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Development of an Optical Defocus-Induced Myopia Model for Guinea Pigs Using Rigid Gas Permeable Contact Lenses

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Objectives: Guinea pigs are a widely used mammalian model for studies of myopia and early ocular growth regulation more generally. The study reported here covers the development of rigid gas permeable (RGP) contact lenses (CLs) for guinea pigs, as an alternative to spectacle lenses for imposing optical defocus, recognized as an important modulator of eye elongation in young animals.

Methods: New Zealand pigmented guinea pigs (*Cavia porcellus*) were used in this study, with the RGP lens design based on developmental corneal shape profiles derived from anterior segment optical coherence tomography data collected across a range of ages, as typically encountered in such studies. The validity of this CL-based approach was examined in a follow-up study, in which the ocular effects of -10 , 0 , and $+5$ diopters [D] RGP lenses, applied as continuous monocular optical defocus treatments, were tracked over 2 weeks, with the fellow untreated eyes of experimental animals serving as contralateral controls. Pretreatment baseline spherical equivalent refractive errors (RE) and axial length (AL) of both eyes were measured, along with follow-up weekly measurements over the wearing period.

Results: There were no differences in any of the ocular parameters between the three groups at baseline, while after two weeks of lens wear, there were significant differences between the -10 D group compared with 0 D and $+5$ D groups in both RE ($P < 0.001$) and AL ($P < 0.05$). Importantly, myopia was observed in all of the guinea pigs fitted with -10 D lenses, and overall, eyes fitted with -10 D lenses showed increased ALs and relative myopia compared with their fellows, while those fitted with $+5$ D lenses showed reduced ALs and relative hyperopia; the plano lens group fell in between (treated–fellow eyes: -10 , 0 , and $+5$ D lenses: -8.25 , -1.0 , and $+0.5$ D, and $+0.16$, $+0.08$, and -0.02 mm, respectively). Also importantly, no significant CL-related adverse ocular effects were observed.

Conclusions: This study provides proof of principle that defocusing RGP CLs are a feasible alternative to spectacle lenses for studies of eye growth regulation in young guinea pigs and experimental myopia specifically, with

potential application in investigations into novel approaches for controlling myopia progression and underlying mechanisms.

Key Words: Lens-induced myopia—Guinea pig—Contact lens.

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INTRODUCTION

Emmetropization, the process by which neonatal refractive errors (RE) are eliminated, depends on the nature and quality of early visual experience. Any disruption to the emmetropization process may lead to abnormal eye growth, as exemplified by the accelerated growth and myopia triggered by form deprivation, which represents an extreme example of altered visual experience. Congenital cataracts and ptosis represent such examples in human infants, with both linked to excessive ocular axial elongation.^{1,2} The parallels in animal model studies involve either the application of diffusing goggles or lid suture, both of which lead to accelerated eye growth and corresponding myopic shifts in RE.^{3,4}

Given that developmental emmetropization serves to correct neonatal RE, arguably models involving the imposition of optical focusing errors on young eyes are more physiologically relevant. As first demonstrated in chicks, young eyes are able to adjust their eye growth to compensate for imposed optical defocus.^{3,5} Specifically, when young eyes are fitted with suitably powered negative lenses to impose hyperopic defocus, eye growth accelerates in compensation, until the eyes become emmetropic with the lenses in place. When the lenses are then removed, the eyes exhibit myopia, equivalent to the power of the fitted lenses. Imposing myopic defocus using positive lenses elicits the opposite growth response, that is, the rate of eye growth slows, with eyes exhibiting hyperopia when the lenses are subsequently removed.⁶ Such compensatory responses have been observed in all animals studied to-date, including guinea pigs, tree shrews, marmosets, and rhesus monkeys, with highly consistent outcomes.⁷ In relation to the juvenile form of human myopia, the possible role of hyperopic defocus as a trigger, arising from inaccurate accommodation during near work, that is, lag of accommodation, and/or a more prolate eye shape, and furthermore, the possibility of controlling myopia progression with positive lenses, have driven interest in understanding the mechanisms underlying defocus-driven eye growth modulation.

Guinea pigs are an important mammalian model for studying the development of refractive error and myopia. As indicated above, guinea pigs respond to both positive and negative lens-imposed defocus, with sign-dependent (opposite), compensatory changes

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in the rate of ocular axial elongation.⁶ Traditionally, to impose defocus, researchers have applied spectacle-mounted lenses mounted on Velcro ring supports and attached through segments of opposing loop Velcro, which are either glued to the hair surrounding the eye undergoing treatment⁶ or to an appropriately positioned aperture on a close-fitting mask enclosing the animal's head.⁸ Both approaches necessitate very frequent monitoring of animals to detect and correct for decentration or detachment of the lenses as the animals move around in their cages and scratch at the Velcro attachments. Prompt action to reattach the lenses is required to minimize the disruption to the defocus treatments, if meaningful data are to be obtained from such studies.

To improve on the above methodology, and at the same time, to ensure the comfort of experimental animals, we explored the feasibility of using rigid gas permeable (RGP) contact lenses (CLs) as an alternative to spectacle lenses for imposing optical defocus and so manipulating eye growth in young guinea pigs. The final contact lens (CL) design along with the procedure followed in finalizing it along with results from a "proof of principle" study, are described in the following sections.

MATERIAL AND METHODS

Animals

A New Zealand strain of pigmented guinea pigs (*Cavia porcellus*) was used in this study. Animals were bred on-site. After weaning at 7 days of age, pups were housed as single sex pairs in transparent plastic wire-top cages (41 cm × 51 cm), with room illumination on a 12-hr/12-hr light/dark cycle. In cages housing CL-wearing animals, the standard cage shavings were covered with a single layer of cardboard to minimize dust and to facilitate recovery of CLs dislodged from the eyes of wearers, either through blinking or scratching.

Animal care and treatments in this study conformed to the Association for Research in Vision and Ophthalmology (ARVO) statement for the Use of Animals in Ophthalmic and Vision Research. Experimental protocols were approved by the Animal Care and Use Committee of the University of California, Berkeley.

Corneal Shape Profiling

An essential first step in designing suitable RGP CLs for the guinea pigs was to determine their anterior corneal curvature, including changes over the anticipated lens wearing period. A key early design decision was the choice of lens diameter. The lens optics needed to be sufficiently large to cover the pupil under all lighting conditions. In an earlier independent study, the pupil diameter of the guinea pig was reported to increase from an average value 4 mm, measured in 3-day-old guinea pigs, to 6.5 mm in adult animals.⁹ To ensure continuous coverage of these relatively large pupils, the lenses needed to cover approximately 90% of their corneas.

