

# Human Optical Axial Length and Defocus

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**PURPOSE.** To investigate the short-term influence of imposed monocular defocus on human optical axial length (the distance from anterior cornea to retinal pigment epithelium) and ocular biometrics.

**METHODS.** Twenty-eight young adult subjects (14 myopes, 14 emmetropes) had eye biometrics measured before and 30 and 60 minutes after exposure to monocular (right eye) defocus. Four different monocular defocus conditions were tested, each on a separate day: control (no defocus), myopic (+3 D defocus), hyperopic (−3 D defocus), and diffuse (0.2 density Bangerter filter) defocus. The fellow eye was optimally corrected (no defocus).

**RESULTS.** Imposed defocus caused small but significant changes in optical axial length ( $P < 0.0001$ ). A significant increase in optical axial length (mean change,  $+8 \pm 14 \mu\text{m}$ ;  $P = 0.03$ ) occurred after hyperopic defocus, and a significant reduction in optical axial length (mean change,  $-13 \pm 14 \mu\text{m}$ ;  $P = 0.0001$ ) was found after myopic defocus. A small increase in optical axial length was observed after diffuse defocus (mean change,  $+6 \pm 13 \mu\text{m}$ ;  $P = 0.053$ ). Choroidal thickness also exhibited some significant changes with certain defocus conditions. No significant difference was found between myopes and emmetropes in the changes in optical axial length or choroidal thickness with defocus.

**CONCLUSIONS.** Significant changes in optical axial length occurred in human subjects after 60 minutes of monocular defocus. The bidirectional optical axial length changes observed in response to defocus implied the human visual system is capable of detecting the presence and sign of defocus and altering optical axial length to move the retina toward the image plane. (*Invest Ophthalmol Vis Sci.* 2010; 51:6262–6269) DOI:10.1167/iovs.10-5457

It is now generally accepted that the quality of the retinal image can influence axial eye growth. A number of different experimental paradigms, applied on a range of different species have illustrated that altering retinal image quality can lead to consistent and predictable changes in eye growth (for reviews, see Refs. 1–3). Disrupting form vision through the use of lid suture<sup>4</sup> and translucent goggles/diffusers<sup>5–7</sup> or manipulating the contrast of the visual environment<sup>8</sup> has been shown to lead to axial elongation and myopia development, proportional

to the degree of image disruption,<sup>6–8</sup> that recovers once normal vision is returned.<sup>5</sup> Furthermore, defocus of the retinal image in both chick and primate animal models, through positive (myopic defocus) or negative lenses (hyperopic defocus), is known to lead to predictable (both direction and magnitude of eye growth) changes in eye growth consistent with the eyes growing to compensate for the imposed defocus.<sup>9–12</sup>

Changes in eye length associated with defocus are modulated by changes in both scleral growth and choroidal thickness, the net effect of which results in an anterior or a posterior movement of the retina toward the image plane.<sup>13–16</sup> Myopic defocus, therefore, leads to a thickening of the choroid and to a decreased scleral growth rate (which results in anterior movement of the retina), and hyperopic defocus leads to a thinning of the choroid and an increase in scleral growth rate (which results in posterior movement of the retina). Choroidal thickness changes in response to imposed defocus have been observed in both avian<sup>14,15</sup> and primate animal<sup>17,18</sup> models and have been demonstrated to occur rapidly and to precede scleral-mediated changes in eye size. Recent studies investigating the time course of choroidal thickness changes in response to defocus have illustrated that these changes can occur remarkably quickly, with only minutes of exposure to defocus required to elicit a response.<sup>19–22</sup>

The majority of work that has contributed to the current understanding of the influence of retinal image quality on eye growth has involved research with animal models. Although similar ocular responses to imposed defocus have been demonstrated in a number of different species, there has been relatively limited research investigating the influence of defocus on eye length in human subjects. There is some evidence, though, that supports the notion that retinal image quality can influence eye length in humans. A variety of different ocular conditions that lead to a disruption in form vision, such as ptosis,<sup>23,24</sup> congenital cataract,<sup>25,26</sup> corneal opacity,<sup>27,28</sup> vitreous hemorrhage,<sup>29</sup> and other ocular diseases,<sup>30</sup> have been found to be associated with abnormal eye growth in young humans, which suggests that relatively large alterations in retinal image quality may influence eye growth in human subjects. However, the influence of more subtle retinal image changes on eye growth in humans remains to be determined.

The relatively recent introduction of highly precise, non-contact methods for measuring eye dimensions has led to the finding that a number of factors can lead to short-term changes in optical axial length, hereafter referred to as axial length (the axial distance from the anterior cornea to the retinal pigment epithelium) of human subjects. Changes in accommodation<sup>31,32</sup> and IOP<sup>33,34</sup> have both been found to be associated with short-term changes in axial length. Furthermore, small but significant diurnal variations have also been noted to occur in human axial length<sup>35–37</sup> that may be mediated by changes in choroidal thickness.<sup>38</sup> Although the use of these highly precise methods of measuring axial length has led to an improved understanding of a number of short-term factors that can influence eye length in humans, no previous study has investigated the influence of defocus on axial length in human eyes. In this study we aimed to examine whether imposing defocus on

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young adult human subjects leads to short-term changes in axial length in a way similar to that observed in other animal species.

