The Effect of Daily Transient +4 D Positive Lens Wear on the Inhibition of Myopia in the Tree Shrew

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PURPOSE. Negative-lens-induced defocus causes accelerated ocular elongation and myopia, whereas positive-lens-induced defocus produces reduced ocular elongation and hyperopia. Short durations of positive lens wear result in markedly stronger temporal effects than do short periods of negative lens wear in the chick model of refractive development. In mammalian and nonhuman primate models, there have been equivocal results in inhibiting myopia by short periods of positive lens wear when compared with data from the chick model. The purpose of the present study was an evaluation of full-time —9.5 D negative lens wear interrupted by short periods of daily +4 D positive lens wear in preventing experimental myopia in the tree shrew.

METHODS. One treatment group wore negative lenses (−9.5 D) binocularly for 23 hours a day (10 hours of which were spent in total darkness), interrupted by 1 hour of wearing positive lenses (+4 D) binocularly for 12 days. Another group of animals wore negative lenses (−9.5 D) binocularly for 23 hours a day, interrupted by two 30-minute periods of positive lens (+4 D) wear daily, again for 12 days. The animals were raised on a 14-hour/10-hour light–dark cycle. Animals wearing −9.5 D lenses binocularly, interrupted by 0-powered lenses for either 1 hour or two 30-minute periods daily for 12 days, acted as controls.

RESULTS. Continuous wear of −9.5 D lenses binocularly induced a −10.8 D myopic shift in refraction. Full-time wear of −9.5 D lenses binocularly, interrupted by 1 hour of 0-power lens wear binocularly, caused a myopic shift of 3.6 D over 12 days, whereas wearing −9.5 D lenses, interrupted by 1 hour every day of +4.0 D lens wear binocularly, whether it was continuous or divided into two 30-minute periods, caused a myopic shift of only 0.7 D over 12 days.

CONCLUSIONS. Daily intermittent +4 D positive lens wear effectively inhibits experimentally induced myopia and may prove a viable approach for preventing myopia progression in children. (Invest Ophthalmol Vis Sci. 2012;53:1593–1601) DOI:10.1167/iovs.11-7859

Ocular growth is closely regulated by the clarity of the image that is received on the retina.1–5 Induced defocus from optical lenses has been demonstrated, in a variety of vertebrate species, to cause altered ocular growth in an attempt by the eye to attain functional emmetropia. More specifically, positive lens-induced defocus, which brings the focus in front of the retina for a relaxed emmetropic eye (imposed myopic defocus), causes slowed ocular growth, whereas negative lens-induced defocus, which places the focus behind the retina in a relaxed emmetropic eye (imposed hyperopic defocus), induces accelerated ocular growth. Consequently, when the defocusing lenses are removed from in front of the eye, the eyes wearing positive lenses are shorter and hyperopic (long-sighted), and the eyes wearing negative lenses are longer and myopic (short-sighted).6,5 Compensation for imposed optical defocus has been observed across several vertebrate species, including fish,6 chicks,4,7 guinea pigs,8 tree shrews,9–11 and primates.12–15

In the chick model of refractive development, it has been demonstrated that the rate of ocular growth can be manipulated to bring about compensation across a wide range of lens-induced defocus (−10 to +15 D), predominantly induced by altered axial ocular dimensions. Less complete compensation was observed for lens powers beyond this range, indicating that the limits of compensation had been reached.7,16 There was also a considerable increase in the variability of responses for lens powers outside this range of compensation. However, in primates, although experiments have shown that anisometric spectacle lenses elicit differential interocular growth, the magnitude of refractive compensation is more limited than that observed in chicks.12,13 This was attributed to primates’ having a narrower effective operating range of the emmetropization mechanism and also to the view that higher amounts of imposed defocus (>±6 D) trigger visual development anomalies, such as amblyopia. Tree shrews have recently been demonstrated to respond to both positive and negative lenses in the appropriate direction for compensation of the imposed defocus; however, the range of compensation in response to positive lenses (up to +6 D) was significantly less than compensation in response to negative lenses (up to −10 D).10,17 Guinea pigs have also been reported to respond to both positive and negative lenses, but again, the range of reliable compensation observed for positive lenses was small.8