When our study was initiated, there was minimal published data covering guinea pig corneal parameters and early developmental changes.⁹ To characterize the overall (average) anterior corneal curvature of young guinea pig eyes, a Visante Anterior Segment Optical Coherence Tomography (OCT) (Zeiss Meditec, Dublin, CA) was used to capture high-resolution images of the anterior ocular segment (Fig. 1), which were subsequently analyzed to derive corneal curvature profiles.¹⁰ The relatively steep corneas

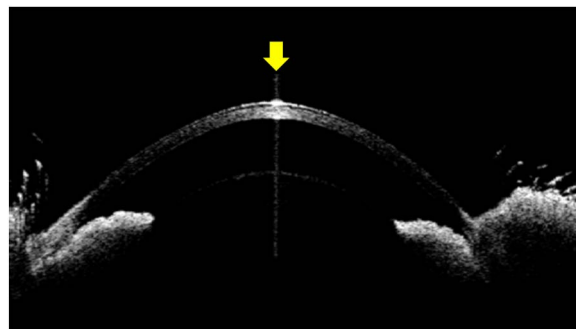


FIG. 1. A typical horizontal scan acquired by anterior segment OCT (Visante) and used for anterior corneal curvature profiling. The location of the bright vertical band (yellow arrow), at the apex of the cornea, indicates good alignment. OCT, optical coherence tomography.

of the guinea pig ruled out the use of available portable topographers without modification. Guinea pigs were handheld but not anesthetized for image capture. To compensate for the superiorly tilted optical axis of the guinea pig eye, animals were held at a slight angle to ensure that images were captured along an axis perpendicular to their pupil plane. Developmental profiles were derived from images collected from three young guinea pigs over the course of 19 days, at each of two time points per week, starting at 3 weeks of age. Images collected from the untreated contralateral (control) eyes of an additional 19 guinea pigs wearing monocular CLs in a later unrelated experiment were used to expand the data set and confirm earlier findings.

Anterior corneal curvature profiles were derived from OCT images using custom MATLAB software (MathWorks, Natick, MA; written by Ethan Bessinger). In brief, after first locating the corneal margins (limbus; Fig. 2a), which are readily identified by the transition from the bright, white sclera to the grainier cornea, the apex of the cornea was located and used as a reference to radially segment the corneal cross-sectional profiles in 15 deg increments (Fig. 2b). This process allowed selection of corresponding corneal points for comparison across the guinea pigs. For analysis, three points, including the central apical point and points 75 deg to its left and right (covering approximately 90% of the corneal area), were selected to correspond to the approximate area of corneal touch for an ideal fitting RGP CL, with minimal apical clearance. The average anterior corneal radius of curvature was estimated as the radius of curvature of the circle drawn through these three points (Fig. 2c). Reported corneal curvature data represent values derived from at least three images captured from the same eye during the same measurement session. Note that this method can also be applied to derive the average radius of curvature of the posterior corneal surface. Although not required for the purpose of this study, a similar algorithm to that applied to calculate corneal power for the human eye (corneal power in diopters = $337.5/\text{radius of curvature in mm}$) can be used to estimate the corneal power of the guinea pig eye from the anterior corneal radius of curvature. In addition to extracting anterior corneal curvature data from collected images, corneal diameter and sagittal depth data were also extracted using built-in segmentation software. In the example shown in Figure 3, values of 6.33 mm and 1.53 mm were obtained for the latter two parameters.

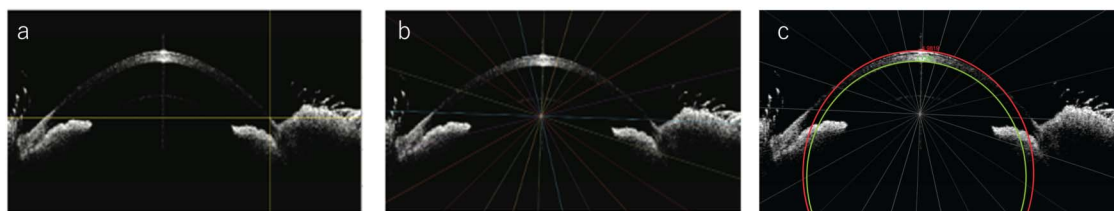


FIG. 2. Graphical representation of the process for deriving corneal radii of curvature from a captured and exported OCT image: left image shows the identification and marking of the right limbus (at the cross-section of the two yellow lines). Once the left limbus is also identified and marked, the software generates radial lines in 15-degree increments (middle image), allowing localization of the corneal apex. Right image includes superimposed red circle, representing the average anterior radius of curvature (based on points 75 deg nasal and temporal from the corneal apex; green circle representing the similarly generated average posterior radius of curvature. OCT, optical coherence tomography.

Contact Lens Design, Fitting, and Evaluation

Fluorosilicone acrylate (Optimum Comfort, Contamac, Ltd, Saffron Walden, UK, contamac.com), a commonly used human RGP CL material, with high oxygen permeability (65%) and good wetting angle, was selected as the lens material. The goal of the final lens design was to have minimal apical clearance, with an aspheric edge lift incorporating three peripheral curves, with finished edges. The derived corneal curvature data were used as the starting point in designing trial CLs for testing, with various overall diameters also tested. The lenses were ordered from Valley Contax, a custom contact lens manufacturer in Eugene, OR.

To insert the lenses, guinea pigs were placed on a laboratory bench, their lower lid gently pulled down, the upper lid lifted to widen the palpebral aperture, and then the lens placed directly on the cornea and the lids released. Guinea pigs were observed for at least 5 minutes after their first exposure to a CL to rule out discomfort, as evidenced by behavioral traits, such as scratching and excessive blinking. Lens removal was facilitated by prior application of nonpreserved artificial tears, as is common practice for the removal of RGP CLs from the eyes of human subjects.

For each animal subject, the fit of the CL was first evaluated under white light and then under cobalt blue light after topical application of sodium fluorescein (Fig. 4). The fit was also evaluated by anterior segment OCT imaging. The same criteria as applied for a minimal apical clearance fit in human eyes were used to judge the appropriateness of the fitting pattern for the guinea pig

eyes. Specifically, a fit was determined to be appropriate when there was no visible apical touch, fluorescein easily entered the postlens tear film, and a minimal amount of fluorescein was visible under the edge of the lens. Appropriate central clearance was also verified using OCT imaging (Fig. 5).

