Effect of Optical Defocus on Choroidal Thickness in Healthy Adults With Presbyopia

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Purpose. To investigate changes in subfoveal choroidal thickness (SFCT) induced by retinal defocus in presbyopic adults.

Methods. Thirty-seven healthy presbyopic subjects (age 57.74 ± 4.06 years) with low refractive errors (+0.08 ± 1.09 Diopters [D]) viewed a distant target (video movie at 6 m) for 60 minutes on two occasions while SFCT was monitored with optical coherence tomography every 20 minutes. On each occasion, both eyes were optimally corrected for distance: one eye acted as control, while the other (experimental) eye viewed through an additional ophthalmic lens: a +2.00 D lens imposing myopic defocus on one occasion and a −2.00 D lens imposing hyperopic defocus on the other occasion.

Results. Baseline SFCT was not different between experimental and control eyes (226 ± 72 μm vs. 232 ± 75 μm; $P = 0.28$). Myopic defocus caused a significant ($P < 0.001$) increase in SFCT in the defocused eye by 20 minutes (and +10 ± 5-μm increase at 60 minutes: $P < 0.001$), while hyperopic defocus caused a significant decrease in SFCT by 20 minutes (and −10 ± 5-μm decrease at 60 minutes: $P < 0.001$) with no change in control eyes.

Conclusions. In presbyopic subjects, imposed myopic retinal defocus caused thickening of SFCT, while hyperopic defocus caused thinning of SFCT. This implies that uncorrected presbyopia, which is associated with hyperopic retinal defocus for near objects and which is highly prevalent in the developing world, would likely be associated with choroidal thinning and possibly reduced choroidal blood flow with prolonged periods in a near visual environment.

Keywords: choroid, optical coherence tomography, choroidal perfusion

Presbyopia describes the inability of the aging eye to accommodate sufficiently to perform near tasks satisfactorily. One consequence of uncorrected presbyopia is that close objects are out of focus, which makes near tasks difficult or impossible without provision of additional plus power: for example, reading glasses.[1,2] However, many people in the developing world do not have access to spectacles, including reading glasses, making uncorrected presbyopia the most common cause of visual impairment worldwide.[3] Although uncorrected presbyopia is usually manifest as difficulty with reading, the degree of retinal defocus depends on the distance of the near object from the uncorrected presbyopic eye, regardless of the task. It is estimated that there are approximately 500 million people with presbyopia in developing countries[4] who have to perform near tasks (e.g., sewing, cooking, weeding, sorting grain, using hand tools) without reading glasses.[5] Near tasks performed with uncorrected presbyopia result in hyperopic retinal defocus in which the image plane is located posterior to the retina. Previous unrelated work investigating refractive development in young animals has shown that imposing hyperopic defocus to the retina causes a rapid decrease in the thickness of the ocular choroid. In contrast, imposing myopic defocus causes a rapid thickening of the choroid.[6–9] Similar rapid changes in choroidal thickness with imposed retinal defocus also have been shown in young humans.[10,11] It has been proposed that the choroid acts as an intermediary in the eye-growth signaling pathway from the retina to the sclera,[12,13] and that these rapid changes in choroidal thickness can indicate pending changes in eye growth and refractive status[14,15] in the developing eye. However, changes in eye growth with defocus are not expected in presbyopic eyes, and it is not known whether changes to choroidal thickness with defocus would occur in presbyopic subjects.

The proposed physiological mechanisms by which the choroid might dynamically increase or decrease in thickness include contraction and relaxation of nonvascular smooth muscle,[13] fluid redistribution as a result of osmotic changes,[16] and changes in choroidal blood flow.[17] Choroidal thickness and choroidal blood flow are correlated in animals[17] and healthy humans,[18,19] with choroidal thinning associated with reduced blood flow. Moreover, the choroid is typically thinner than normal, with reduced choroidal blood flow in patients with AMD[20–23] and those with diabetic retinopathy (DR).[24–27] The functional relationship between choroidal thinning and reduced blood flow in AMD or DR is not yet clear, although it has been suggested[28] that choroidal thinning may lead to increased

vascular resistance, reduced choroidal blood flow, ischemia, and progression of DR.

The aim of this study was to determine whether hyperopic and myopic retinal defocus imposed in the presbyopic eye might also cause rapid thinning and thickening of the choroid, as it does in young animals and humans.

