New York, NY, USA). The image in which the crystalline lens was at maximum thickness (Fig. 2A) was selected for off-line analysis of distances in the mid horizontal plane using a program written in MatLab (Version R2013b; MathWorks, Natick, MA, USA). The ocular perimeter was defined to include the anterior surface of the cornea and the retina/choroid boundary (Fig. 2B). For each eye, 20 measurements were made of three internal parameters: anterior chamber depth (including corneal thickness), crystalline lens thickness, and vitreous chamber depth (from the posterior surface of the lens to the retina/choroid boundary), at  $6^\circ$  intervals between  $-60^\circ$  and  $+60^\circ$  referenced to the center of the crystalline lens (the intersection of the lens equator with the line connecting the anterior and posterior poles). These parameters were summed to obtain off-axis OLs (i.e., from the anterior cornea to the retinal/choroidal interface, the same as defined for the *in-vivo* ultrasound measures). The optic axis was assigned a value of  $0^\circ$  (see Fig. 2). Positive eccentricities denote temporal retina, and negative values denote nasal retina. The center of the optic nerve head was located approximately  $9^\circ$  temporal to the optic axis.

To describe regional shape changes, several zones were defined. The peripapillary zone<sup>36</sup> (PPZ) was defined as  $0^\circ$  to  $+18^\circ$ , a zone centered on the optic nerve but larger than the

optic disc (Fig. 2). The remaining peripheral zones between  $\pm 18^\circ$  and  $\pm 60^\circ$  were divided into temporal ( $+18^\circ$  to  $+60^\circ$ ) and nasal ( $-18^\circ$  to  $-60^\circ$ ) regions (Fig. 2). For some analyses, values corresponding to the  $+24^\circ$  to  $+36^\circ$  and  $-6^\circ$  to  $-24^\circ$  zones



**FIGURE 2.** **(A)** Sample image of a mid-horizontal section of a frozen eye with eye shape parameters overlaid. The center of the lens, defined as the intersection of the lens equator with the anterior and posterior poles, was used as the reference point for all measures. The three distances summed to calculate OLs were: anterior chamber depth (AC); crystalline lens thickness (Lens); and vitreous chamber depth (Vitreous). The PPZ was defined as the area including  $0^\circ$  to  $+18^\circ$ , centered on the optic nerve head. The zone between  $18^\circ$  and  $60^\circ$  was defined as the peripheral retina. The *two large white arrows* indicate the approximate off-axis refraction positions. **(B)** The *inset* shows an enlargement of the PPZ zone. The *dotted line* illustrates the location of the traced surface to which OL measures were made.



**TABLE 1.** On-Axis Refractive Errors and OLs (Measured In Vivo by A-Scan Ultrasonography) After Lens Treatment

Lens Type	N	Eye	Central Refractive Error (D)		OL (mm)	
			Mean	SE	Mean	SE
−4 D	18	Fellow	2.73	0.37	7.980	0.026
		Lens-wearing	−1.60	0.38	8.065	0.030
		Difference	−4.33	0.33	0.085	0.017
		<i>P</i>	0.000		0.000	
−4/0 D	19	Fellow	1.45	0.24	8.029	0.035
		Lens-wearing	−2.40	0.41	8.067	0.029
		Difference	−3.83	0.40	0.040	0.018
		<i>P</i>	0.000		0.050	
0 D	14	Fellow	1.16	0.62	8.018	0.052
		Lens-wearing	−0.51	0.69	8.040	0.044
		Difference	−1.67	0.42	0.022	0.022
		<i>P</i>	0.001		0.347	
+4/0 D	14	Fellow	0.89	0.23	8.150	0.035
		Lens-wearing	0.57	0.53	8.189	0.036
		Difference	−0.32	0.42	0.039	0.023
		<i>P</i>	0.231		0.107	
+4 D	18	Fellow	1.59	0.65	8.171	0.028
		Lens-wearing	2.32	0.63	8.159	0.034
		Difference	0.73	0.40	−0.013	0.021
		<i>P</i>	0.043		0.553	

*P* values show the significance of differences between the lens-wearing and fellow eyes from matched pairs *t*-tests. *N*, number of animals.

were averaged to represent the dual defocus (transition) zone, values for the +42° to +60° and −30° to −60° zones averaged to represent the single vision peripheral zone, and values between 0° and +18° averaged to represent the exclusive central plano/PPZ zone (Fig. 1B).

### Data Analysis and Presentation

Data are presented as means ± the SEM. Differences between lens-wearing and fellow non lens-wearing eyes (interocular difference, IOD) were compared using paired *t*-tests. Intergroup comparisons of IOD used 1-way ANOVA with familywise corrections for multiple comparisons, except in the case of eye shape data, for which a 2-way mixed model ANOVA and Holm-Sidak post hoc tests were used. Correlations were based on Pearson's and linear regression analyses. SigmaPlot V12.5

(Systat Software, Inc., San Jose, CA, USA) was used in these analyses.