Trial lenses were designed to have minimal apical clearance, with an aspheric edge lift incorporating three peripheral curves, with finished edges. Trial lens designs spanning various base optic radii (see results) and overall diameters were tested. For the 6.0-mm diameter trial lens, which proved to be optimal for young guinea pigs, the optic zone diameter was 4.0 mm, and the peripheral curves were 3.6, 6.0, and 8.0 mm, with corresponding widths of 0.6, 0.2, and 0.2 mm, respectively. The optimal base curve for the 6.0 mm diameter lens was 3.38 mm (99.85 D) (see results for more details). While a smaller, 5.5 mm diameter lens offered an interpalpebral fit, it proved to be too easily blinked out when the anterior lens surface became excessively dry. The relatively low blink rate of guinea pigs (see results) was a disadvantage in this respect.

Over the lens wearing period, the behavior of the guinea pigs was carefully observed and recorded. The guinea pigs were found to tolerate the CLs very well, based on both behavioral observations and follow-up ocular assessment. Behaviorally, no excessive blinking or scratching was observed, either immediately following lens insertion or over the course of lens wear, and their corneas did not show any evidence of epithelial disruption, as detectable by sodium fluorescein staining after lens removal. In fact, the fellow, nonlens wearing eyes of these animals often showed evidence of superficial corneal epithelial defects, from which the corneas of the lens-wearing eyes appeared protected. Overall, the final lens design also proved to be easy to insert and remove.

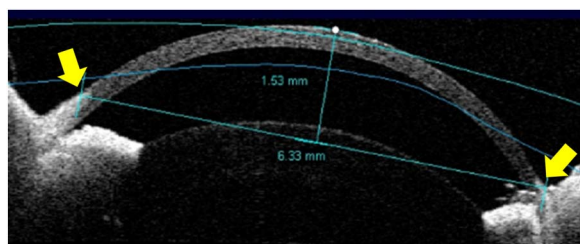


FIG. 3. Representative anterior segment image captured by the Zeiss Visante OCT. The limbus or corneal boundary is readily identified as the transition from the bright white sclera to the grainier peripheral cornea (yellow arrows). The instrument's built-in caliper software was used to measure both the corneal diameters, defined as the limbus-to-limbus distance, and the sagittal depth, defined as the distance from the corneal apex to the line connecting the opposite limbal points. OCT, optical coherence tomography.

Optical Power-Dependent Changes in Eye Growth and Refractive Error

After confirming the biocompatibility of our custom designed RGP CLs, test lenses based on the same design as described above, and of -10 , 0 , or $+5$ D power, were ordered and tested for their ability to induce RE. The optical power of requested lenses was verified on receipt in all cases before their use. At 2 weeks of age, three groups of guinea pigs had their right eyes fitted with single-vision RGP CLs (-10 , 0 , or $+5$ D; $n=4$ per group), with their fellow left eyes serving as untreated controls. The animals were monitored hourly during the first 12-hr light cycle to ensure that the

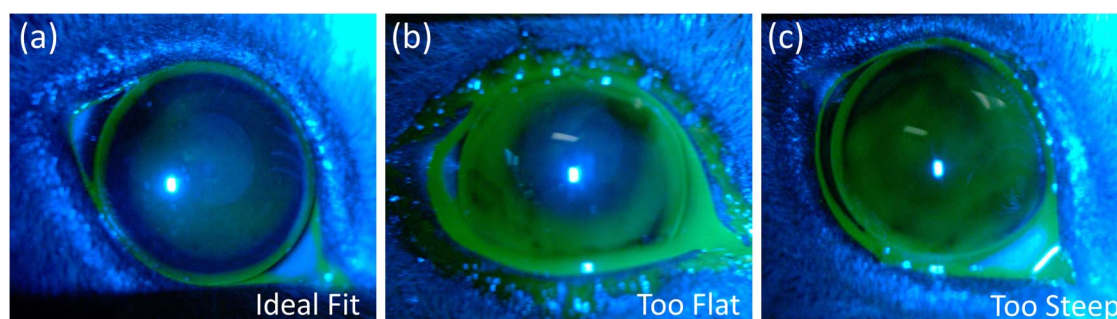


FIG. 4. In vivo evaluation of trial RGP CLs using topical sodium fluorescein. Examples of (a) an ideal fitting lens, with minimal apical clearance and an appropriately small edge lift; (b) lens that is too flat, as evidenced by the absence of fluorescein under the central region of the lens and excessive fluorescein pooling under its periphery, and (c) lens that is too steep, with excessive fluorescein pooling under the center of the lens and minimal edge lift. CLs, contact lenses; RGP, rigid gas permeable.

lenses remained in place and to monitor for any early signs of adverse effects. They were subsequently followed over a treatment period of 2 weeks, during which the lenses were replaced each morning with a clean lens, with the recently worn lens digitally rubbed with and then soaked in Boston Simplus (Boston, Bausch and Lomb, Rochester, NY). Lenses underwent additional treatment with a protein remover (Brand) on an as needed basis, typically about once per week. The lens parameters, including the back optic radius, which were remeasured at the end of the 2-week monitoring period, showed no change over this period.

Before the commencement of lens wear, ocular baseline data were collected using a battery of ocular procedures. They included optical biometry, using a Lenstar (Haag-Streit, Köniz, Switzerland), high-resolution anterior segment imaging, using a Visante OCT instrument (Zeiss), and cycloplegic retinoscopy. Thus axial length (AL), corneal curvature, and refractive error data were collected, with the same measurements repeated at timed intervals over the experimental period (days 0 [baseline], 7, and 14 days). For all measurements, animals remained alert and were simply swaddled with an absorbent pad to keep them comfortable, still, and in proper alignment with the measuring device. Measurements were conducted at the same time of day over the study period to

avoid any possible confounding effect of circadian rhythms in eye growth.¹¹

Refractive errors were measured using streak retinoscopy on awake animals, 30 min after the application of two drops of 1% cyclopentolate hydrochloride (Bausch & Lomb, Rochester, NY), spaced 5 min apart. Refractive errors were recorded along the two principal meridians and are reported as spherical equivalent refractive errors (SERs), that is, the average of the results for the two principal meridians.