A sequential lens-rearing strategy, in which a small magnitude of defocus is imposed binocularly at the start of treatment and is increased sequentially as compensation occurs, has shown consistent responses to larger degrees of positive-lens defocus in both primate18 and tree shrew.10 Recent findings indicate that it is not only the amount of defocus used in a particular sequential step change, but also the actual duration of the treatment period for positive-lens defocus in mammalian models that is important in compensation responses.10 These findings are of particular interest in relation to the possibility of intervention in human refractive development, in particular the prevention of axial myopia. The effects of imposed myopic defocus in the chick, induced by short durations of positive lens wear demonstrate markedly stronger temporal effects than short periods of negative lens wear. Indeed, short
periods of positive lens wear effectively inhibit much longer periods of negative-lens-induced hyperopic defocus in the chick.\textsuperscript{18–21} The mechanisms underlying positive-lens defocus may therefore be important in the context of prophylactic interventions for human myopia.\textsuperscript{22} For this reason, translation of findings observed in the chick model to mammalian models is an important step toward progress to human trials. To this end studies by Norton et al.\textsuperscript{17} on tree shrews and by Kee et al.\textsuperscript{23} on nonhuman primates are pertinent, in that they tested the effectiveness of intermittent positive, plano, and negative-lens interventions. In tree shrews, 45 minutes of restricted viewing at distances >1 m, with animals wearing plano lenses monocularly, was a stronger antidote to the myopiagenic stimulus of a −5 D lens than were positive lenses worn monocularly.\textsuperscript{17} In nonhuman primates a 15-minute wearing schedule four times daily was reported to inhibit negative-lens-induced myopia, and plano-lens interruption was found to be more effective than positive-lens interruption.\textsuperscript{23} These findings are contrary to expectations based on findings from the chick model of refractive development. Norton et al.\textsuperscript{17} found that only 11 tree shrews of 30 underwent a hyperopic shift in refraction in response to intermittent wear of positive lenses, when compared to the consistent hyperopic response in chicks. The authors suggested that “the chick retina may be more sensitive to myopic defocus than tree shrews or the cartilaginous sclera in chick may more easily transmit signals to limit axial elongation of the eye.”\textsuperscript{17} However, Kee et al.\textsuperscript{23} suggested that the reason for their finding that intermittent positive lenses were less effective in slowing myopia than plano lenses were in nonhuman primates may be that the power of the positive lens was too high and fell outside the emmetropization response range in monkeys.

The purpose of the present study was to examine whether in the tree shrew model of refractive development, in which ocular growth responses to a range of positive lens powers was recently well characterized,\textsuperscript{10} intermittent binocular positive-lens wear has a strong inhibitory effect on experimentally induced myopia when viewing distance is unrestricted.

**Materials and Methods**

**Experimental Paradigms**

Maternally reared tree shrews (*Tupaia belangeri*) from our breeding colony were used in the present study. On the 14th day after eye opening, which occurred at the age of 21.4 ± 0.3 days (mean ± SEM) after birth, the animals were removed from the maternal cage and allocated to one of the experimental groups. The average illumination at the floor of the cage was 265 lux, and lighting was on a 14-hour light/10-hour dark cycle. Food and water were available ad libitum. All animal procedures were performed in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

On the 14th day after eye opening, a head-mounted goggle was affixed to the skull with a technique that has been reported.\textsuperscript{24} The goggle enabled the placing of optical lenses accurately in front of both eyes. The animals were allowed to recover from the anesthesia, and the head-mounted goggle containing the lenses was clipped to the dental acrylic head pedestal on the 15th day after eye opening.

**Experimental Groups**

Tree shrews were treated with −9.5 D lenses fitted over both eyes (*n* = 25) or plano (0 D) lenses fitted over both eyes (*n* = 5), or they received no treatment (*n* = 5). Animals fitted with −9.5 D lenses were randomly allocated to one of five groups on the basis of whether they wore the −9.5 D lenses binocularly continuously for 24 hours with no interruptions (*n* = 5) or wore +4.0 D lenses once a day binocularly for 60 minutes (+9.5 D/−4.0 D [1] group; *n* = 5) or 0 D lenses (+9.5 D/0 D [2] group; *n* = 5). Other animals had their −9.5 D lens wear interrupted binocularly twice daily for 30 minutes on each occasion with +4.0 D lenses (+9.5 D/+4.0 D [2] group; *n* = 5) or 0 D lenses (+9.5 D/0 D [2] group; *n* = 5). The 60 minute interruptions were initiated 6 hours 45 minutes after the lights-on cycle started, and the 30 minute interruptions were initiated 4 hours 30 minutes and 9 hours 30 minutes after the daily lights-on cycle started. The changeover of lenses was achieved by replacing the clip-on goggle containing the −9.5 D negative lenses with another clip-on goggle containing either +4.0 D, 0 D, or −9.5 D lenses. The lens changeover procedure took less than 10 seconds. During the period when the replacement goggles were worn, the nest box was removed from the cage so that the animal was exposed to a visual experience with the alternate lenses. At other times the animals were allowed to self-regulate their use of the nest box within the open-mesh cage. The data for the plano lens group were from an earlier study in our laboratory on positive lens effects on eye growth,\textsuperscript{10} in which similarly treated animals wore (powered lenses) continuously, and for which we had measurements at similar time points (days 0, 7, and 14 from the start of treatment). This group was used to compare the effects of plano lenses alone (as opposed to unrestricted vision) on ocular growth and refraction.