Methods

Subjects and Experimental Protocol

A total of 37 healthy presbyopic subjects aged between 50 years[29] and 67 years (mean ± SD: 57.74 ± 4.06 years; 23 females) with low spherical equivalent refraction (SER) (mean +0.08 ± 1.09 Diopters [D]; range −3.00 to +3.00 D) were recruited. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Research Ethics Committee of the China Medical University Hospital, Taichung, Taiwan (no. CMUH104-REC3-068). Informed consent was obtained from all subjects in writing. The inclusion criteria were as follows: age 50 to 70 years, emmetropia or low refractive error (SER between +3.00 D and −3.00 D) requiring a near addition for reading, normal visual acuity of logMAR 0.00 or better, and normal corrected near acuity (N5 at 40 cm or better). Subjects had no systemic or ocular pathology (e.g., no diabetes or hypertension, and no glaucoma, significant macular changes, or previous ocular surgery) on screening by a consultant ophthalmologist. Subjects attended the two measurement sessions on different days. Measures were made at the same time of day for each subject (between 12 noon and 5 PM) to avoid the confounding effects of diurnal fluctuations in choroidal thickness.[30] In addition, before each session, subjects viewed a video movie for 20 minutes, seated at 6 m from the screen wearing their habitual distance correction for both eyes (i.e., no defocus), to stabilize choroidal thickness and reduce any effects of prior exercise[31] or postural changes.

At the first visit, the dominant eye of each subject was determined with a simple pointing task.[32] The dominant eye was pseudo-randomly assigned to be either the experimental eye or the contralateral control eye using a permuted-block design with a block size of four. Following the stabilization period, subjects viewed a video movie binocularly at 6 m for 60 minutes wearing their habitual distance correction for both eyes, but with the experimental eye viewing through an additional full-aperture ophthalmic lens (either +2.00 D or −2.00 D) to impose either myopic or hyperopic monocular defocus. Subjects were randomly assigned to receive either hyperopic or myopic defocus to the experimental eye at the first visit, and the procedure was repeated with the opposite sign of defocus at the second visit. Optical coherence tomography (OCT) scans of the retina and choroid were made at 20-minute intervals in both eyes during the 60-minute viewing time. To ensure reasonably large pupil diameters, which facilitate rapid OCT measures, the ambient lighting was maintained at approximately 10 lux (as adopted in a previous similar study[10]) measured with a Digital Light Meter (TES-335; TES Electrical Electronic Corp., Taipei, Taiwan; http://www.tes.com.tw/).

Choroidal Thickness Measurement

A Nidek RS-3000 RetinaScan Advance (Nidek Co., Ltd., Aichi, Japan; http://www.nidek-intl.com/) spectral-domain OCT (SD-OCT) was used to obtain cross-sectional chorioretinal images of both eyes in the "Choroidal" and "UltraFine" scanning modes using the 9-mm "Macula Line" function centered on the fovea. The OCT images were exported as bitmap image files. The files were de-identified, and two masked investigators used ImageJ software (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA) to independently identify the inner and outer choroidal borders and manually measure subfoveal choroidal thickness (SFCT) using the measure function in ImageJ. ImageJ provides distance measurements in pixels, so a scaling factor (1 pixel = 3.01 ± 0.01 μm) was applied to determine choroidal thickness. The scaling factor was obtained by analyzing a subset of 25 images using the inbuilt "measure" function of the NAVIS-EX software (Nidek; http://www.nidek.co.jp/) as described previously.[10]

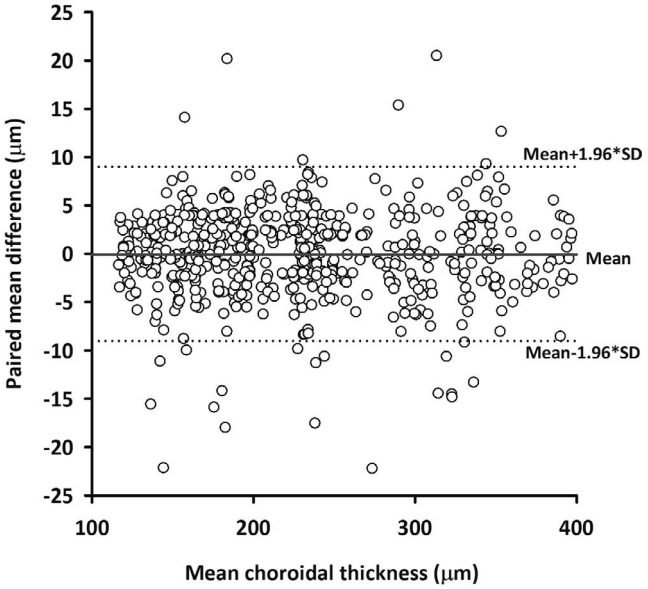

Figure 1. Bland-Altman plot of interobserver agreement on SFCT measures between the two masked investigators. The mean interobserver difference was 0 ± 5 μm (95% CI −9 to +9 μm).