The choice for ocular biometry of the Lenstar, a commercially available low coherence reflectometry device, over high-frequency A-scan ultrasonography, was driven in part by the need to avoid the use of ultrasound gel on the corneas of these CL-wearing animals, while also avoiding the need for general anesthesia, as required for the latter procedure. Readings from the Lenstar instrument represent an average of at least five high-quality recordings per the manufacturer's recommendations.

Statistical Analyses and Data Representation

All data were recorded using Excel 2013 (Redmond, WA). Statistical analyses made use of Stata version 14 (College Station, TX), while Prism 7 (La Jolla, CA) was used for graphical analyses. Data collected from animals subjected to extended (2 weeks) CL wear are reported as mean interocular differences (treated eye—control (fellow) eye) and as changes over time, normalized to the baseline values, along with standard errors of the mean in all cases. Repeated measures ANOVAs were used for initial analyses of temporal patterns. As differences between treated and fellow eyes represent continuous variables and were normally distributed, they were compared using paired t-tests. Differences between each time interval pair were also compared using paired t-tests, with Bonferroni correction applied. Differences with a *P*-value less than 0.05 were considered statistically significant.

RESULTS

Natural (Development) History of Change in Corneal Curvature and Diameter

The data collected during the CL design phase also allowed us to track corneal development. Measurements of anterior corneal curvature from the right eyes of three guinea pigs revealed slight, but statistically insignificant, corneal flattening over the 19-day

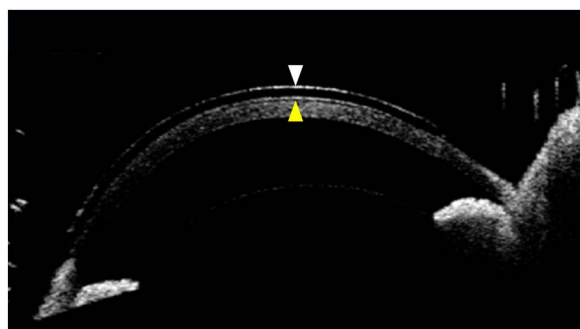


FIG. 5. Anterior segment OCT image captured from a guinea pig wearing a RGP CL; the front and back surface of the CL are visible as two thin, bright bands (white and yellow arrowheads), with a dark space between them; an additional, very thin dark space is visible between the posterior surface of the CL and the anterior surface of the cornea, confirming the presence of a thin, underlying layer of tears and thus an appropriate lens fit. CLs, contact lenses; RGP, rigid gas permeable; OCT, optical coherence tomography.

monitoring period. This trend was reflected in the mean corneal power, which decreased from 98.6 ± 1.2 D to 97.3 ± 4.3 D in the horizontal meridian, and from 102.7 ± 0.52 D to 96.8 ± 1.2 D in the vertical meridian (Fig. 6a). The median corneal power, derived from data from all three animals and measurement time points, was 98.4 D (range: 97.4–104.88 D). There was no significant change in the horizontal corneal power but a significant reduction in vertical corneal power, reflecting progressive corneal flattening over the 19-day monitoring period (repeated measures ANOVA, $P=0.10$ and 0.03 , respectively). These data were used to design our trial CL fitting set, which included a total of 12 lenses, with base curves surrounding the above median value in 2 D steps. Corneal diameters, which were also tracked in these three guinea pigs, increased from a mean of 5.88 ± 0.02 to 6.43 ± 0.12 mm over the 19-day monitoring period, although this change was also not statistically significant ($P=0.16$). These data are shown in Figure 6b.

Contact Lens-Induced Myopic Changes

The monocular application of -10 D CLs, starting at 2 weeks of age in four animals, resulted in a significant myopic shift in SER in the CL-wearing eyes, from a baseline mean value of $+5.63 \pm 1.90$ D to -4.88 ± 2.50 D after 2 weeks of CL wear ($P=0.0045$, Table 1 and Fig. 7a). Although changes in refractive error were also noted in the CL-wearing eyes of the 0 D CL group ($n=4$), they were small and not statistically significant ($P=0.34$). The $+5$ D CL group ($n=4$) showed no significant changes in either the lens-wearing or fellow eyes over the 2-week CL wearing period ($P=0.59$). In terms of AL, the -10 D CL group exhibited a significant increase in AL in their CL-wearing eyes, from a mean of 6.96 ± 0.03 mm at baseline to 7.63 ± 0.08 mm after 2 weeks ($P=0.002$, Table 1 and Fig. 7b). On the other hand, neither the 0 D nor $+5$ D power CLs groups showed significant lens-induced changes over the 2-week treatment period. In summary, while wearing -10 D CL induced significant myopic shifts and accelerated axial elongation, the effects on RE and axial elongation of 0 D and $+5$ D lenses, expressed in this way, were subtle and not statistically significant.

Table 2 and Figure 8 present the changes from baseline in interocular differences in REs and ALs after 2 weeks of lens wear for the three groups of animals categorized by the power of the CLs worn. The -10 D CL group exhibited a substantial myopic shift in RE, averaging -8.25 ± 1.59 D at the end of the treatment period, contrasting with the much smaller change in the plano (0 D) CL group, albeit in the same direction, averaging -1.00 ± 1.77 D, and the very small positive shift recorded by the $+5$ D CL group, that is, $+0.50 \pm 1.66$ D. In relation to AL and consistent with the RE changes, the -10 D CL group exhibited the largest increase, averaging 0.16 ± 0.05 mm, compared with the plano CL group, which recorded a very small increase, of 0.08 ± 0.03 mm, and the opposite, albeit very small change in $+5$ D CL group, of -0.02 ± 0.04 mm. These intergroup differences were statistically significant for both RE ($P<0.0001$) and AL ($P<0.0004$; Table 2).

DISCUSSION

Described herein is a novel method for imposing optical defocus on the eyes of guinea pigs, a commonly used animal model for studying myopia. The following discussion puts our findings into context and covers the strength and weaknesses of this approach. In relation to the measurement protocols applied in this study, we specifically discuss the relative merits of our choice of the Lenstar for measuring AL over A-scan ultrasonography, as used in older, classical studies involving the chick model,¹² and to a lesser extent, the guinea pig,¹³ the former being a relatively new approach for collecting such data in guinea pig-based myopia research.