**Refraction and Ocular Dimension Measurements**

In vivo optical and structural data were collected using retinoscopy and A-scan ultrasonography (10-MHz probe) at the start of the treatment period (day 0), and the measurements were repeated after 5 and 12 days of lens-defocus treatment. The plano lens group from an earlier study had their measurements taken at days 0, 7, and 14, as mentioned earlier. Measurement procedures are described in detail elsewhere.\textsuperscript{25} Measurements were taken while the animal was anesthetized with ketamine (90 mg/kg) and xylazine (10 mg/kg), and 1% tropicamide was used to dilate the pupil and act as a mild cycloplegic agent. Although tropicamide is a weaker cycloplegic, it was preferred against stronger cycloplegic agents such as atropine, which has been shown to affect ocular growth.\textsuperscript{26–29} Refractive data were corrected for the working distance of the lens from the cornea (5 mm). However, the correction for the small-eye artifact\textsuperscript{29} was not applied. Corneal curvature measurements were taken in triplicate with a modified Bausch and Lomb (Rochester, NY) one-position keratometer.

Lenses were cleaned regularly at each goggle changeover. Also, they were assessed and any that were obviously scratched were replaced with new ones at the next changeover.

**Statistical Analysis**

Because the treatment was binocular, there was the likelihood of a high correlation between observations from the right and left eyes of an animal, which would lead to a false statistical significance value if the data were pooled.\textsuperscript{30} Analyses were performed separately on data from the right and left eyes of animals in each group, and the statistical comparisons presented are from just one eye of each animal. Repeated measures one-way ANOVA with Bonferroni’s post hoc test was used to compare the measurements at different time points (days 0, 5, and 12) in individual groups. One-way ANOVA with the Bonferroni post hoc test was also used to assess differences between the three groups at each of the time points. Two-way ANOVA was used when analysis was performed across different groups and time points. All group data are presented as the mean and 1 SEM (mean ± SEM), unless otherwise specified (all analyses: GraphPad software; GraphPad, Inc., San Diego, CA).

**Results**

The difference between the right and left eyes of binocularly treated animals was not significant in the positive-lens and 0 power lens intervention groups or the negative-lens full-time treated group. The results of statistical comparisons between the right eyes in the seven groups were similar to those be-
tween the left eyes, and so only the results of the right eyes are presented.

The refractive state measured at the start of treatment was not significantly different between the right eyes of animals across all seven groups (one-way ANOVA, \( P = 0.50 \); Fig. 1A, Table 1). In keeping with refraction findings, there was no significant difference in the mean vitreous chamber depths between the seven groups at the start of the treatment period (one-way ANOVA, \( P = 0.96 \); Fig. 1B) or in the mean axial length (one-way ANOVA, \( P = 0.83 \); Table 1).

Five days after the start of treatment, the seven groups showed significant differences in refraction (one-way ANOVA, \( P < 0.0001 \); Fig. 1C, Table 1). Further analysis revealed that the \(-9.5 \) D treated group was significantly different from all other groups (\( P < 0.01 \), Bonferroni’s multiple-comparison test).

Vitreous chamber depth was significantly different between the seven groups, consistent with the refractive findings 5 days after the start of the lens treatment (one-way ANOVA, \( P < 0.0001 \); Fig. 1D, Table 1). Further analysis revealed that the vitreous chamber depth of the \(-9.5 \) D continuous-wear group was significantly longer than the mean vitreous chamber depth of the \(-9.5 \) D/+4.0 D (1), the \(-9.5 \) D/+4.0 D (2), the plano, and the normal groups (\( P < 0.05 \); Bonferroni’s multiple-comparison test). There were no significant differences between the \(-9.5 \) D continuous-wear group and the \(-9.5 \) D/0 D (1) and \(-9.5 \) D/0 D (2) groups after 5 days of treatment.