## RESULTS

As expected, the negative UF lens induced increased elongation of lens-wearing eyes and relative myopia, while the positive UF lens inhibited elongation of the vitreous chamber, thereby inducing slight relative hyperopia. Interestingly, both PF lenses induced elongation in the PPZ, despite containing power of opposite signs in their peripheries.

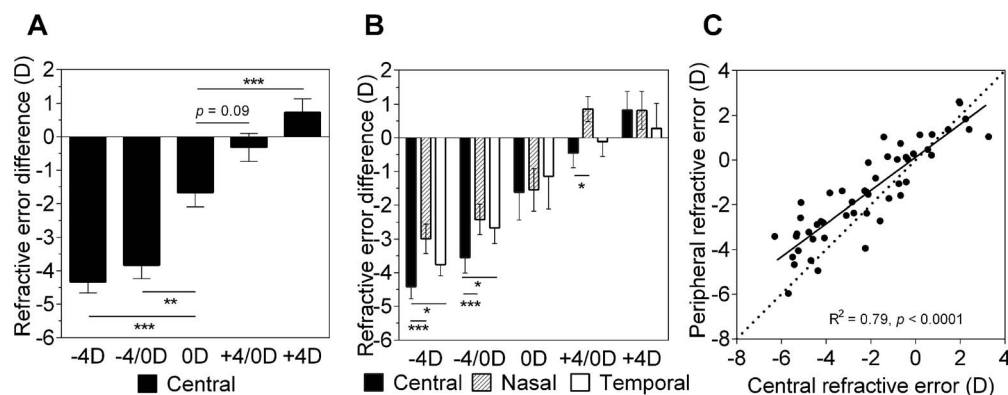
### The Effect of Lens Design on Refractive Error

**Central (On-Axis) Refractive Error.** The −4 D UF lens induced relative myopia (IOD,  $-4.3 \pm 0.3$  D;  $P < 0.001$ ; Table 1, Fig. 3A). Likewise, the −4/0 D PF lens, which had negative power limited to its periphery, also induced relative myopia of a similar amount to, and not significantly different from that seen with the −4 D UF lens (IOD,  $-3.8 \pm 0.4$  D;  $P < 0.001$ ; Table 1, Fig. 3A). The plano UF lens also induced slight myopia (IOD,  $-1.7 \pm 0.4$  D;  $P < 0.001$ ), but this was significantly less than that induced by the −4 D UF lens (by 2.7 D;  $P < 0.001$ ) and the −4/0 D PF lens (by 2.2 D;  $P < 0.001$ ).

For the plus lens series, only the +4 D UF lens induced statistically significant relative hyperopia (+4 D IOD:  $+0.7 \pm 0.4$  D,  $P = 0.04$ ; +4/0D:  $-0.3 \pm 0.4$  D,  $P = 0.23$ ; Table 1, Fig. 3A), although there was no significant difference in the treatment effects of the +4 D UF and +4/0 D PF lenses ( $P = 0.23$ ).

**Peripheral Refractive Error.** The absolute refractive error in the temporal retina was more myopic than the nasal retina in all eyes ( $P < 0.01$  in all cases; Table 2). However, since within each lens-group the mean IOD in refractive error in the nasal and temporal retina did not statistically differ (nasal-temporal difference: −4 D UF,  $-0.8 \pm 0.5$  D,  $P = 0.09$ ; −4/0 D PF,  $-0.3 \pm 0.4$  D,  $P = 0.29$ ; 0 D UF,  $+0.40 \pm 0.8$  D,  $P = 0.37$ ; +4/0 D PF,  $-1.0 \pm 0.3$  D,  $P = 0.06$ ; +4 D UF,  $+0.5 \pm 0.7$  D,  $P = 0.30$ ), these nasal and temporal values were averaged in further analyses of the peripheral changes, which tended to mimic those observed on-axis (Fig. 3B).

Both −4 D UF and −4/0 D PF lenses induced off-axis (peripheral) myopia (IOD,  $-3.4 \pm 0.3$  and  $-2.5 \pm 0.4$  D, respectively;  $P < 0.001$  in both cases; Fig. 3B), and there was no significant difference in their treatment effects (difference =  $-0.8$  D, NS). For both lens types, the induced changes were more myopic than that induced by the plano UF lens (by  $-2.0$



**FIGURE 3.** The effect of lens treatment on myopia. (A) The interocular difference in spherical equivalent refractive error, measured centrally (entire set). (B) Interocular difference in refractive error measured centrally and in the periphery (subset in which off-axis measures were made). (C) Correlation of interocular difference in peripheral refractive error and interocular difference in central refractive error. \*\*\* $P < 0.001$ ; \*\* $P < 0.01$ ; \* $P < 0.05$ .