Use of Contact Lenses as Alternative to Spectacle Lenses in Myopia Research

Although widely used in humans to correct myopia, CLs have been rarely used for myopia research involving animal models. The norm for studies involving imposed optical defocus has been spectacle lenses, with variable methods used to affix the lenses, depending on the animal model used and the specific study in question. As discussed in the introduction, both Velcro

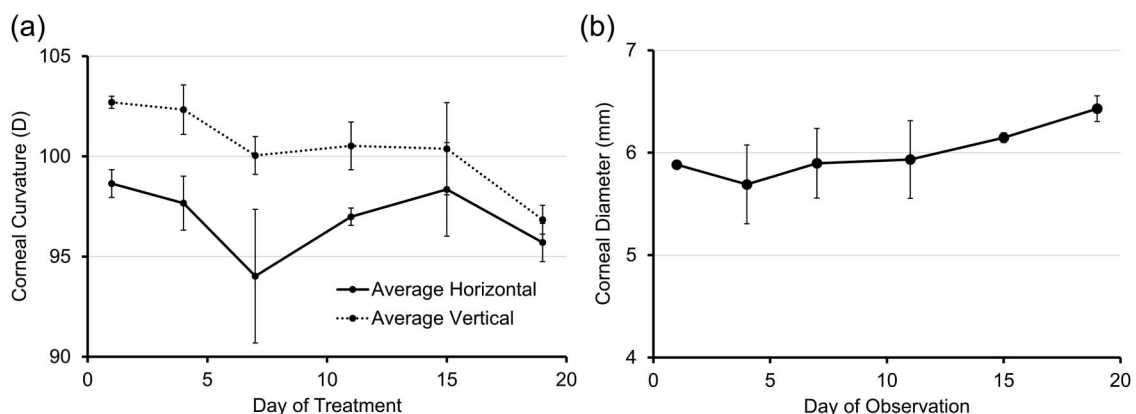


FIG. 6. Mean corneal power (a) and corneal diameter (b) for the right eyes of three guinea pigs plotted against time over a 19-day monitoring period, starting at 3 weeks of age. Corneal powers representing both horizontal and vertical meridians are shown, with each colored line representing the average value for one guinea pig, derived from at least three images, captured at each time point. Error bars represent the standard error of the group mean. There was significant flattening in the vertical meridian (i.e., a decrease in power), and a subtle but not significant increase in corneal diameter over the monitoring period.

TABLE 1. RE and AL (Means, SEs) of Guinea Pigs Fitted With Monocular −10, 0, and +5 D RGPs From 2 Weeks of Age

Parameters	−10 D CL	Fellow Eye	P	0 D CL	Fellow Eye	P	+5 D CL	Fellow Eye	P
Refraction (D)									
Baseline	5.63±1.90	5.75±2.07	0.32	4.63±0.95	5.44±0.66	0.08	3.59±0.44	4.19±0.28	0.06
1 week	0.13±1.53	3.81±0.31	0.0003*	2.44±0.83	4.56±0.94	0.04	3.06±0.99	4.08±0.27	0.24
2 weeks	−4.88±2.50	3.50±1.02	0.0045*	1.91±1.18	3.72±0.58	0.09	3.16±0.99	4.10±0.26	0.79
Difference after 2 weeks from baseline	−10.5±1.97	−2.25±1.74	0.0019*	−2.72±2.11	−1.72±0.44	0.34	−0.44±1.36	−0.94±1.23	0.59
AL (mm)									
Baseline	6.96±0.03	6.94±0.10	0.25	6.96±0.08	6.98±0.08	0.31	6.99±0.02	6.98±0.02	0.28
1 week	7.38±0.07	7.23±0.09	0.002*	7.28±0.13	7.20±0.08	0.11	7.30±0.03	7.24±0.03	0.08
2 weeks	7.63±0.08	7.44±0.10	0.002*	7.47±0.14	7.40±0.12	0.02	7.40±0.04	7.41±0.03	0.64
Difference after 2 weeks from baseline	0.67±0.05	0.51±0.03	0.0071*	0.50±0.07	0.43±0.04	0.02	0.41±0.02	0.44±0.02	0.3

P values show results of experimental and fellow eyes compared statistically; *significant differences.
AL, axial length; CLs, contact lenses; RE, refractive errors; RGP, rigid gas permeable; SE, standard error.