After 12 days of treatment, there was a significant difference in ocular refraction between the seven groups (one-way ANOVA, \( P < 0.0001 \); Fig. 1E, Table 1). Analysis revealed that the \(-9.5 \) D continuous-wear group had significantly less hyperopia (relative myopia) than all other groups (\( P < 0.001 \)). In addition, the \(-9.5 \) D/+4.0 D (1) group had significantly more hyperopia than did the \(-9.5 \) D/0 D (1) and (2) groups (\( P < 0.001 \)) and the \(-9.5 \) D/+4.0 D (2) group had significantly more hyperopia than the \(-9.5 \) D/0 D (2) group had (\( P < 0.05 \)).

The structural correlate to the significant differences in ocular refraction was differences in vitreous chamber depth (Fig. 1F). There were no significant differences in corneal radius, anterior chamber depth, or lens thickness at any of the measurement times across any of the groups (\( P > 0.05 \); data not shown). The mean vitreous chamber depth of the continuous-wear \(-9.5 \) D group was significantly longer than the mean vitreous chamber depth of each of the other groups (one-way ANOVA, \( P < 0.05 \); Fig. 1F, Table 1). Statistical analysis of axial length differences at 12 days of treatment (data not shown) showed the continuous-wear \(-9.5 \) D group had a significantly longer mean axial length than \(-9.5 \) D/+4.0 D (1) and (2) groups (\( P < 0.01 \)) and the plano and normal groups.

**Figure 1.** Mean ocular refraction and vitreous chamber depth at baseline (A, B), 5 days (C, D), and 12 days (E, F) of treatment for the seven groups. Groups (1) had one 60-minute interruption from \(-9.5 \) D lens wear with the stated lens power and groups (2) had two 30 minute interruptions of \(-9.5 \) D lens wear with the stated lens power. \( n = 5 \) each group (*\( P < 0.05 \); **\( P < 0.01 \); ***\( P < 0.001 \)). Individual data points shown by symbols. Error bars, 1 SEM.
### Table 1. Ocular Refraction and Structural Dimensions of Both Eyes of the Three Shrews in the Experimental Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Time Points</th>
<th>Refraction (D)</th>
<th>Corneal Radius (mm)</th>
<th>Anterior Chamber Depth (mm)</th>
<th>Lens Thickness (mm)</th>
<th>Vitreous Chamber Depth (mm)</th>
<th>Axial Length (mm)</th>
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<td></td>
<td></td>
<td>RE</td>
<td>LE</td>
<td>RE</td>
<td>LE</td>
<td>RE</td>
<td>LE</td>
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<tr>
<td>−9.5 D</td>
<td>Day 0</td>
<td>11.6 ± 0.3</td>
<td>11.5 ± 0.3</td>
<td>3.37 ± 0.03</td>
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<td>Day 5</td>
<td>4.5 ± 0.9</td>
<td>4.5 ± 0.9</td>
<td>3.32 ± 0.03</td>
<td>3.34 ± 0.04</td>
<td>1.09 ± 0.02</td>
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<td>Day 12</td>
<td>0.8 ± 0.5</td>
<td>0.7 ± 0.5</td>
<td>3.40 ± 0.02</td>
<td>3.38 ± 0.03</td>
<td>1.08 ± 0.01</td>
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<td>Day 5</td>
<td>8.8 ± 0.7</td>
<td>9.1 ± 0.6</td>
<td>3.23 ± 0.04</td>