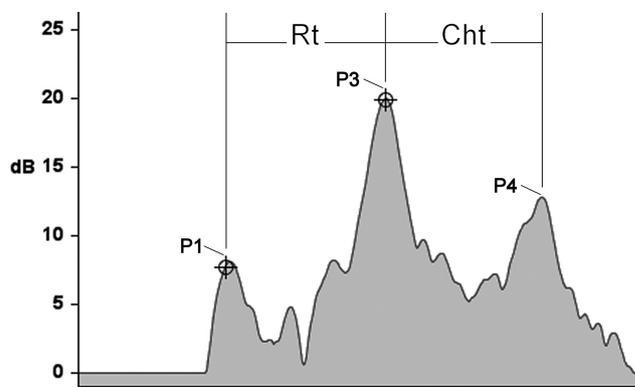
## METHODS

Twenty-eight young adult subjects (mean age,  $25 \pm 3$  years; range, 20–31 years; 17 women, 11 men) participated in this study. Subjects were recruited primarily from the students and staff of our university. All subjects were free of any ocular or systemic disease and had no history of significant ocular trauma or surgery. Our subjects exhibited a range of ethnic backgrounds: Caucasian ( $n = 15$ ), East Asian ( $n = 8$ ), and Indian ( $n = 5$ ). Approval was obtained from the university human research ethics committee before commencement of the study, and all subjects gave written informed consent to participate. All subjects were treated in accordance with the Declaration of Helsinki.

Before the study, each subject underwent an eye examination to ensure good ocular health and to determine their refractive status. All subjects had normal visual acuity of logMAR 0.00 or better. Subjects were classified according to their spherical equivalent subjective spectacle refraction in their right eye as either emmetropic (spherical equivalent refraction between +0.75 and  $-0.75$  DS) or myopic (spherical equivalent refraction  $\geq -1.25$  DS). The mean spherical equivalent refraction was  $-4.48 \pm 2.67$  DS in myopic subjects and  $-0.26 \pm 0.37$  DS in emmetropic subjects. No subject exhibited anisometropia of greater than 1.00 DS or cylindrical refraction of greater than 1.50 DC. Four of the myopic subjects were soft contact lens wearers, but they did not wear contact lenses for at least 1 week before testing or at all throughout the duration of their involvement in the study.

After these preliminary tests, a protocol was conducted to investigate the influence of four different levels of monocular defocus, imposed for a period of 60 minutes on axial length (and a comprehensive range of other ocular biometric measures). All ocular biometric measures were carried out using the Lenstar LS 900 optical biometer (Lenstar LS 900; Haag Streit AG, Koeniz, Switzerland). Five ocular biometric measures were collected from each subject at each measurement session and were later averaged. The Lenstar LS 900 is a non-contact optical biometer based on the principle of optical low-coherence reflectometry. It provides a comprehensive range of ocular axial biometric measurements including corneal thickness (CCT), anterior chamber depth (ACD), lens thickness (LT), and axial length (AxL [distance from anterior cornea to retinal pigment epithelium]) simultaneously in a single measurement procedure. The ocular biometric measurements from the Lenstar instrument have been shown to be reliable, highly precise, and comparable with previously validated instruments.<sup>39–42</sup> Manual analysis of the individual A-scan data with the Lenstar instrument's software also allows measurements of retinal thickness to be made. This is achieved through manual adjustment of the screen cursor locations to align with peaks originating from the inner limiting membrane (P1) and the retinal pigment epithelium (P3) (Fig. 1). After this manual adjustment, the instrument outputs the geometric distance between these two retinal peaks (i.e., retinal thickness).

Previous investigators,<sup>38</sup> using an optical biometer based on similar principles, have noted that in some subjects, peaks in the A-scan data are also present posterior to the reproducible peak originating from the retinal pigment epithelium (P3). Because this posterior peak (P4) is assumed to originate from the choroid/sclera interface, determination of the distance from P3 to P4 allows an estimate of choroidal thickness to be made. We have also found that in some subjects, this posterior peak is visible; hence, further manual re-positioning of the on-screen retinal cursor location, to be aligned with P3 and P4 in the individual A-scan data from the posterior eye with the instrument's software, allows a measurement of choroidal thickness. To determine the geometric distances between peaks in the A-scan, the Lenstar instrument converts optical path lengths into geometric lengths, using assumed refractive indices of the ocular media. The exact refractive index used by the instrument is proprietary information; however, our method to



**FIGURE 1.** Example of an individual A-scan plot from the Lenstar instrument's software originating from the posterior eye for a subject in whom three prominent peaks were visible. P1 is thought to have originated from reflection of the inner limiting membrane, P3 from the retinal pigment epithelium, and P4 from the choroid/sclera interface. Manual adjustment of the two retinal cursor locations in the A-scan allows determination of RT (distance from P1 to P3) and ChT (distance from P3 to P4). Axial length measures the distance from the anterior cornea to P3.

determine choroidal thickness assumes the same refractive index for retinal and choroidal tissues, an assumption consistent with previously validated interferometric methods of determining choroidal thickness.<sup>43</sup> We have found the magnitude of choroidal thickness (P3–P4 distance) estimated with the Lenstar instrument (range,  $\sim 200$ – $400$   $\mu\text{m}$ ) is typically within a range similar to that noted by Brown et al.<sup>38</sup> Figure 1 illustrates the A-scan waveform from the posterior eye for a representative subject from the Lenstar instrument and an overview of the retinal thickness (RT) and choroidal thickness (ChT) measures.