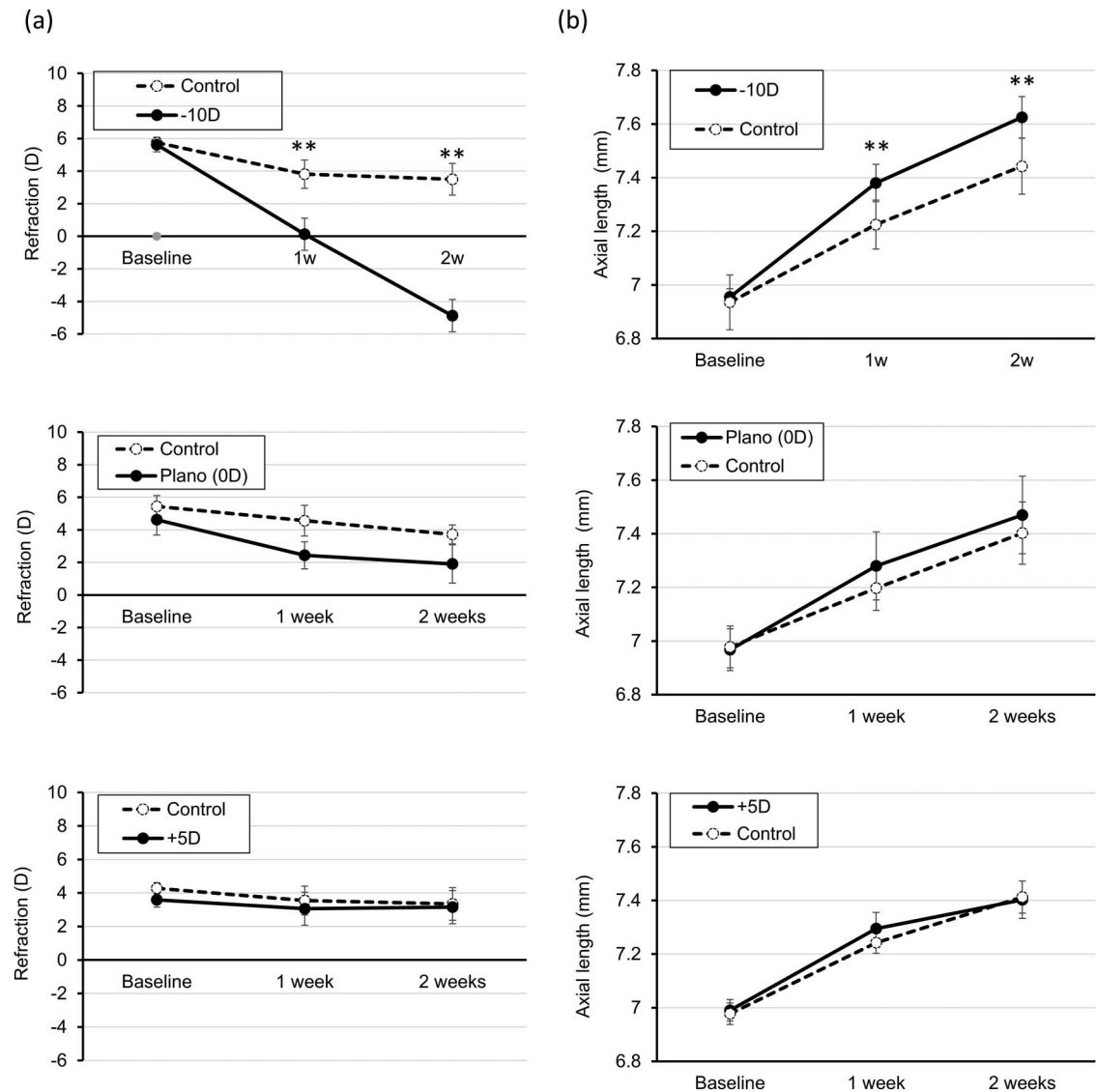


FIG. 7. RE (expressed as SER) (a) and axial lengths (b) of monocular RGP CL-wearing guinea pigs plotted against time over the 2-week monitoring period. Mean data (and standard errors) for eyes wearing −10, 0, and +5 D CLs (solid lines) and their untreated, fellow control eyes (dotted lines) shown. ***P*<0.01. CLs, contact lenses; RE, refractive errors; RGP, rigid gas permeable; SER, spherical equivalent refractive error.

TABLE 2. Changes in Interocular Differences in RE and AL Between 2 Weeks and Baseline in Each of the Three CL-Wearing Group

Ocular Parameter	−10 D CL	0 CL	+5 CL	<i>P</i>
RE (D)	−8.25±1.59	−1.00±1.77	0.50±0.66	<0.0001 ^a
AL (mm)	0.16±0.05	0.08±0.03	−0.02±0.04	0.0004 ^a

^aStatistically significant interocular differences between groups, normalized to baseline values, based on ANOVA

AL, axial length; CL, contact lens; RE, refractive errors.

supports affixed to periorbital hair and face masks have been used in past guinea pig studies.^{6,13} However, unintentional disruption to such defocus treatments, for example, through detachment of the Velcro supports, can have significant implications for intended treatment effects, with even very brief interruptions to lens-imposed hyperopic defocus or diffuser treatments potentially disrupting ocular growth responses. Specifically, in form-deprived monkeys¹⁴ and negative lens-treated tree shrews,¹⁵ just 1 hour of normal vision is effective in preventing experimentally induced myopia, and in the guinea pig, just 36 min of normal vision is sufficient to prevent the expected responses to myopia-inducing treatments.¹⁶

The use of RGP CLs as an alternative to Velcro-mounted spectacle lenses in guinea pigs met our expectations as a more reliable treatment. They were very rarely accidentally dislodged from the eye, with the practical advantage of allowing for less frequent monitoring of the animals, which was especially advantageous for studies involving extended treatment durations. Although soft CLs have been used successfully in marmosets, they were not considered a viable alternative to RGP lenses for the guinea pig due to their very low blink rate (evaluated at <2 blinks per min). Thus, they were not trialed. The RGP lenses also proved to be well tolerated by our animal subjects, as judged by the absence of any abnormal behavioral responses, such as excessive blinking, scratching, or other signs of stress, such as weight loss or fear of the experimenter. In addition, except for slight corneal swelling (discussed further below), no abnormal ocular signs, such as corneal irritation or infection or conjunctival hyperemia, were observed. Indeed, the RGP CLs appeared to protect the corneal epithelium from mild trauma and dehydration, as the animals moved around in their cages, as reflected in reduced fluorescein staining in CL wearing eyes compared with their fellows, and as alluded to earlier.

Developmental Changes and Contact Lens Defocus-Induced Experimental Myopia

When fitted with −10D lenses, the guinea pigs developed significant myopia in their CL-wearing eyes over the 14-day treatment period, with the mean interocular difference in refractive error reaching approximately −8.25 D. Considered by themselves, the −10 D CL-wearing eyes alone showed a myopic shift in refractive error of −10.5 D relative to their baseline value, while their untreated eyes fellow controls) changed by only −2.25 D over the same 14-day period, reflecting normal developmental emmetropization.

Our findings in relation to normal emmetropization are also consistent with findings of others. For example, Zhou et al.¹⁷ reported moderate hyperopia in 3-week-old guinea pigs (+3.27 D), with a decline in hyperopia thereafter, albeit at a slower rate than observed in our study. In a second study involving much younger animals, Howlett and McFadden reported a rapid decline in neonatal hyperopia, from an average of +4.40 D at birth to +0.70 D at 30 days of age.⁹ The mean refractive error of +3.77 D for the untreated fellow eyes of our animals at 28 days of age (experimental day 14) lies between the findings of these two studies.

We used the same CL power (−10 D) in all animals to induce myopia, as is typical of studies involving imposed optical defocus, whether involving CLs or spectacle lenses. Because the RE of young animals can be expected to vary naturally, especially during the more rapid, early phase of emmetropization, the amount of hyperopic defocus to which individual animals are exposed in the presence of a defocusing lens can also be expected to vary. For eyes wearing RGP CLs, the net hyperopic defocus imposed is expected to show further interanimal variation, as a byproduct of subtle variations in the tear lens created between the back surface of the CL and the anterior corneal surface. Although we did not consistently record RE with the CLs in place, we did confirm with retinoscopy that all guinea pigs experienced hyperopic defocus with the −10 D CLs in place, as evidenced by the presence of “against motion.” Nonetheless, one might expect more variability in the initially imposed optical defocus and thus the responses of animals wearing RGP CLs over those wearing other optical defocusing devices, for example, spectacle lenses, assuming lens wear was not otherwise disrupted over the treatment period.