<td>3.35 ± 0.06</td>
<td>1.09 ± 0.02</td>
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<tr>
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<td>Day 12</td>
<td>7.4 ± 0.5</td>
<td>6.8 ± 0.8</td>
<td>3.30 ± 0.05</td>
<td>3.29 ± 0.03</td>
<td>1.07 ± 0.01</td>
<td>1.08 ± 0.02</td>
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<td>−9.5 D/0 D (1)</td>
<td>Day 0</td>
<td>11.3 ± 0.8</td>
<td>11.1 ± 0.8</td>
<td>3.35 ± 0.06</td>
<td>3.39 ± 0.07</td>
<td>1.03 ± 0.02</td>
<td>1.01 ± 0.02</td>
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<tr>
<td></td>
<td>Day 5</td>
<td>10.6 ± 0.8</td>
<td>11.1 ± 0.5</td>
<td>3.35 ± 0.06</td>
<td>3.39 ± 0.07</td>
<td>1.07 ± 0.01</td>
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<td>Day 12</td>
<td>11.0 ± 0.4</td>
<td>10.9 ± 0.5</td>
<td>3.35 ± 0.05</td>
<td>3.31 ± 0.05</td>
<td>1.09 ± 0.02</td>
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<tr>
<td></td>
<td>Day 5</td>
<td>8.6 ± 0.7</td>
<td>8.1 ± 0.4</td>
<td>3.52 ± 0.01</td>
<td>3.32 ± 0.01</td>
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<td></td>
<td>Day 12</td>
<td>6.8 ± 0.6</td>
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<td>1.10 ± 0.02</td>
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<tr>
<td>−9.5 D/4.0 D (1)</td>
<td>Day 0</td>
<td>10.6 ± 0.5</td>
<td>11.0 ± 0.6</td>
<td>3.27 ± 0.03</td>
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<td>Day 5</td>
<td>9.7 ± 0.5</td>
<td>9.8 ± 0.3</td>
<td>3.28 ± 0.02</td>
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<td>Day 12</td>
<td>9.5 ± 0.6</td>
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<td>3.32 ± 0.05</td>
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<td>Day 5</td>
<td>8.5 ± 0.7</td>
<td>9.0 ± 0.4</td>
<td>3.54 ± 0.04</td>
<td>3.29 ± 0.04</td>
<td>1.03 ± 0.02</td>
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<tr>
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<td>Day 12</td>
<td>8.6 ± 0.5</td>
<td>8.2 ± 0.8</td>
<td>3.37 ± 0.03</td>
<td>3.35 ± 0.04</td>
<td>1.07 ± 0.02</td>
<td>1.05 ± 0.02</td>
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<tr>
<td>Normal</td>
<td>Day 0</td>
<td>10.2 ± 0.3</td>
<td>9.9 ± 0.2</td>
<td>Measures not taken</td>
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<td>1.08 ± 0.05</td>
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<td>Day 7</td>
<td>8.8 ± 0.5</td>
<td>8.6 ± 0.5</td>
<td>3.20 ± 0.01</td>
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<td>Day 14</td>
<td>8.1 ± 0.4</td>
<td>7.8 ± 0.5</td>
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<td>3.28 ± 0.02</td>
<td>1.12 ± 0.02</td>
<td>1.11 ± 0.02</td>
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* n = 5 in all groups. Data are expressed as the mean ± SE. Shading of data indicate significantly different results from the −9.5 D full-time wear group for each parameter: □ P < 0.05; □□ P < 0.01; □□□ P < 0.001.
(P < 0.05) had. There were no significant differences between any other groups.