IOP was also measured at each session using the Ocular Response Analyzer instrument (ORA; Reichert, Depew, NY). The ORA is a non-contact tonometer that provides reproducible measures of IOP<sup>44</sup> that have been found to compare favorably with those obtained through Goldmann applanation tonometry.<sup>45</sup> All measurements were collected according to manufacturer instructions, with a total of four IOP measurements taken at each measurement session and later averaged. The ORA instrument provides two estimates of IOP: IOPg, which is calibrated against Goldmann applanation tonometry, and IOPcc, which takes into account corneal biomechanical factors and has been reported to be less influenced by corneal thickness than other tonometric techniques.<sup>45</sup> In our population, IOPcc and IOPg were similar; hence, we used only IOPcc as the estimate of intraocular pressure in this study.

For each subject, the experiment was conducted over four separate days, with each of the four different defocus conditions tested on a different day. We have previously found that significant diurnal variations occur in IOP and ocular biometrics, with the largest magnitude of changes occurring immediately after waking and late in the evening.<sup>37</sup> Therefore, to ensure these changes did not confound our results, all measurements were carried out between 9:00 am and 14:00 pm and at least 2 hours after each subject's reported time of waking. To allow measurements to be collected as efficiently as possible after each of the defocus conditions, without substantially changing the ambient lighting levels, the room lighting was kept at low photopic levels for all subjects throughout the entire protocol (room illuminance was  $\sim 10$  lux).

For each measurement day, subjects wore a trial frame with their best distance spherocylindrical correction in their left eye and one of four different defocus conditions in their right eye. The four different defocus conditions were as follows: control condition—subjects wore their best distance spherocylindrical correction in both eyes (i.e., no defocus); myopic defocus condition—subjects wore their best distance correction, with an extra +3.00 DS over the right eye; hyperopic

defocus condition—subjects wore their best distance correction with an extra  $-3.00$  DS over their right eye; diffuse defocus condition—subjects wore their best distance correction, with an 0.2 density Bangerter filter over their right eye. The Bangerter filter is a translucent filter that imposes diffuse image blur<sup>46</sup> and has previously been used to induce deprivation myopia in primates.<sup>7</sup>

The order of testing of the four defocus conditions was randomized among subjects, and for each of the four conditions the following measurement protocol was carried out. Before any measurements, a period of 20 minutes of distance viewing through the best distance spherocylindrical refraction (e.g., watching television at a distance of 6 m) was observed to minimize the risk that any previous visual tasks performed by the subjects might influence the results. After this distance viewing, baseline measurements of axial length and IOP were carried out. The appropriate defocus lens was then introduced in front of the right eye, and the subjects continued binocular distance viewing (watching television) for another 30 minutes with the imposed monocular defocus. Immediately after this 30-minute period of defocus, measures of axial length and IOP were repeated. Subjects then continued distance viewing for another 30 minutes, and a final measurement of axial length and IOP was taken (i.e., after 60 minutes of defocus). The laboratory was arranged with the optical biometer in proximity to the subject, to allow axial length measures to be taken quickly after each period of defocus. Ocular biometry was always performed before the IOP measures. All measurements were taken on the right eye (i.e., the eye experiencing the defocus) for all measurement sessions on all measurement days. However to investigate any potential crossover effects on the “non-defocused” eye, axial length measures of the left eye were also carried out at baseline and after the 60-minute distance viewing task on each measurement day.

In this protocol, a monocular defocus paradigm was used to produce hyperopic defocus in the right eye. Therefore, we had to assume that subjects were less likely to accommodate through the  $-3$  D lens (hence, eliminating the hyperopic defocus) if the defocus was imposed monocularly rather than binocularly because clear distance vision was still available for the left eye with relaxed accommodation. However, to confirm the accommodation level used under each of the monocular defocus conditions, a control experiment was carried out on a subset of 13 subjects (6 myopes, 7 emmetropes). In this experiment, objective measures of ocular refraction from the left eye before and during each of the defocus conditions were captured using an autorefractor (Canon R1; Canon USA, Lake Success, NY) while subjects maintained clear distance fixation. This autorefractor (the Canon R1) is an open-field, infrared optometer that has been used extensively in previous refractive error and accommodation research and has been found to provide reliable measures of spherical refraction.<sup>47</sup> At each measurement (i.e., before and during defocus for each of the four defocus conditions), the mean spherical equivalent refraction was derived from five readings, and the change in refraction during defocus was determined to ascertain the accommodation level under each of the conditions.

After data collection, the ocular biometric and IOP data from each subject at each measurement session were averaged. A repeated-measures ANOVA with two within-subjects factors (defocus and time) and one between-subjects factor (refractive error) was carried out for each of the measured variables. Pairwise comparisons with Bonferroni correction were performed for any variables with significant within-subjects effects. For all variables, ANOVA was carried out on the mean data from each session, and for those variables demonstrating a significant within-subjects effect of defocus, or significant defocus by time interaction, ANOVA was additionally run for the mean change from baseline data.