The negative power CL-wearing eyes elongated at a faster rate than their fellows, as reflected in their larger ALs, with most of the axial elongation occurring during the first week of treatment. Compared

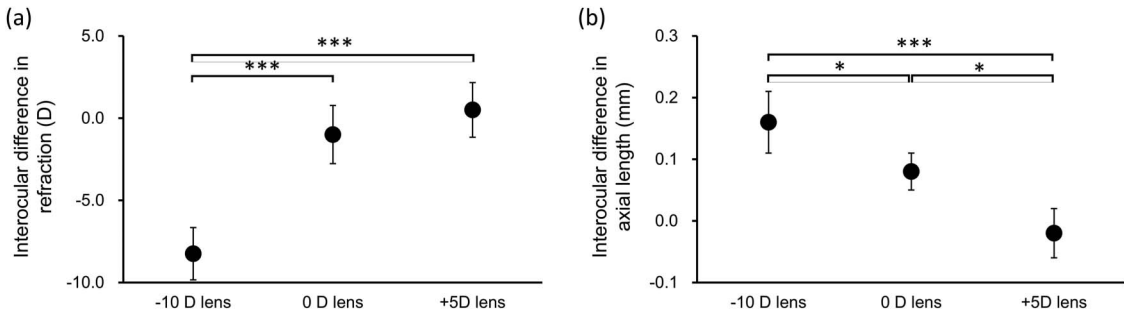


FIG. 8. Changes in interocular differences from baseline, after 2 weeks of monocular CL wear, in RE (a) and AL (b), plotted as means and standard errors, for −10, 0, and +5 D CL wearing groups. **P*<0.05, ****P*<0.001. AL, axial length; CLs, contact lenses; RE; refractive errors.

with the changes reported in a previous study using -4 D spectacle lenses,⁶ the magnitude of the induced interocular difference in AL is nearly double, reflecting the higher (-10 D) lens power used for myopia induction in the current study and consistent with a defocus (dose)-dependent response. Nonetheless, it is possible that the greater reliability of the CL-based optical defocus treatment, that is, in providing continuous defocus, as discussed above, may also be a contributing factor. Compared with their fellows, eyes fitted with plano lenses exhibited slightly longer on average ALs, while those fitted with $+5$ D lenses recorded slightly shorter ALs on average. The latter results are consistent with compensation to imposed myopic defocus, as predicted for the $+5$ D lenses, after accounting for the fact that the lenses would have also served to correct the existing hyperopia of these young eyes. The use of higher power positive lenses combined with longer treatment periods, as planned for a follow-up study, are expected to provide more convincing evidence of compensation to imposed myopic defocus.

In this study, a significant difference in corneal curvature between lens-wearing eyes and their fellows was observed on day 21, but not at any other time point. Over the treatment period, the corneas of untreated eyes showed a slight relative steepening, while the corneas of treated eyes continued to flatten at a steady rate. Although these differences may represent random variation, given the small number of animals involved, such patterns of change have also been reported by others, in tree shrews,¹⁸ primates,¹⁹ and guinea pigs.¹⁶ For example, Zhou et al.¹⁶ reported a similar pattern in young guinea pigs to that described here, albeit at an earlier age. Specifically, they reported the corneal curvature to decline significantly, that is, flatten, in the first week of life followed by a “rebound” steepening over the following 1 week, before once again slowly flattening. In our study, such steepening in the fellow, untreated eyes occurred later, between weeks 2 and 3, corresponding to 3.5 and 4.5 weeks of age. Notably, we did not see such steepening in the CL-wearing eyes of our animals, perhaps reflecting the restraining influence of the rigid CLs. Indeed, the corneas of the lens-wearing eyes of our guinea pigs tended to flatten relative to the corneas of their untreated fellows. In the absence of the CLs, such changes are expected to partly neutralize the myopic shift caused by the CL-induced increase in AL. In the case of eyes wearing $+5$ D lenses, such corneal curvature changes are expected to have the opposite effect and, in this context, do not offer an explanation for the only small refractive error changes observed with the latter.

The discussion of observed anterior corneal curvature changes in our guinea pig subjects would not be complete without reference to the study of Howlett and McFadden,⁹ who observed corneal flattening in their guinea pigs from 3.1 mm at 2 days of age to 4.4 mm at 300 days of age, with an average rate of flattening of $4.3 \mu\text{m}/\text{day}$. The rate of corneal flattening observed in the fellow untreated eyes of our guinea pigs is substantially higher over a much smaller time window. This difference likely reflects, at least in part, the different measurement techniques applied in our two studies, that is, anterior segment OCT compared with video keratometry in the latter study. The image processing algorithm applied in the current study yielded an anterior corneal radius of curvature approximating the central 70% of the cornea, whereas the derived radius of curvature in the study of Howlett and McFadden is assumed to represent the central 40% of the cornea.⁹ Assuming that the guinea pig cornea is aspheric, with the central cornea being steeper than the peripheral cornea, as in humans and as hinted at in OCT images, this would account for our flatter corneal curvature data.

Strengths and Limitations

The adoption of RGP CLs to impose optical defocus in young guinea pigs has a number of strengths. In contrast to the Velcro-mounted lenses, which, in our hands, detached three times per week on average across animals, dislodgement of the CLs was rare, and at most, once per week. Apart from the reduced disruption to the treatment due to lens loss over the course of longitudinal studies, this CL-based approach also carries the additional advantage of allowing the future testing of multifocal CL designs in the guinea pig. For studies involving regular topical pharmacological treatments, the easier access to eyes undergoing myopia-inducing defocus manipulations with CLs over spectacle lenses provided to be yet another advantage, as confirmed in our recent atropine study.²⁰ Data from such CL trials are predicted to be more readily translated to human clinical trials. The adopted ocular measurement protocols also have many merits, including their suitability for frequent tracking of changes in ocular parameters over time, as not possible with protocols requiring general or topical anesthesia. Of note, none of the procedures, used either to evaluate the CL fits or to subsequently track induced ocular changes, required anesthesia of either type. In the case of general anesthesia, apart from animal welfare considerations, that is, its potential adverse effects on general development, if used too frequently in young animals, it is also known to cause alterations in blood flow and intraocular pressure, both of which may influence recorded biometric data.²¹