TABLE 2. On-Axis and Off-Axis Refractive Errors, Measured in a Subset of Animals

Lens Type	N	Eye	Subset Central Refractive Error (D)		Subset Nasal Refractive Error (D)		Subset Temporal Refractive Error (D)	
			Mean	SE	Mean	SE	Mean	SE
−4 D	13	Fellow	2.65	0.47	3.54	0.28	0.10	0.41
		Lens-wearing	−1.77	0.49	0.56	0.52	−3.66	0.46
		Difference	−4.42	0.37	−2.99	0.44	−3.76	0.33
		P	0.000		0.000		0.000	
−4/0 D	13	Fellow	1.39	0.28	2.97	0.31	−0.64	0.26
		Lens-wearing	−2.16	0.51	0.55	0.42	−3.31	0.43
		Difference	−3.55	0.46	−2.42	0.45	−2.67	0.47
		P	0.000		0.000		0.000	
0 D	5	Fellow	1.47	1.29	3.24	0.56	−0.53	1.11
		Lens-wearing	−0.14	1.49	1.73	0.85	−1.67	1.39
		Difference	−1.62	0.82	−1.55	0.63	−1.14	0.97
		P	0.137		0.035		0.152	
+4/0 D	11	Fellow	0.95	0.28	2.42	0.27	−0.68	0.29
		Lens-wearing	0.50	0.62	3.27	0.52	−0.80	0.63
		Difference	−0.45	0.44	0.85	0.37	−0.11	0.44
		P	0.257		0.080		0.440	
+4 D	9	Fellow	0.77	0.88	2.37	0.76	−0.43	0.57
		Lens-wearing	1.60	1.05	3.18	0.91	−0.15	1.12
		Difference	0.83	0.55	0.81	0.56	0.28	0.74
		P	0.086		0.093		0.358	

P values show the significance of differences between the lens-wearing and fellow eyes from matched pair's *t*-tests. This subset is representative of all animals, since there was no statistical difference between the central refractive errors in this subset and in the full set of animals shown in Table 1 ( $P = 0.79$ ). N, number of animals.

D,  $P = 0.003$ , −4 D UF; −1.2 D, NS, −4/0 D PF). In contrast, the +4 D UF and +4/0 D PF lenses induced less peripheral myopia than that induced by the UF plano lenses (relatively hyperopic by +1.9 D,  $P = 0.02$  for +4 D lens; by +1.7 D,  $P = 0.02$  for +4/0 D lens; Fig. 3B).

**Central (On-Axis) Versus Peripheral (Off-Axis) Refractive Errors.** Relative to on-axis refractive errors, −4 D UF, −4/0 D PF, and +4/0 D PF lenses induced significantly less myopia in the nasal retinal field (by: 4 D UF,  $1.4 \pm 0.4$  D,  $P < 0.001$ ; −4/0 D PF,  $1.1 \pm 0.4$  D,  $P < 0.001$ ; +4/0 D PF,  $1.3 \pm 0.3$  D,  $P = 0.046$ ; Fig. 3B; Table 2). Likewise, the −4 D UF and −4/0 D PF lenses also induced less myopia in the temporal periphery, relative to on-axis refractive errors (by: 4 D UF,  $0.6 \pm 0.3$  D,  $P = 0.047$ ; −4/0 D PF,  $0.9 \pm 0.4$  D,  $P = 0.044$ ; Fig. 3B; Table 2). Therefore, different lens designs induced greater myopic shifts on-axis than in the periphery. This relative peripheral “hyperopia” (or more correctly, greater central myopia) was supported by a strong positive correlation between the IODs in central and averaged peripheral refractive errors across individual animals ( $R = 0.9$ ,  $P < 0.001$ , Fig. 3C), with deviation of this regression

function from a 1:1 correspondence with larger on-axis myopic shifts (Fig. 3C).

### OL (Measured In Vivo On-Axis)

As expected, the −4 D UF lenses enhanced ocular elongation ( $85 \pm 17 \mu\text{m}$ ;  $P < 0.001$ , Table 1) by  $64 \mu\text{m}$  more than the relative elongation induced by plano UF lenses ( $P = 0.03$ ). The −4/0 D PF lens also enhanced ocular elongation ( $40 \pm 18 \mu\text{m}$ ;  $P = 0.05$ , Table 1), although the difference was slightly less than that seen with the −4 D UF lens (by  $-46 \mu\text{m}$ ,  $P = 0.08$ ).