Interobserver Variation in Measurement of SFCT

Repeatability of the measures between observers was assessed with Bland-Altman analysis.[33] The mean interobserver difference and 95% limits of agreement (see Fig. 1) were mean ± 1 SD: 0 ± 5 μm (95% confidence interval [CI] −9 to +9 μm).

Data Analysis

Statistical analyses were performed using IBM SPSS Statistics 20 (IBM, Armonk, NY, USA) and Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA; http://www.microsoft.com). The Shapiro-Wilk's W test was used to confirm that the data sets were normally distributed. Changes in SFCT were measured as absolute changes in microns with reference to baseline SFCT at time zero (start of the relevant 60-minute observation period). Because changes in SFCT were measured in the same subjects and at regular 20-minute intervals, the statistical model used was repeated measures ANOVA with general linear model with two within-subject factors (time and experimental versus control eye) and one between-subject factor (refractive status). Post hoc pairwise comparisons with Bonferroni correction were performed for any variables with a significant within-subject effect and interactions.

Results

The mean baseline SFCT in the 37 experimental eyes (before application of defocus) was not different from that in

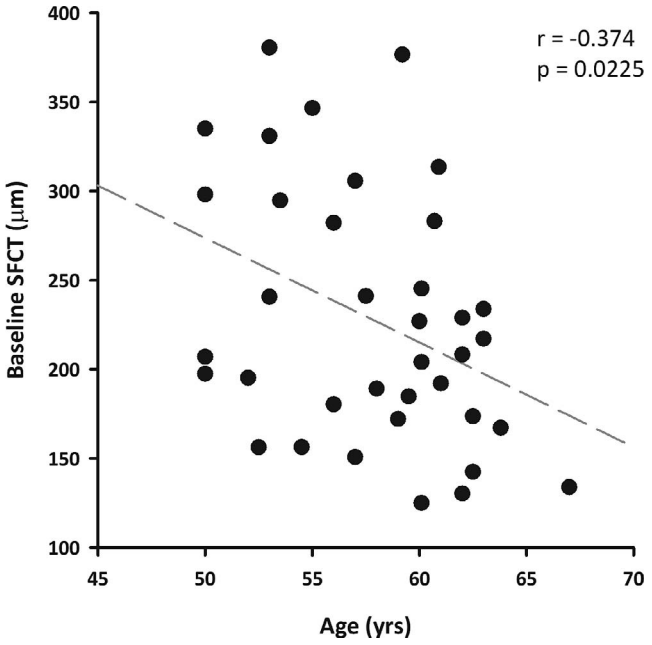

FIGURE 2. Relationship between age and baseline SFCT (i.e., with no defocus). The data suggest a reduction in SFCT of 6 μm per year in the age range 50 to 67 years ($n = 37$).

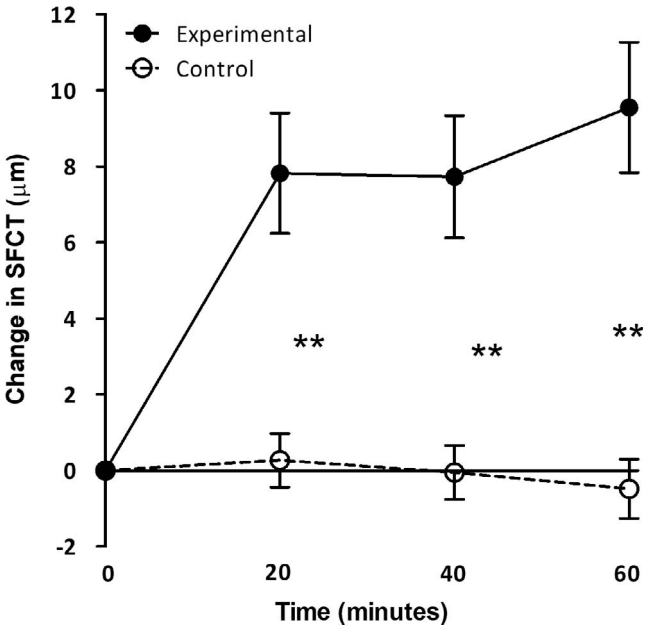

FIGURE 3. Time course of changes in SFCT in response to 2.00 D of monocular myopic retinal defocus applied to the experimental eye. Data: means ± 95% CI: $n = 37$ experimental and 37 control eyes; ** indicates mean SFCT significantly greater than baseline value ($P < 0.001$) and also significantly greater than control ($P < 0.001$) at the same time point.