The primary aim of this study was to demonstrate the feasibility of developing a CL defocus model in guinea pigs. Although its small sample size served this aim, it was not sufficiently large to meet the requirements of typical, myopia-related optical defocus studies. Nonetheless, we offer as further validation of this approach results from our follow-up studies making use of this CL model and involving large animal numbers.^{20,22} The choice of a -10 D lens power for myopia induction over a lower power, for example, -5 D, reflected the needs of planned studies, which were to be significantly longer than the more common, 2-week treatment periods, as used in many already published spectacle lens studies in guinea pigs.^{6,20,23} Importantly, the rate of axial elongation is expected to normalize once full compensation to the imposed defocus is achieved, occurring sooner with the -5 D lens compared with the -10 D lens, and potentially confounding the results of longer-term intervention studies making use of the former. The method of corneal shape profiling is a potential limitation of this study, although the acquired data met our needs of providing sufficiently accurate data from which to design a RGP guinea pig CL trial set. Nonetheless, it is important to note that the anterior segment OCT used was designed for human subjects, and in this application, the positioning of a person's head against a forehead rest allows for standardization of the working distance, which is not easily controlled in imaging the eyes of hand-held animals, as was the case for our guinea pigs. As a substitute, we made use of a built-in image quality indicator for good alignment (the presence of a bright streak at the corneal apex), which was also confirmed in most collected images. In addition, the same experienced examiners were involved in data collection, and multiple images captured at each time point, to minimize measurement error. Apart from these practical issues, our choice of instrument did not allow the ready extraction of reliable corneal shape data, which are critical to studies of ocular optical aberrations and retinal image quality metrics. Nonetheless, for our purpose, the derived average corneal

curvature data proved to be sufficiently informative for the initial RGP CLs design phase of this project. As a final aside, in the interest of ensuring continuous exposure to imposed optical defocus while lights were on across each day, the lenses were worn continuously. Although corneal edema was observed in some animals, it was unlikely to alter the visual experience of the animals, as it was consistently mild, with no more significant corneal complications emerging; it also did not interfere with any of our optically-based ocular measurements.

CONCLUSIONS

Rigid gas permeable CLs proved to be a viable alternative to spectacle lenses for imposing optical defocus in our young New Zealand pigmented guinea pigs, including sustained hyperopic defocus to induce myopia. In the latter case, significant myopia was successfully induced over a 14-day treatment period. The CLs were also well tolerated.

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REFERENCES

- Hoyt CS, Stone RD, Fromer C, et al. Monocular axial myopia associated with neonatal eyelid closure in human infants. *Am J Ophthalmol* 1981;91:197–200.
- Rabin J, Van Sluyters RC, Malach R. Emmetropization: A vision-dependent phenomenon. *Invest Ophthalmol Vis Sci* 1981;20:561–564.
- Schaeffel F, Feldkaemper M. Animal models in myopia research. *Clin Exp Optom* 2015;98:507–517.
- Wildsoet CF. Active emmetropization-evidence for its existence and ramifications for clinical practice. *Ophthalmic Physiol Opt* 1997;17:279–290.
- Schaeffel F, Glasser A, Howland HC. Accommodation, refractive error and eye growth in chickens. *Vis Res* 1988;28:639–657.
- Howlett MH, McFadden SA. Spectacle lens compensation in the pigmented guinea pig. *Vis Res* 2009;49:219–227.
- Troilo D, Smith EL 3rd, Nickla DL, et al. IMI-Report on experimental models of emmetropization and myopia. *Invest Ophthalmol Vis Sci* 2019;60:M31–M88.
- Lu F, Zhou X, Zhao H, et al. Axial myopia induced by a monocularly-deprived facemask in Guinea pigs: A non-invasive and effective model. *Exp Eye Res* 2006;82:628–636.
- Howlett MH, McFadden SA. Emmetropization and schematic eye models in developing pigmented guinea pigs. *Vis Res* 2007;47:1178–1190.
- Penner V, Rocha G. Use of the visante for anterior segment ocular coherence tomography. *Tech Ophthalmol* 2007;5:67–77.
- Nickla DL, Wildsoet C, Wallman J. The circadian rhythm in intraocular pressure and its relation to diurnal ocular growth changes in chicks. *Exp Eye Res* 1998;66:183–193.
- Wallman J, Wildsoet C, Xu A, et al. Moving the retina: Choroidal modulation of refractive state. *Vis Res* 1995;35:37–50.
- Howlett MH, McFadden SA. Form-deprivation myopia in the guinea pig (*Cavia porcellus*). *Vis Res* 2006;46:267–283.
- Smith EL 3rd, Hung LF, Kee CS, et al. Effects of brief periods of unrestricted vision on the development of form-deprivation myopia in monkeys. *Invest Ophthalmol Vis Sci* 2002;43:291–299.
- Shaikh AW, Siegwart JT Jr., Norton TT. Effect of interrupted lens wear on compensation for a minus lens in tree shrews. *Optom Vis Sci* 1999;76:308–315.
- Leotta AJ, Bowrey HE, Zeng G, et al. Temporal properties of the myopic response to defocus in the guinea pig. *Ophthalmic Physiol Opt* 2013;33:227–244.
- Zhou X, Qu J, Xie R, et al. Normal development of refractive state and ocular dimensions in guinea pigs. *Vis Res* 2006;46:2815–2823.
- Norton TT, McBrien NA. Normal development of refractive state and ocular component dimensions in the tree shrew (*Tupaia belangeri*). *Vis Res* 1992;32:833–842.
- Bradley DV, Fernandes A, Lynn M, et al. Emmetropization in the rhesus monkey (*Macaca mulatta*): Birth to young adulthood. *Invest Ophthalmol Vis Sci* 1999;40:214–229.
- Zhu Q, Goto S, Singh S, et al. Daily or less frequent topical 1% atropine slows defocus-induced myopia progression in contact lens-wearing Guinea pigs. *Transl Vis Sci Technol* 2022;11:26.
- Mikhail M, Sabri K, Levin AV. Effect of anesthesia on intraocular pressure measurement in children. *Surv Ophthalmol* 2017;62:648–658.
- Goto S, Muroy SE, Zhang Y, et al. Gene expression signatures of contact lens-induced myopia in Guinea pig retinal pigment epithelium. *Invest Ophthalmol Vis Sci* 2022;63:25.
- Zhou X, Lu F, Xie R, et al. Recovery from axial myopia induced by a monocularly deprived facemask in adolescent (7-week-old) Guinea pigs. *Vis Res* 2007;47:1103–1111.