**Timeline of Treatment Effects: Changes at 5 and 12 Days**

Analysis of group mean refractive and biometric measurements at both the 5 and 12 day assessment points are shown in Figure 2 and demonstrate that treatment effects continued throughout the 12-day assessment period. In terms of changes in refraction, Figure 2A shows that the hyperopic refractive error was still decreasing from the 5 to 12 day time point in the −9.5 D/0 D (1) and −9.5 D/0 D (2) lens–treated groups (green and red circles), whereas the refractive error in the −9.5 D/+4.0 D (1) and −9.5 D/+4.0 D (2) lens–treated groups leveled off at 5 through 12 days of treatment.

**One versus Two Interventions**

Analysis of the mean refractive and biometric measurements of the one and two intervention groups at each measurement time (days 0, 5, and 12) revealed no significant differences between one 60-minute intervention and two 30-minute interventions for either lens power. The number in parenthesis in the figure key relates to one 60-minute or two 30-minute interventions of either lens treatment. The number in parenthesis in the figure key relates to one 60-minute or two 30-minute interventions of either lens power thus enabled the data to be combined for the two groups of 0 D interventions and the two groups of +4.0 D interventions in all further analyses.

**Plano and +4.0 D Intervention Groups**

The +4.0 D positive lens intervention for 60 minutes in every 14 hours of the light cycle (13 hours of −9.5 D negative lens wear) was found to prevent the development of lens-induced myopia in tree shrews more effectively than a 60-minute intervention with 0 D (plano) lenses after 12 days of treatment. Specifically, continuous treatment with −9.5 D lenses binocularly produced a relative myopic shift in refraction of 10.8 D, whereas treatment with 0 D (plano) lenses binocularly for 1 hour every day induced a relative myopic shift in refraction of 3.6 D, and +4.0 D lenses binocularly for 1 hour every day caused a relative myopic shift in refraction of just 0.7 D. The typical decrease in hyperopic refraction (emmetropization) over this period in the tree shrews is given by the normal group that underwent a mean myopic shift in refraction over the 12 days of 1.6 D. The change in vitreous chamber depth after 12 days of treatment is shown in Figure 4B and is the structural cause of the refractive differences between groups (Fig. 4A). Not only did the −9.5 D continuous-wear group have a significant relative myopic shift in refraction compared to all other groups, but there was also a significantly greater mean relative myopic shift in refraction in the −9.5 D/0 D (1 and 2) group than in the −9.5 D/+4.0 D (1 and 2) group (P < 0.01). In keeping with this finding, the −9.5 D/0 D (1 and 2) group had a significantly longer mean vitreous chamber depth than the −9.5 D/+4.0 D (1 and 2) group had (P < 0.05, unpaired t-test).

**DISCUSSION**

The principal finding of the present study is that intervention with positive lenses was significantly more effective in preventing the development of experimentally induced myopia than was plano lens intervention (equivalent to removing the myopia inducing lens) in this mammalian model. Just 60 minutes of +4 D lens wear completely prevented experimentally induced myopia (13 hours of −9.5 D wear for remainder of the light cycle) over a 12-day period, whereas, during the same period, 60 minutes of plano lens wear prevented only 70% of induced myopia. Over the same 12-day period normal eyes showed a reduction in hyperopia of 1.6 D compared with a reduction of just 0.7 D in the eyes that had positive-lens treatment for 1 hour every day. Changes in refraction over the 12-day period correlated closely with the structural change in vitreous chamber depth across all groups (r = 0.86). Thus, daily application of +4 D positive lenses inhibited the axial elongation of the eye that occurs in myopia. It is this excessive axial elongation that is the major cause of the consequential pathologic changes in patients with high degrees of myopia. The potential significance of this finding is that, with a similar paradigm, the results can be replicated in humans. It may be possible, by using a specific-power positive lens (i.e., amount of imposed myopic defocus) in children with developing myopia for a single period of less than 1 hour a day, to prevent the development of moderate to high myopia. Based on studies in mammalian models of refractive error, including nonhuman primates, it has been found that the range of positive lens powers over which the eye demonstrates a compensatory response (i.e., to emmetropize is significantly more limited than found in the chick).4,7,6,10–15,25 Thus, the specific power of positive lenses chosen in human trials is a critical criterion in ensuring that the
level of defocus imposed is within the compensatory emmetropization response range of humans.

In the present study, the dioptric amount of positive-lens defocus used (+4.0 D) was established by earlier work that determined the upper threshold amount of positive lens-defocus to which the tree shrew eye reliably responded by developing relative hyperopia compared with normal eyes.10 When powers of +6.0 D were applied binocularly to tree shrews, there was significantly increased variation in response, with some eyes developing relative myopia and marked differences in refraction between the two eyes of an animal.10,17 The period chosen was also carefully selected so that the total amount of exposure to the positive or plano binocular lenses was less than that necessary for plano lenses to completely stop experimentally induced myopia in tree shrews, which was found to be 2 hours.24 The finding that 60 minutes of positive lens wear per day was sufficient, not only in preventing the development of myopia, but also in inducing relative hyperopia compared to age-matched normal animals over the same period, indicates that a wearing period of less than 60 minutes would still have completely prevented the experimentally induced myopia in this mammalian model.

Norton et al.17 found that only 37% (11/30) of tree shrews wearing a positive lens for 45 minutes (in a controlled viewing environment) a day developed less than 1.5 D of myopia relative to the fellow control eye, whereas the present study found that 100% of tree shrews, wearing +4.0 D lenses for 60 minutes a day, showed complete inhibition of myopia.10,17 The difference in the limited effectiveness of low-powered positive lenses (+3, +4, +5 D) in Norton et al. in preventing the progression of myopia by a negative lens, compared with the consistency of results of binocularly worn +4 D lenses in completely preventing myopia in the present study is intriguing. The different results are most likely explained by the differences in experimental paradigms between the two studies. In the present study, animals were treated binocularly, had no restriction on their natural viewing while wearing positive lenses, and were younger when treatment was started (15 days after eye opening). Norton et al. treated the animals monocularity and compared the effects against the contralateral eye;

**Figure 3.** Ocular refraction (A, C) and vitreous chamber depth (B, D) data of individual animals from the 0 D intervention groups 1 (dashed blue lines) and 2 (solid blue lines) (A, B) and the +4.0 D intervention groups 1 (dashed gray lines) and 2 (solid gray lines) (C, D).