The +4 D UF lens had minimal effect on ocular elongation ( $-13 \pm 21 \mu\text{m}$ , NS), while the +4/0 D PF lens slightly enhanced ocular elongation (IOD of  $39 \mu\text{m}$ ) although not significantly so relative to the change induced by the +4 D UF lens ( $P = 0.10$ ). Nonetheless, there is only a  $1 \mu\text{m}$  difference between the effects of the two PF lenses ( $P = 0.98$ ; Table 1, Fig. 4A), both of which were not significantly different from that of the plano UF lens. As expected, animals exhibiting greater interocular elongation had greater on-axis relative myopia ( $R = 0.56$ ,  $P <$

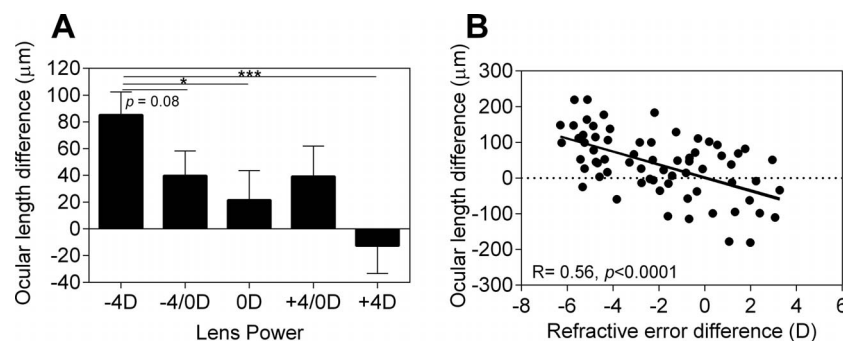
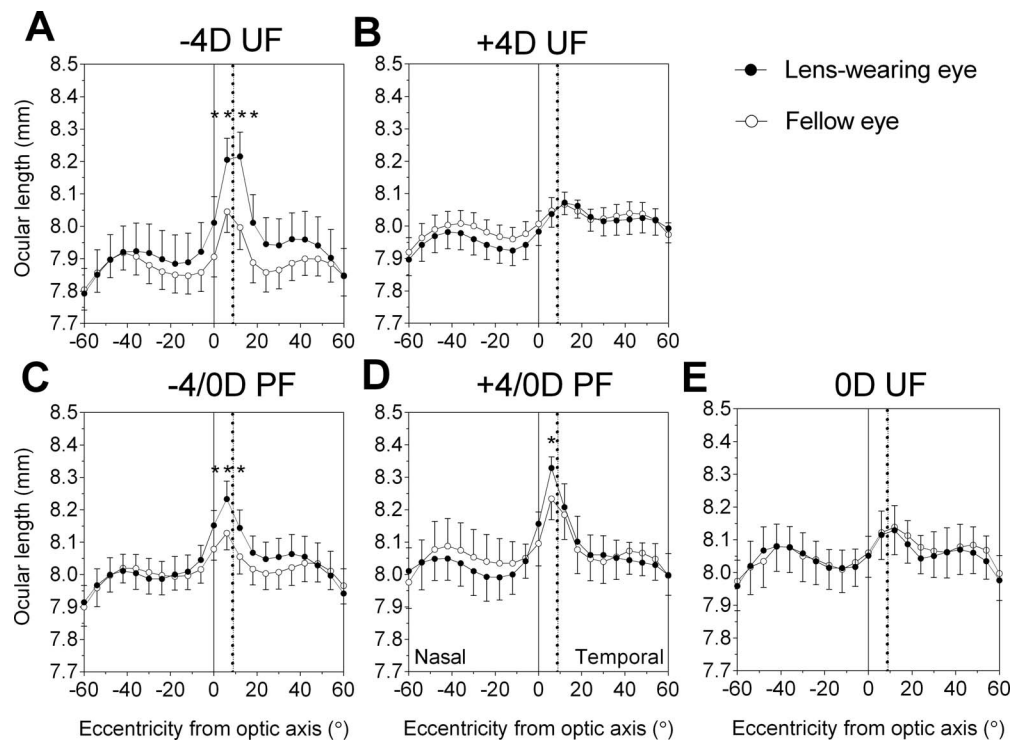


FIGURE 4. The effects of lens treatments on ocular elongation in vivo. (A) Interocular differences (treated-fellow eyes) in OL measured by A-scan ultrasonography. (B) Interocular differences in OLs plotted against interocular differences in on-axis refractive errors. \*\* $P < 0.01$ ; \* $P < 0.05$ .