Given the partly subjective nature of the determination of RT and ChT, manual analysis of the A-scan data from the posterior eye from the Lenstar instrument was performed by two independent masked observers to avoid the risk of bias. Each observer determined RT and ChT on each of the five individual scans from each subject at each of the measurement sessions. The average measurement from the two ob-

servers for each subject from each session was used as the measure of RT and ChT from that session. Consistent peaks could not be detected from the inner retina (P1) for four subjects and from the choroid/sclera interface (P4) for five subjects, which meant that data from 24 and 23 subjects was available for RT and ChT, respectively. Estimates from the two observers generally correlated closely with a correlation coefficient ( $r$ ) of 0.94 and 0.97 for the two observers' estimates of ChT and RT, respectively.

To provide an assessment of the precision of each of the ocular parameters measured, the average coefficient of variation for each measurement session (derived from all sessions for all subjects) was calculated. The mean coefficient of variation was found to be 0.04% for AxL, 0.50% for CCT, 0.53% for ACD, 0.88% for LT, 3.4% for RT, 5.8% for ChT, and 7.8% for IOPcc.

## RESULTS

Sixty minutes of exposure to monocular defocus was found to lead to significant changes in axial length in our population of young adult subjects. The mean change in axial length for each of the four defocus conditions is presented in Table 1 and Figure 2A. Repeated-measures ANOVA revealed a significant influence of defocus and a significant defocus by time interaction for the change in axial length from baseline ( $P < 0.0001$ ). Pairwise comparisons revealed that for the control condition (no defocus), there was no significant change in axial length from baseline at 30 (mean change,  $-2 \pm 11 \mu\text{m}$ ;  $P > 0.05$ ) or 60 minutes (mean change,  $0 \pm 11 \mu\text{m}$ ;  $P > 0.05$ ). After exposure to myopic defocus, a significant reduction in axial length was observed at both 30 minutes (mean change,  $-9 \pm 10 \mu\text{m}$ ;  $P = 0.0001$ ) and 60 minutes (mean change,  $-13 \pm 14 \mu\text{m}$ ;  $P = 0.0001$ ). Significant axial elongation of the eye was observed after exposure to hyperopic defocus at both 30 minutes (mean change,  $+5 \pm 10 \mu\text{m}$ ;  $P = 0.03$ ) and 60 minutes (mean change,  $+8 \pm 14 \mu\text{m}$ ;  $P = 0.03$ ). The difference in the change in axial length between the myopic and hyperopic defocus conditions was highly statistically significant ( $P < 0.0001$ ) at both 30 and 60 minutes. On average, there was also a small increase in axial length after exposure to diffuse defocus, with a mean change of  $+5 \pm 14 \mu\text{m}$  at 30 minutes that was not statistically significant ( $P = 0.2$ ) and a mean change of  $+6 \pm 13 \mu\text{m}$  after 60 minutes that bordered on statistical significance ( $P = 0.053$ ). There was no significant difference between the axial length measures at baseline (i.e., before defocus) on any of the four measurement days (mean baseline axial lengths were  $24.56 \pm 1.44$ ,  $24.56 \pm 1.44$ ,  $24.56 \pm 1.44$ , and  $24.56 \pm 1.43$  mm for the control, myopic defocus, hyperopic defocus, and diffuse defocus conditions, respectively).

The axial length data exhibited a significant between-subjects effect of refractive error ( $P = 0.01$ ), indicating a longer axial length on average in our myopic subjects, as expected (mean baseline axial length was  $25.36 \pm 1.42$  mm for the myopes and  $23.75 \pm 0.84$  for the emmetropes). However, there was no significant effect of refraction on the change in axial length after exposure to defocus ( $P = 0.2$ ) and no significant refractive error by defocus interaction ( $P = 0.4$ ), indicating a similar pattern of change after exposure to defocus in the emmetropic and myopic populations we tested.

Table 1 also presents the mean changes in retinal and choroidal thickness measures derived from manual analysis of the A-scan data. Repeated-measures ANOVA revealed that the change in choroidal thickness exhibited a significant effect of defocus and a significant defocus by time interaction. Pairwise comparisons revealed that the myopic defocus condition resulted in a thickening of the choroid compared with baseline that reached statistical significance after 60 minutes of expo-

TABLE 1. Change in Ocular Biometrics from Baseline after 30 and 60 Minutes of Exposure to Defocus

	Change from Baseline ( $\mu\text{m}$ ) Mean $\pm$ SD				P	
	Control (no defocus)	3 D Myopic Defocus	3 D Hyperopic Defocus	Diffuse Defocus	Defocus	Defocus by Time*
Axial length ( $n = 28$ )						
30 min	$-2 \pm 11$	$-9 \pm 10^*$	$5 \pm 10^*$	$5 \pm 14$	$<0.0001$	$<0.0001$
60 min	$0 \pm 12$	$-13 \pm 14^*$	$8 \pm 14^*$	$6 \pm 13$		
Retinal thickness ( $n = 24$ )						
30 min	$0 \pm 5$	$-1 \pm 5$	$-1 \pm 4$	$-1 \pm 4$	0.793	0.372
60 min	$-1 \pm 7$	$-2 \pm 5$	$-1 \pm 4$	$-2 \pm 4$		
Choroidal thickness ( $n = 23$ )						
30 min	$2 \pm 15$	$7 \pm 13$	$-8 \pm 16$	$1 \pm 11$	0.002	0.0003
60 min	$5 \pm 15$	$12 \pm 16^*$	$-3 \pm 14$	$-6 \pm 12$		

Repeated-measures ANOVA revealed a significant effect of defocus on change in axial length and choroidal thickness ( $P < 0.01$ ). Changes in the other parameters were not statistically significant ( $P > 0.05$ ).