**Figure 4.** Mean differences in (A) ocular refraction and (B) vitreous chamber depth from baseline measures after 12 days of binocular lens treatment. Groups 1 and 2 had a total of 60 minutes of interruption of −9.5 D lens wear with either a 0 D or +4.0 D lens every day. n = 5 or n = 10 in each group as indicated (***P < 0.01; **P < 0.001). Individual data points shown by symbols. Error bars, 1 SEM.
viewing distance was restricted during positive lens treatment, and therefore nothing closer than 1 m was viewed; and animals began treatment at a later age (24 days after eye opening). Recently, it has been demonstrated that the starting age of treatment is critical in maximizing the response to optical intervention in tree shrew refractive development, with more effective compensation to positive lenses occurring when treatment is started around 15 days after eye opening, when the animals are still in the late infantile phase of ocular growth. The evidence seems clear that the critical factors in optimizing inhibition of myopia with positive lenses worn intermittently, at least in mammalian models, are the age at which treatment is initiated and the provision of unrestricted binocular viewing.

The present study found that two periods (two 30-minute sessions per day) of +4.0 D or plano lens wear was no different from one period (1 hour, one session a day) in protecting against negative lens–induced myopia (Figs. 1C, 1E; Table 1). Although this finding differs from those in some studies in the chick, in which greater inhibition occurred with multiple periods of intermittent wear of positive lenses rather than a single period of wear of the same overall duration, results in chicks have not consistently shown this effect. One experiment found that the reduced ocular elongation in response to positive lens wear was similar for 14 episodes of 2 minutes each and 4 episodes of 7 minutes each. Although it is known that the temporal characteristics of the emmetropization mechanism show broad similarities across a wide variety of species including chicks, tree shrews, and monkeys, responses to lens defocus are much faster in chick models than in mammalian models of refractive development.

Kee et al., in a study similar to the present one but conducted in monkeys, did not show that transient interruption of negative lens–induced myopia in a binocular paradigm with +4.5 D lenses for four 15-minute periods a day was more effective in preventing experimentally induced myopia than a similar paradigm using plano lenses. In fact, they found that unrestricted vision (four periods of binocular plano lens wear for 15 minutes a day) was more effective in counteracting the effects of negative lens wear (−3.0 D for the rest of the day) than was binocular positive lens wear (four periods of +4.5 D lens wear for 15 minutes a day) in monkeys. The authors stated that several of the monkeys in the −3.0 D/+4.5 D group exhibited myopic changes shortly after the onset of the lens wear, which effectively increased the degree of myopic defocus, potentially producing a blur signal outside the operating range of the emmetropization process in monkeys.

In the present study, no restriction was imposed on the tree shrews’ viewing environment, with the animals able to view objects over a range of distances from 5 m away (length of holding room) to 5 cm (as close as the food bowl). Despite this variation in focusing distances, and therefore presumably various levels of defocus on the retina, the final refractive state was very similar across animals within each group, at both 5 and 12 days of treatment. Although the measured refractive state by retinoscopy at day 0 was approximately +1.0 to +1.10 D, this measure does not take into account the artifact of retinoscopy found in small eyes, which in tree shrews of this age is approximately +5.0 D. This result means that, when animals were wearing −9.5 D lenses binocularly, the hyperopic defocus on the retina, when viewing distant objects, could be as high as 14.5 D if no accommodation was invoked. When the animals were wearing plano lenses, approximately 5.0 D of hyperopic defocus could be present at distance. When they had the +4.0 D lenses fitted, the likely outcome would be 1.0 D of hyperopic defocus at distance. Taking account of the depth of focus of the tree shrew eye, this level of defocus would be likely to provide a clear image on the retina and to act as a STOP signal for ocular growth, as has been proposed.

The fact that this signal was present for only 60 minutes each day indicates that the temporal integration of this STOP signal was sufficient to override the myopiagenic signal of the −9.5 D lenses worn for the remainder of each day (13 hours of the 14 hour light cycle). Although the +4 D lenses are unlikely to have imposed actual myopic defocus on the retina in unaccommodated eyes for distance viewing, what is not known from the results of the present experiment is whether the tree shrews accommodated normally when viewing near objects (e.g., their food, water, or internal cage environment). When the animals wore the −9.5 D lenses, the level of hyperopic defocus when viewing near objects would be more than 15 D, well beyond the accommodative amplitude of the tree shrew. When they wore the plano lenses for 1 hour per day, they would effectively have a level of hyperopic defocus similar to that of untreated animals (Fig. 2A) when viewing near objects and would accommodate normally. However, when wearing the +4 D lenses for 1 hour a day, the animals had their distance focal plane shifted myopically by 4 D. In this situation, it is the amount of accommodation that the tree shrew eye would use for viewing near objects decreased by 4 D, or do the animals experience up to 4 D of myopic defocus relative to normal animals?