**FIGURE 5.** Mean OLs measured ex vivo from images of sectioned eyes for lens-wearing eyes (*filled circles*) and their untreated fellow eyes (*open circles*) or untreated eyes (*open triangles*). (A)  $-4$  D UF lens. (B)  $+4$  D UF lens. (C)  $-4/0$  D PF lens. (D)  $+4/0$  D PF lens. (E)  $0$  D UF lens. Error bars: Standard errors. OL distances were measured from the front of the cornea to the back of the retina, at  $6^\circ$  intervals. The optic axis is located at  $0^\circ$ . The temporal location of the optic nerve is represented by the vertical dotted line. Asterisks (\*) indicates the eccentricities in which significant differences ( $P < 0.05$ ) were found from Holm-Sidak comparisons between the lens-wearing and the fellow eyes.

0.001; Fig. 4B). Nonetheless, while the  $-4/0$  D lens produced more relative myopia than in the plano group (Fig. 3A), the associated IOD in OL was not as great as might be expected ( $P = 0.9$ ; Fig. 4A). However, the IOD in the vitreous chamber for the  $-4/0$  D group was statistically larger than that in the plano group (by  $40 \mu\text{m}$ ,  $P < 0.05$ ).

### Eye Shape

OL parameters measured from high resolution images of sectioned eyes within the  $+60^\circ$  to  $-60^\circ$  zone (centered on the optic axis) were compared to obtain insight into induced ocular shape changes (see Fig. 2). For consistency with the ultrasonography data described above, only OLs are described here, but data for individual components are shown in Supplementary Figure S2. For all eyes, OLs varied significantly with eccentricity from the optic axis ( $F$  values from 9.48–36.44,  $P < 0.001$ ; Fig. 5), with the largest values recorded within the PPZ ( $18^\circ$  wide zone centered on the optic nerve), reflecting the backward displacement of the eye wall (shallow pit) centered around and including the optic nerve head (see Fig. 2). This pit also was present in fellow eyes of lens-treated animals (Fig. 5) and in untreated animals (Supplementary Fig. S3). However, for all lens designs except the  $0$  D UF and  $+4$  D UF lenses, OLs within the PPZ were significantly increased for lens-wearing eyes relative to their fellows (Fig. 5).

Comparison of the IOD in OLs within the PPZ across all lens groups identified the  $-4$  D UF lens group as having the largest OL change,  $219 \pm 50 \mu\text{m}$  (at  $+12^\circ$ ; Fig. 6A), which was significantly greater than that observed with plano UF lenses (by  $226 \mu\text{m}$ ,  $P < 0.001$ ; Fig. 6A). In contrast, the maximum elongation for the  $+4$  D UF lens group was only  $16 \pm 26 \mu\text{m}$  (at

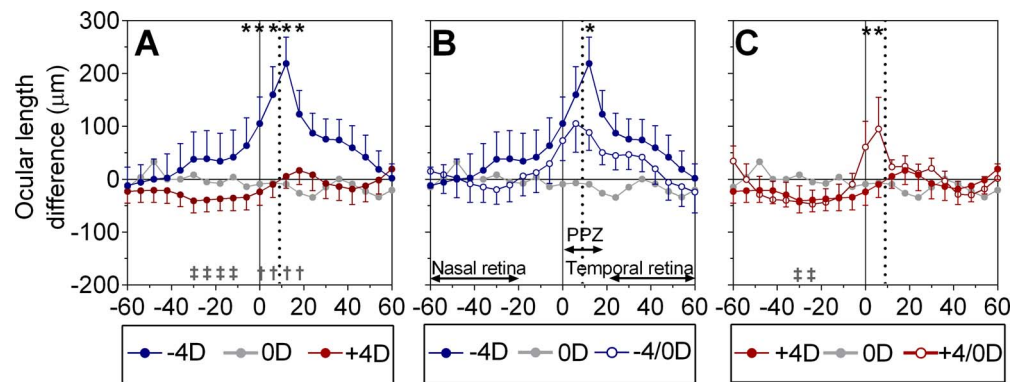
$+18^\circ$ ), similar to the change in the plano UF group ( $P = 0.86$ , Fig. 6A).

Compared to the  $-4$  D UF lens, the  $-4/0$  D PF lens induced significantly less elongation within the PPZ, by  $-130 \mu\text{m}$  ( $P = 0.028$ , Fig. 6B). In contrast, the  $+4/0$  D PF lens induced significantly more elongation than the  $+4$  D UF lens within the PPZ (IOD greater by  $105 \mu\text{m}$ ,  $P = 0.013$ ). These opposing trends seen when the effects of the  $-4/0$  and  $+4/0$  D PF lenses are compared to their respective  $-4$  D and  $+4$  D UF controls reflects the similar patterns of increased elongation within the PPZ for the  $-4/0$  D and  $+4/0$  D PF lenses (cf. Figs. 6B, 6C).