\* Statistically significant change from baseline (Bonferroni-corrected pairwise comparison  $P < 0.05$ ).

sure to defocus (mean change,  $+12 \pm 16 \mu\text{m}$ ;  $P = 0.004$ ). On average, the choroid exhibited a small degree of thinning with both the hyperopic and the diffuse defocus conditions, but these changes in thickness did not reach statistical significance ( $P > 0.05$ ). The difference in the change in choroidal thickness between the myopic and hyperopic defocus conditions was statistically significant ( $P < 0.01$ ) at both 30 and 60 minutes. There was no significant between-subjects effect of refractive error evident in the mean choroidal thickness (mean baseline choroidal thickness:  $259 \pm 43 \mu\text{m}$ , myopes;  $269 \pm 44 \mu\text{m}$ , emmetropes;  $P = 0.603$ ) or in the change in choroidal thickness with defocus. Figure 3 illustrates the change in choroidal thickness and axial length after 60 minutes of defocus. It is evident that the choroidal thickness changes were typically of similar magnitude but opposite in direction to the axial length changes. Analysis of covariance (ANCOVA) revealed a statistically significant ( $P < 0.01$ ) negative association between the change in axial length and the change in choroidal thickness after 60 minutes of exposure to defocus ( $r = -0.37$ ; slope =  $-0.32$ ). No significant changes were found in retinal thickness associated with defocus.

None of the anterior eye biometric measures (CCT, LT, ACD) exhibited significant changes after defocus. The changes in CCT observed after exposure to defocus were, on average  $<1 \mu\text{m}$ , and no significant defocus or time by defocus interaction effects were observed. Neither ACD nor LT exhibited any significant effect of defocus or time by defocus interaction. Additionally, no significant between-subjects effects of refractive error were observed for CCT (mean corneal thickness at baseline:  $0.544 \pm 0.026 \text{ mm}$ , myopes;  $0.546 \pm 0.029 \text{ mm}$ , emmetropes), ACD (mean ACD:  $3.18 \pm 0.25 \text{ mm}$ , myopes;  $3.07 \pm 0.26 \text{ mm}$ , emmetropes) or LT (mean LT at baseline:  $3.54 \pm 0.14 \text{ mm}$ , myopes;  $3.66 \pm 0.24 \text{ mm}$ , emmetropes) ( $P > 0.05$ ).

Few statistically significant changes were observed in the fellow eye data after the 60-minute test period. The mean change in axial length in the fellow (left) eye after 60 minutes of exposure to defocus in the right eye is illustrated in Figure 2B. Repeated-measures ANOVA revealed no significant effect of defocus ( $P = 0.16$ ) and no significant time by defocus interaction ( $P = 0.384$ ), indicating no significant change in the axial length of the left eye after defocus of the right eye. The

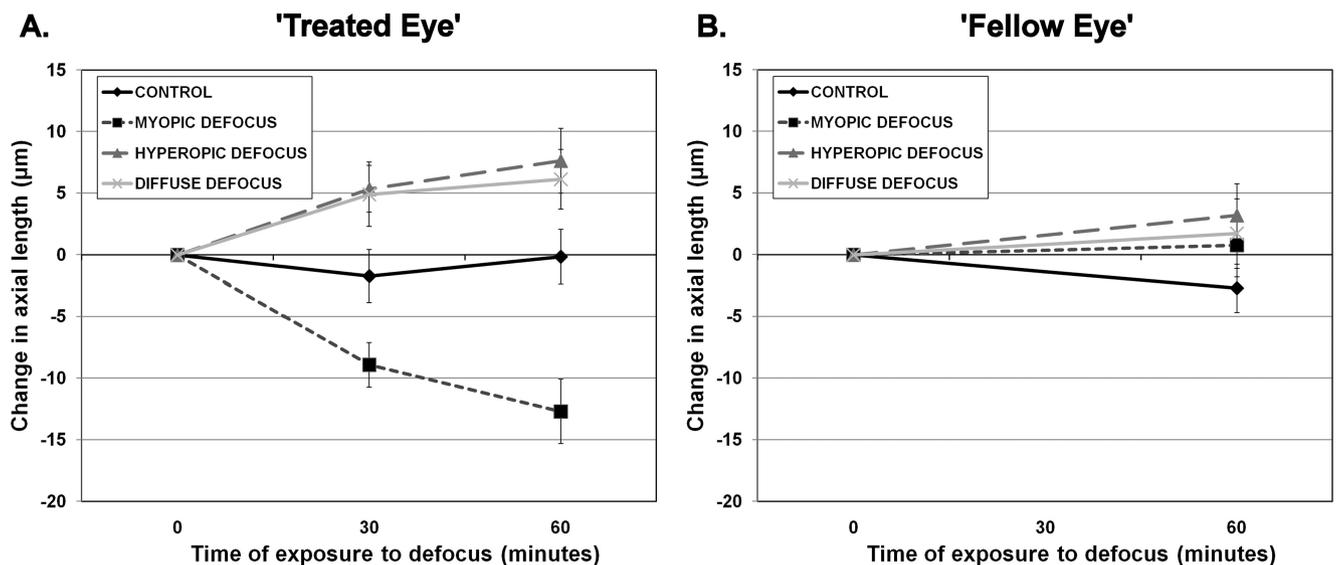
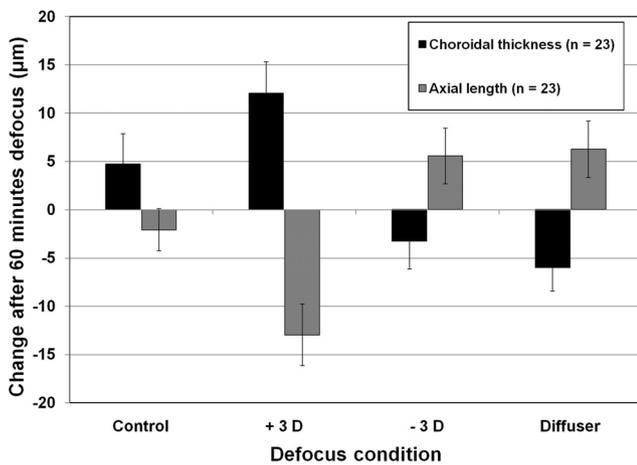