As can be observed in Figure 2, the rate of treatment effect was greatest within the first 5 days and declined during the next 7 days, although differences between +4 D binocular lens treatment and plano lens treatment were still increasing during the later treatment stage. This trend was particularly obvious in the ocular refraction data (Fig. 2A) where both groups treated with +4 D lenses showed no reduction in measured hyperopia from 5 to 12 days of treatment, whereas both groups treated with plano lenses continued to show decreases in measured hyperopia over the whole 12-day treatment period. These findings are reflected in the changes in vitreous chamber depth (Fig. 2B) and axial length (Fig. 2C) over the same treatment periods.

Why does the imposition of +4 D positive, full-field lenses for 1 hour daily completely prevent the development of experimentally induced myopia in the tree shrew? In a recent study in chicks, the investigators used two-zone lenses to impose either myopic or hyperopic defocus on the peripheral or central retina, with the other zone having 0 power. Results showed that positive-lens (myopic) defocus was more robust in influencing refractive development than was negative-lens (hyperopic) defocus and that myopic defocus on the peripheral retina induced more hyperopia on-axis than did central myopic defocus. Another study in chicks, with a Fresnel lens designed to apply dual-focus lenses of concentric annuli of alternating positive and negative power across the retina, showed that the final on-axis central refractive error fell between the two competing optical powers, although always producing a more hyperopic end point than the numerical mean of the two lens powers, again demonstrating that myopic defocus is more robust than hyperopic defocus in influencing the refractive end point. A study by Liu and Wildsoet, along with a recent study in primates by Smith, demonstrated that myopic defocus on the peripheral retina induces hyperopic changes in the on-axis refractive end point. However, the specific contribution of central, midperipheral, and peripheral retinal defocus is complex to titrate because of eye movements. In a recent study of 6- to 12-year-old Chinese children with mild degrees of myopia, a novel spectacle lens design was used that had peripheral positive additions with central distance correction. After 12 months no significant reduction in myopia progression was found between children wearing the novel lens designs or those wearing a standard single-vision lens to correct their myopia. Thus, the finding in
the present study of complete prevention of induced myopia in tree shrews by imposing full-field +4 D lenses intermittently suggests that the effect of providing either a clear or slightly myopic defocused image to most of the retinal surface, rather than just correcting peripheral hyperopic defocus, is the more likely factor inhibiting the axial elongation of the eye and consequent myopia in the tree shrew model. Other recent studies on adolescent children offer further support that positive lens defocus over a wide retinal area, rather than just in the peripheral retina, is more effective in preventing myopia. Phillips demonstrated that a +2 D level of myopic defocus at near in 11-year-old children was effective in slowing the progression of myopia. Use of a dual-focus contact lens, containing the distance correction and +2 D greater than the distance correction in a concentric design, so that the eye experienced 2 D of myopic defocus as well as clear vision, was found to reduce myopia progression by 35% and axial elongation by 49% in a 10-month period. In addition, in a recent study of a concentric bifocal contact lens design used in children in Hong Kong, Lam et al. reported a slowing of myopia over a 2-year period by approximately 35%, owing to reduced axial elongation compared with controls. Finally, a study reported that wearing +3 D lenses binocularly in children with medium to high myopia for 30 minutes each day for a period of 2 years caused progression to cease in 30% of cases. These findings in adolescent children add support to the possibility that small amounts of myopic defocus, rather than just clear retinal images, are the most effective visual stimulus in preventing progression of myopia.

In summary, the present study demonstrated that daily transient +4 D positive-lens wear of only 1 hour a day is significantly more effective than 0 D lens wear at preventing experimentally induced myopia in a mammalian model of refractive development. The results have important implications with respect to a noninvasive optical treatment that could be applied to prevent myopia in children. However, before any large-scale clinical trial in adolescent humans is implemented, pilot studies should be conducted to determine the optimum level of positive lens power relative to distance refractive state, the optimal minimum period per day to apply this positive lens-defocus, the optimal stage in myopia development to apply the treatment, and the duration of treatment necessary to prevent progression of myopia.

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