These OL changes were not due to changes in the crystalline lens thickness (Supplementary Figs. S2A–C) but arose primarily from expansion of the vitreous chamber depth (Supplementary Figs. S2D–F). Interestingly, the anterior chamber appeared significantly reduced in eyes wearing  $+4/0$  D PF lenses, and deeper in eyes wearing plano lenses, these changes effectively counteracting the posterior PPZ elongation in the first case, while contributing to the small myopic offset observed in the latter case (Supplementary Figs. S2H–J).

On-axis OLs, and the combined depths of the vitreous chamber depth and crystalline lens measured in vivo by ultrasonography were well correlated with the equivalent lengths measured at  $0^\circ$  by ex vivo eye shape analysis ( $R = 0.76$ ,  $R = 0.73$ ,  $P < 0.001$  in both cases, Supplementary Fig. S4).<sup>36</sup> Also importantly, the IODs in on-axis refractive errors correlated well with the IODs in OL at  $0^\circ$  measured ex vivo ( $R = 0.52$ ,  $0.54$ ,  $0.49$ , respectively;  $P < 0.001$  in all cases).

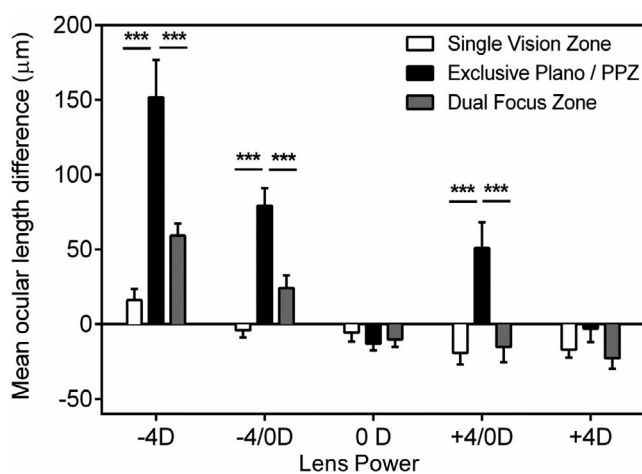
**Regional Variation in Eye Shape.** The IODs in OLs for nasal and temporal peripheral zones were compared. For  $-4$  D UF and  $+4$  D UF lenses, average elongation was less nasally than temporally (by  $46.23 \mu\text{m}$ ,  $P < 0.001$  and  $27.92 \mu\text{m}$ ,  $P = 0.05$ ), while there was no significant difference between



**FIGURE 6.** The IODs in ocular distances measured ex vivo from images of sectioned eyes. Comparison of the IODs is shown between the control plano (0 D UF) lens group and (A) the  $-4$  D and  $+4$  D UF groups, (B) the  $-4/0$  D PF and  $-4$  D UF groups, and (C) the  $+4/0$  D PF and  $+4$  D UF groups. Asterisks (\*) indicate the eccentricities in which significant differences ( $P < 0.05$ ) were found from Holm-Sidak comparisons between the two powered lens groups. Comparisons to the plano (0 D UF) lens group also are shown: †Indicates a significant difference ( $P < 0.05$ ) between the  $-4$  D and 0 D UF groups. ‡Indicates a significant difference ( $P < 0.05$ ) between the  $+4$  D and 0 D UF (in [A]) or  $+4/0$  D and 0 D groups (in [C]). The optic nerve was located at  $+9^\circ$  and is represented by the dotted vertical line.

equivalent nasal and temporal IODs in the other lens groups ( $-4/0$  D PF, by  $22.73 \mu\text{m}$ ;  $+4/0$  D PF, by  $23.23 \mu\text{m}$ ;  $+4$  D UF, by  $27.92 \mu\text{m}$ ; 0 D UF, by  $-19.79 \mu\text{m}$ ;  $P > 0.05$  in all cases).

The IODs in ocular distances calculated for the three lens defocus zones also were compared. In this comparison, the  $-4$  D UF,  $-4/0$  D PF and  $+4/0$  D PF lens groups all exhibited significantly greater induced elongation within the plano/PPZ compared to the single vision zone or the equivalent area in the UF lenses ( $-4$  D UF, by  $136 \mu\text{m}$ ,  $P < 0.001$ ;  $-4/0$  D PF, by  $83 \mu\text{m}$ ,  $P < 0.001$ ;  $+4/0$  D PF, by  $70 \mu\text{m}$ ,  $P < 0.001$ ; Fig. 7). Similarly, the plano/PPZ area also was elongated more than the dual vision (transition) zone ( $-4$  D UF, by  $92 \mu\text{m}$ ,  $P < 0.001$ ;  $-4/0$  D PF, by  $55 \mu\text{m}$ ,  $P < 0.001$ ;  $+4/0$  D PF, by  $66 \mu\text{m}$ ,  $P < 0.001$ ; Fig. 7). The exceptions were the  $+4$  D UF lens and 0 D UF groups, which did not show lens-induced changes in the PPZ area. Therefore, PF lenses with either positive or negative defocus in the periphery enhanced central elongation in the PPZ area despite its very limited direct exposure to defocus.