FIGURE 2. Mean change in axial length in the treated (right) eye (A) after 30 and 60 minutes of monocular defocus for all subjects ( $n = 28$ ) and mean axial length change in the fellow (left) eye (B) after the 60 minutes of monocular defocus imposed on the right eye. Repeated-measures ANOVA revealed a significant influence of defocus on the change in axial length of the treated (right) eye ( $P < 0.0001$ ) but no significant change in the axial length of the fellow (left) eye. Error bars represent SEM.



**FIGURE 3.** Mean change in choroidal thickness and axial length after 60 minutes of exposure to monocular defocus for the subset of 23 subjects with reliable choroidal thickness data. Repeated-measures ANOVA revealed a significant influence of defocus on the change in choroidal thickness and axial length ( $P < 0.01$ ). Error bars represent SEM.

mean change in axial length after 60 minutes was  $-3 \pm 10 \mu\text{m}$ ,  $+1 \pm 14 \mu\text{m}$ ,  $+3 \pm 13 \mu\text{m}$ , and  $+2 \pm 15 \mu\text{m}$  for the control, hyperopic, myopic, and diffuse defocus conditions, respectively. The fellow eye retinal and choroidal thickness data also exhibited no significant effect of defocus or time by defocus interaction ( $P > 0.05$ ). Similarly, only small changes were evident in the anterior eye biometrics of the fellow eye after exposure of the right eye to defocus. The CCT of the left eye did exhibit a significant change after defocus of the right eye ( $P = 0.01$ ). Significant thinning of the left cornea was evident after 60 minutes of exposure of the right eye to hyperopic and diffuse defocus only ( $P < 0.05$ ). The magnitude of the observed changes in CCT, however, were very small ( $-1.2 \pm 2.3 \mu\text{m}$  and  $-1.1 \pm 1.7 \mu\text{m}$  for the hyperopic and diffuse defocus conditions, respectively). No significant effects of defocus or defocus by time interactions were evident in the data from the left eye for ACD or LT ( $P > 0.05$ ).

The average changes in IOP across all conditions were  $<0.6$  mm Hg, and there were no statistically significant effects of defocus or time by defocus interaction observed ( $P > 0.05$ ). There was also no significant between-subjects effects of refractive error or refractive error by defocus interaction ( $P > 0.05$ ) for IOP (mean IOP at baseline:  $14.56 \pm 2.15$  mm Hg, myopes;  $14.80 \pm 2.86$  mm Hg, emmetropes). These findings indicate that IOP was similar between the myopic and emmetropic populations and that they both exhibited no significant change after exposure to defocus.

Analysis of the autorefraction data (Canon R1; Canon USA) from the control experiment revealed only small changes in accommodation associated with the different defocus conditions. The changes were substantially smaller than the magnitude of the defocusing lenses and were not statistically significant ( $P = 0.48$ ). Mean changes in accommodation of  $-0.05 \pm 0.26$  D,  $-0.10 \pm 0.22$  D,  $-0.09 \pm 0.15$  D, and  $+0.02 \pm 0.23$  D were observed during the control, hyperopic, myopic, and diffuse defocus conditions, respectively.

## DISCUSSION

We have shown that exposing young adult human eyes to periods of monocular defocus can lead to significant changes in axial length (i.e., distance from anterior cornea to retinal pigment epithelium). The changes we observed after 60 minutes

of defocus exposure were bidirectional in nature, with a significant increase in axial length after exposure to hyperopic defocus (image plane behind the retina) and a significant decrease in axial length after exposure to myopic defocus (image plane in front of the retina). Although the changes we have observed were small in magnitude, they were consistently observed in both myopic and emmetropic subjects, were highly statistically significant, and are consistent with the human visual system detecting both the presence and the sign of defocus and altering axial length in a manner that would move the retina toward the image plane. Our findings are consistent with reports in avian,<sup>14-16,19</sup> primate,<sup>17</sup> and other mammalian<sup>48</sup> species in which ocular changes occur in response to myopic and hyperopic defocus that result in predictable movements of the position of the retina in the direction of the image plane. However, this is the first study to illustrate that short-term exposure to retinal image defocus can also lead to changes in axial length in human subjects.