**FIGURE 7.** Regional variation in the effects of different lens types on the mean IOD in OLS measured ex vivo from mid-horizontal sections. Comparison is shown for the average distances across Single Vision, Exclusive Plano/PPZ, or Dual Focus Zones for PF lenses and the equivalent area for UF lenses. See Methods for zone definitions and Figure 2 for a schematic illustration. Statistical comparisons were based on Holm-Sidak after 2-way ANOVA. \*\*\* $P < 0.001$ , denotes significant difference from Exclusive Plano/PPZ.

## DISCUSSION

Central (on-axis) myopia arising from hyperopic defocus imposed on the retinal periphery has been reported previously in chicks<sup>16</sup> and monkeys.<sup>40</sup> These examples made use of spectacle lenses incorporating a central plano zone and peripheral  $-5$  D power zone and a central aperture within a negative lens, respectively. In chicks,<sup>16</sup> the size of the plano zone had to be increased beyond 50% (5.5 mm in a 10 mm diameter lens) to substantially reduce the magnitude of the defocus response, compared to the response to a UF plano lens. In the current study, an exclusive plano central zone of approximately  $20^\circ$  (arising from a 5 mm plano center in a 12 mm lens) together with a pure peripheral  $-4$  D powered zone, proved sufficient to induce central myopia in our guinea pig model. Peripheral  $+4$  D power also influenced central refractive error, but in the opposite direction, inducing hyperopia relative to plano controls.

Novel to the present study, changes in eye shape brought about by the various lens designs also were examined. Thus, this study adds to the small, but growing body of literature concerning myopia and eye shape. Smith et al.<sup>27</sup> showed that compensatory changes in eye shape could be elicited in response to local myopic defocus of the nasal visual field, whereby local reductions in elongation were observed in the temporal retina. Here, we show that peripheral hyperopic defocus can induce central axial elongation. Together, these studies demonstrate that peripheral vision can influence eye shape, independent of central vision. They additionally lend support for correcting interventions of myopia that use peripheral defocus.<sup>30,32</sup>

Similar to previous studies, we demonstrated a strong nasal-temporal asymmetry in refractive error, where the nasal field (projecting onto temporal retina) was more myopic, reflecting that this region bordered the optic nerve head and showed greater elongation in the corresponding ocular segment. This asymmetry is consistent with that reported in monkeys,<sup>41</sup> marmosets (Totonelly KC, et al. *IOVS* 2008;49:ARVO E-Abstract 3589), and those commonly observed in humans.<sup>42</sup>

For central (on-axis) refractive errors, eyes that had worn the  $-4/0$  D PF lens became myopic, while eyes that had worn  $+4/0$  D PF became slightly, although not significantly, hyperopic. Despite these differential effects on central refractive error, both types of lenses induced similar increases in OL centrally, as measured by ultrasonography. These differences in refractive error using streak retinoscopy may



be partly explained by a contribution of the reduced eye lengths in the adjacent nasal retina in the  $-4/0$  D PF lens group (Fig. 6C, steak retinoscopy by its nature is not a purely local measure) as well as differential effects of these two lens types on the anterior ocular segment. For example, the reduced anterior chamber in the  $+4/0$  D PF group (Supplementary Fig. S2J) may be associated with corneal flattening, which would tend to neutralize, at least in part, the effect on refractive error of increased ocular elongation. Modulation of corneal development in response to changes at the back of the eye has been described in the guinea pig previously (McFadden SA, et al. *IOVS* 2010;51:ARVO E-Abstract 1192).<sup>43</sup> Indeed, chick studies point to independent emmetropization pathways for the anterior and posterior segments.<sup>44</sup> Therefore, it may be possible for eyes to reach emmetropia via multiple mechanisms, one of which involves changes in the anterior segment optics, although its regulation is not well understood.

Plano lenses induced a small amount of myopia ( $-1.7$  D) despite no significant change in OL. However, there was an increase in the anterior chamber, which is consistent with an increase in the power of the cornea as previously reported.<sup>4</sup> The reason for this effect on the anterior chamber/cornea is unknown, but is unlikely to be due to form deprivation as lenses were kept very clean, the effect is independent of the sign of defocus and also occurs with diffuser wear.<sup>4,5</sup> In the current study, this nonspecific effect of lens-wear was taken into account by comparing the difference between eyes in the experimental groups to the plano group.