Significant changes also occurred in choroidal thickness associated with defocus, and these choroidal changes were significantly associated with the changes in axial length. On average, the choroid was found to thicken with the myopic defocus condition and to become thinner with the hyperopic defocus. However, it was only the choroidal thickening with the myopic defocus condition that showed a statistically significant change from baseline. This slight discrepancy between axial length (which showed significant changes with both myopic and hyperopic defocus) and choroidal thickness changes was likely to be due to the lower precision of the estimates of choroidal thickness (mean coefficient of variation, 5.8%) compared with axial length (mean coefficient of variation, 0.04%) data. Further investigation of the influence of defocus on choroidal thickness using a more precise measurement technique (e.g., optical coherence tomography<sup>49</sup>) therefore seems warranted.

Given that rapid axial length responses to defocus have been shown to be mediated by choroidal thickness change in both avian<sup>14-16,19</sup> and primate<sup>17,18</sup> species and that we found significant changes in choroidal thickness associated with certain defocus conditions, it is likely that choroidal thickness change also underlies the rapid, bidirectional axial length changes we observed in our present study of human subjects. The exact mechanism underlying these changes in the choroid are unknown; however, changes in the tone of choroidal non-vascular smooth muscle or alterations in choroidal blood flow have been suggested as two potential causes of defocus-induced choroidal thickness change.<sup>50</sup> Studies with animals have noted some significant changes in choroidal blood flow in eyes recovering from retinal image-mediated ocular growth,<sup>51</sup> and human research has demonstrated that choroidal blood flow can be altered by visual input (e.g., light-dark transitions,<sup>52</sup> flickering blue light<sup>53</sup>). Therefore, future research investigating the influence of defocus on choroidal blood flow may help in our understanding of the underlying cause of defocus-induced choroidal thickness changes in human subjects.

Previous work with chicks,<sup>6</sup> primates,<sup>7</sup> and other mammals<sup>54</sup> has illustrated that disrupting form vision with translucent occluders leads to significant axial elongation.<sup>6,7</sup> Our subjects showed smaller increases in axial length after 60 minutes of exposure to diffuse defocus (i.e., Bangerter filters) than they did with the hyperopic defocus condition. This may imply that the human eye is less sensitive to changes in image quality induced with this diffuse defocus than to spectacle lens-induced (defocus) changes. However, previous animal studies have illustrated that responses are greater for larger disruptions to image quality,<sup>6,7</sup> so it is possible that a denser diffusing lens might have a larger effect on axial length changes. Previous studies have also noted some differences in

the time course of ocular change in chicks in response to diffuse and to spectacle lens defocus, with axial elongation in response to hyperopic lens-induced defocus noted to be more rapid than the response to diffusers,<sup>55</sup> and it has also been suggested that the ocular changes produced by diffusers and spectacle lenses may have different underlying mechanisms.<sup>56</sup>

The magnitude of change in axial length after spectacle lens-induced defocus in our young adult human subjects were relatively small, with on average 8  $\mu\text{m}$  of increase and 13  $\mu\text{m}$  of decrease in axial length observed after 60 minutes of exposure to hyperopic defocus and myopic defocus, respectively. Previous studies in chicks have noted a substantially larger magnitude of ocular change after similar short periods of spectacle lens-induced defocus. Kee et al.<sup>55</sup> reported changes in choroidal thickness of approximately 60  $\mu\text{m}$  after 1 hour of exposure to hyperopic defocus, Zhu et al.<sup>19</sup> found an 89  $\mu\text{m}$  difference in choroidal thickness between eyes exposed to 1 hour of hyperopic defocus and eyes exposed to 1 hour of myopic defocus, and Nickla<sup>21</sup> reported a 46  $\mu\text{m}$  increase in choroidal thickness after 1 hour of exposure to a +10 D lens. The difference in magnitude of ocular change in humans compared with these previous animal studies most likely represents a difference between species in the ability of the choroid to change thickness, particularly given that choroidal changes associated with longer periods of defocus have been shown to be substantially smaller in primates<sup>17,18</sup> than in chicks.<sup>14,15</sup> Some of the difference in the observed magnitude of ocular change in humans compared with findings in other species may also relate to the age of our subjects. Our subjects were all young adults, whereas previous animal studies typically used infant animals. Further research is required to determine whether the short-term ocular response to defocus in humans changes with age.

We found on average that the magnitude of decrease in axial length after exposure to myopic defocus was larger and more highly statistically significant than the average magnitude of increase in axial length after exposure to hyperopic defocus (of equal dioptric magnitude). This implies that the human eye could be more sensitive to myopic defocus or that in the short term the human eye can more readily reduce its length than it can elongate (which, in turn, suggests that the choroid can more readily expand than it can become thin). Previous findings in chicks are consistent with this notion, with a number of studies reporting myopic defocus to have a stronger influence on ocular parameters than hyperopic defocus.<sup>20,57-59</sup>

In our short-term monocular defocus test paradigm, we found no significant changes occurring in axial length of the fellow eye (i.e., significant changes in eye length were confined to the eye that was exposed to defocus). This suggests that the changes observed are a local ocular response to defocus and is consistent with previous animal studies illustrating that both form deprivation<sup>60</sup> and lens-induced,<sup>61</sup> defocus-mediated eye growth do not require an intact optic nerve and that defocus imposed on local retinal regions in both chicks<sup>62-64</sup> and primates<sup>65</sup> leads to altered eye growth localized to those retinal regions.

The opposite direction of axial length changes we observed after exposure to myopic and hyperopic defocus suggests that the human visual system is capable of detecting the sign of imposed defocus and altering axial length accordingly. How the eye can distinguish between positive and negative defocus, however, remains to be determined. Our study was performed without cycloplegia (i.e., with natural accommodation), with normal levels of ocular higher order aberrations, in a natural "polychromatic" visual environment. Therefore, directional cues associated with ocular characteristics such as accommodation, ocular monochromatic aberrations, or chromatic aberrations might have been used to detect the sign of defocus.

Further research is clearly required to determine which of these or other cues are the most important for the human visual system in detecting defocus and modulating axial length.

Previous studies with human subjects have demonstrated that significant accommodation is associated with a small axial elongation of the eye.<sup>31,32</sup> It has been suggested that this axial length change may be attributed to the mechanical effects of ciliary muscle contraction. Given that accommodation was not strictly controlled in our study (i.e., no cycloplegia was used), it is possible that accommodation during our hyperopic defocus condition could have contributed to the observed axial elongation. However, we consider this unlikely because we found no significant change in anterior chamber depth or lens thickness with defocus, which suggests there was minimal change in accommodation associated with the different defocus conditions. The results from the control experiment also indicate that subjects maintained fixation through the non-defocused eye because only minimal changes in accommodation were associated with the monocular defocus conditions. If the right eye with the hyperopic defocus was accommodating during the experiment, we might also have expected to see a reduction in axial length in the fellow left eye because this eye would have experienced myopic defocus during the 60-minute experiment. There was also no significant change in IOP after the hyperopic defocus condition, which further suggests subjects were not accommodating substantially during this condition because it has been shown that accommodation can lead to significant decreases in IOP.<sup>66</sup> Taken together, these findings suggest it is unlikely that accommodation-induced axial elongation influenced the results of the hyperopic defocus condition.

There have been a number of different studies investigating the influence of optical blur on a range of visual functions, such as visual acuity and contrast sensitivity in human subjects. Significant changes in visual acuity<sup>67-69</sup> and contrast sensitivity<sup>67,70,71</sup> have been noted after a period of short-term exposure to defocus. Our findings of significant changes in axial length after exposure to defocus may help to explain (at least in small part) some of these previously noted changes in visual function associated with adaptation to blur (e.g., the small reduction in axial length after exposure to myopic defocus would be expected to slightly reduce the amount of blur). However, the magnitude of change in axial length is relatively small and would not be expected to lead to the same magnitude of change in vision that has been previously documented (e.g., George and Rosenfield<sup>68</sup> noted approximately two lines of improvement in vision after 2 hours of exposure to +2.50 D defocus), which suggests that other mechanisms (e.g., neural adaptation) are also involved in these previously documented phenomena.

While the changes that we have observed in our present study are short-term in nature, these findings may have significant implications for the influence of retinal image quality on the longer term control of eye growth. As longer term exposure to defocus in a number of different species can lead to substantial ocular refractive changes, the short-term changes that we have observed in human eyes in response to defocus may also be important for longer term refractive error development in humans. The cumulative effects of longer periods of retinal image defocus (e.g., increased ocular aberrations or lag of accommodation associated with long periods of near work), might therefore be expected to lead to larger changes in axial length over longer periods of time. Further research is required however to investigate the relationship between axial length change, the magnitude and sign of defocus and the natural time course of these changes.

We found no significant differences between our myopic and emmetropic subjects in terms of the changes in axial

length after exposure to defocus. This implies that the small changes in axial length that we have observed in response to defocus are a phenomenon that occurs regardless of refractive error. If these short-term ocular changes in response to defocus are important for longer term refractive error development, then patients developing myopia may be involved in larger amounts of visual activities associated with hyperopic defocus (e.g., near work with significant lag of accommodation), or may have greater amounts of hyperopic defocus associated with their normal visual tasks (e.g., greater lag of accommodation at near, or greater increase in ocular aberrations associated with near work). It is also possible that myopes exhibit differences in their longer term ocular response to defocus (e.g., the response to imposed defocus for longer than 60 minutes may differ between the refractive groups). Our subjects were also all young adults. It is therefore possible that at younger ages when subjects are developing myopia and the eyes are naturally growing more rapidly, that the response to defocus may differ.

In conclusion, we have demonstrated for the first time that imposing a short period of defocus on the human visual system leads to significant changes in axial length. These changes are bi-directional in nature, consistent with previous findings in experimental animals, and suggest that the human visual system is capable of detecting the sign of defocus and altering axial length accordingly to move the position of the retina toward the image plane. While further research is required to more comprehensively describe the characteristic features of the response of the human visual system to defocus, these findings of short-term ocular change associated with defocus may have significant implications for human refractive error development.

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