An interesting finding of the current study is the significant elongation that occurred about the optic nerve, i.e., in the PPZ, in eyes developing myopia, such as induced by the  $-4$  D UF lenses. This observation is consistent with observations in guinea pigs developing form deprivation myopia (Zeng G, et al. *IOVS* 2011; 52:ARVO E-Abstract 3923). Interestingly, imposed peripheral defocus also induced ocular expansion within the PPZ, irrespective of its sign. This effect in the region of the PPZ cannot be explained by an attenuation of the imposed defocus over the lens wearing period; for the  $-4/0$  D and  $+4/0$  D lenses, the effective imposed peripheral defocus at the end of the lens-wearing period is estimated to average  $-5.2$  D and  $+2.7$  D (taking into account the peripheral refractive error of untreated eyes of  $+1.3$  D, and lens vertex distance).

It is important to acknowledge that although a proportion of central retina primarily received input through the plano region of the spectacle lens, Figure 1 shows that the temporal side of the PPZ could receive two focal planes, arising from the central plano and the powered peripheral regions of the imposed spectacle lens. Additionally, eye movements would have allowed the peripheral retina to receive some exposure to the central plano area in the PF lenses. The guinea pig possesses horizontal eye movements<sup>39</sup> similar to that found in the rabbit<sup>45</sup> and possesses a sophisticated array of muscles, including two medial rectus muscles,<sup>46</sup> sufficient for lateral eye movements. Therefore, the PPZ region (but typically not the central axis) could experience simultaneous input from two focal planes. Based on the way the guinea pig eye responds to deliberately imposed dual focal planes in a Fresnel lens design,<sup>37</sup> one would expect the eye to respond to the average of these two planes of focus ( $+2$  D for  $+4$  D and  $0$  D;  $-2$  D for  $-4$  D and  $0$  D). However, the degree of central myopia from wearing a UF  $-4$  D lens was similar to that arising from the  $-4/0$  D PF lens. Therefore, it is unlikely that this central myopic response was from dual focal planes imposed on central retina, but genuinely arose from peripheral retinal defocus.

Similarly, in terms of eye shape, we might expect that if the area around the optic disk was influenced by dual focal planes, an averaged response might occur. For example, if the PPZ were to have been directly impacted by the defocus imposed

by peripheral zone of the  $+4/0$  D lens and the central plano zone, one might expect an average of that seen with the  $+4$  UF lens and the plano lens. However, while the former generally inhibited elongation, and the latter plano lens had limited impact, the  $+4/0$  D lens caused increased elongation within the PPZ. As noted above, this response near the optic disk was almost identical to that seen with the  $-4/0$  D lens, suggesting that the response in this zone was unlikely to be due to some kind of integrated spatial or temporal response to two different focal planes.

Interestingly, ocular elongation was inhibited rather than enhanced on the opposite (nasal) side by the  $+4/0$  D PF lens relative to that seen in eyes wearing plano lenses, matching the significant peripheral inhibition seen with the  $+4$  D UF lens. Given that the optic nerve head typically is a photoreceptor-free area and photoreceptor density is likely sparser in its immediate surround, these observations together suggest that there may be a critical area of retina required for the accurate decoding of either clear vision or the sign of imposed defocus, below which the detection of blur may occur, resulting in enhanced growth. Indeed, preliminary evidence suggests that lesions of the retina in the PPZ also result in enhanced PPZ elongation and myopia (McFadden SA, et al. *IOVS* 2014;55:ARVO E-Abstract 3601).

It is possible that nonvisual factors also contribute to the observed enhanced elongation in the PPZ. These may involve mechanical factors, such as IOP and/or extraocular muscle forces. As in primates, the guinea pig lamina cribrosa, which straddles the optic nerve head, is a highly organized sieve-like structure, with radially-organized collagen beams, interspersed with elastin, GFAP and fibronectin.<sup>47</sup> The lamina cribrosa also is reported to have a greater proportion of elastin<sup>48</sup> than the surrounding sclera, which may make it more susceptible to posterior displacement than the adjacent sclera, especially if IOP is elevated.

It is interesting to note the similarity of our findings with the posterior displacement of the lamina cribrosa in human glaucomatous eyes.<sup>49</sup> The lamina cribrosa thins in glaucoma, and also in high myopia.<sup>50</sup> Given the observed strong relationship between myopia and glaucoma<sup>51,52</sup> and reports in some, albeit not all, studies of higher IOP in myopes compared to nonmyopes,<sup>51,53,54</sup> the apparent link reported here between myopic changes in ocular dimensions and posterior displacement within the PPZ centered on the optic nerve head, warrants further investigation.

In summary, lenses with defocusing power restricted to the periphery can change central (on-axis) refractive errors. In the guinea pig model, positive and negative peripheral defocus also enhanced ocular elongation in the PPZ, centered on the optic nerve. Given the well-established relationship between glaucoma and myopia in humans, this change in the optic nerve head during the development of myopia deserves further study.

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