contralateral control eyes (SFCT[exper] = 226 ± 72 μm versus SFCT(control) = 232 ± 75 μm; $P = 0.28$). There was no correlation between SFCT and SER of the subjects (SER range −3.00 D to +3.00 D; $r = -0.008$; $P = 0.96$), but there was a mild/moderate correlation between SFCT and age (range 50 to 67 years; Pearson coefficient, $r = -0.374$; $P = 0.0225$), with a slope indicating a reduction in SFCT of 6 μm per year (Fig. 2).

Myopic Defocus: Change in SFCT Versus Time

When experimental eyes were exposed to 2.00 D of myopic defocus for 60 minutes, mean SFCT increased (+10 ± 5 μm at 60 minutes; $P < 0.001$; Fig. 3). However, the increase was already significant by 20 minutes of exposure (+8 ± 5 μm; $P < 0.001$), whether the increase was compared with baseline SFCT of that eye or with the SFCT of the control eye at the same time point. During the 60 minutes, SFCT in the contralateral control eyes (with no defocus) did not change ($P > 0.44$ for all times).

Hyperopic Defocus: Change in SFCT Versus Time

When experimental eyes were exposed to 2.00 D of hyperopic defocus for 60 minutes, mean SFCT decreased (−10 ± 5 μm at 60 minutes; $P < 0.001$; Fig. 4). However, the decrease was already significant by 20 minutes of exposure (−8 ± 4 μm; $P < 0.001$). During the 60 minutes, SFCT in the contralateral control eyes (no defocus) did not change ($P > 0.28$ for all times).

Defocus-Induced Changes Versus Baseline SFCT and Age

Baseline SFCT (without defocus) varied widely among subjects in the study (range: 117 to 396 μm).

Figure 5A illustrates the changes in SFCT induced by both myopic and hyperopic defocus plotted against age-adjusted baseline SFCT, in which age-adjusted baseline SFCT = Baseline SFCT − ([subject age − mean age] × m), where mean age = 57.74 years and $m = 6$ μm per year (see Fig. 2). The thinning associated with hyperopic defocus was approximately 10 μm, independent of baseline SFCT. The thickening associated with myopic defocus appeared to decrease somewhat with age-adjusted baseline SFCT. Figure 5B shows the changes in SFCT induced by myopic and hyperopic defocus plotted against age.

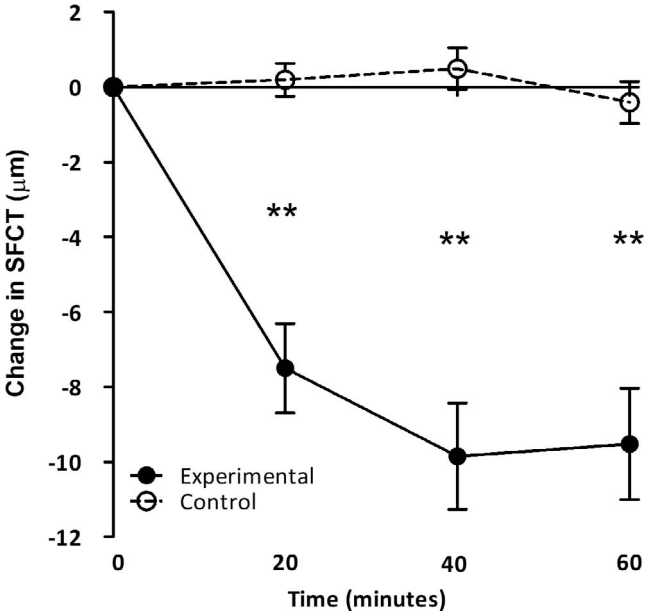

FIGURE 4. Time course of changes in SFCT in response to 2.00 D of monocular hyperopic retinal defocus applied to the experimental eye. Data: means ± 95% CI: $n = 37$ experimental and 37 control eyes; ** indicates mean SFCT significantly less than baseline value ($P < 0.001$) and also significantly less than control ($P < 0.001$) at the same time point.

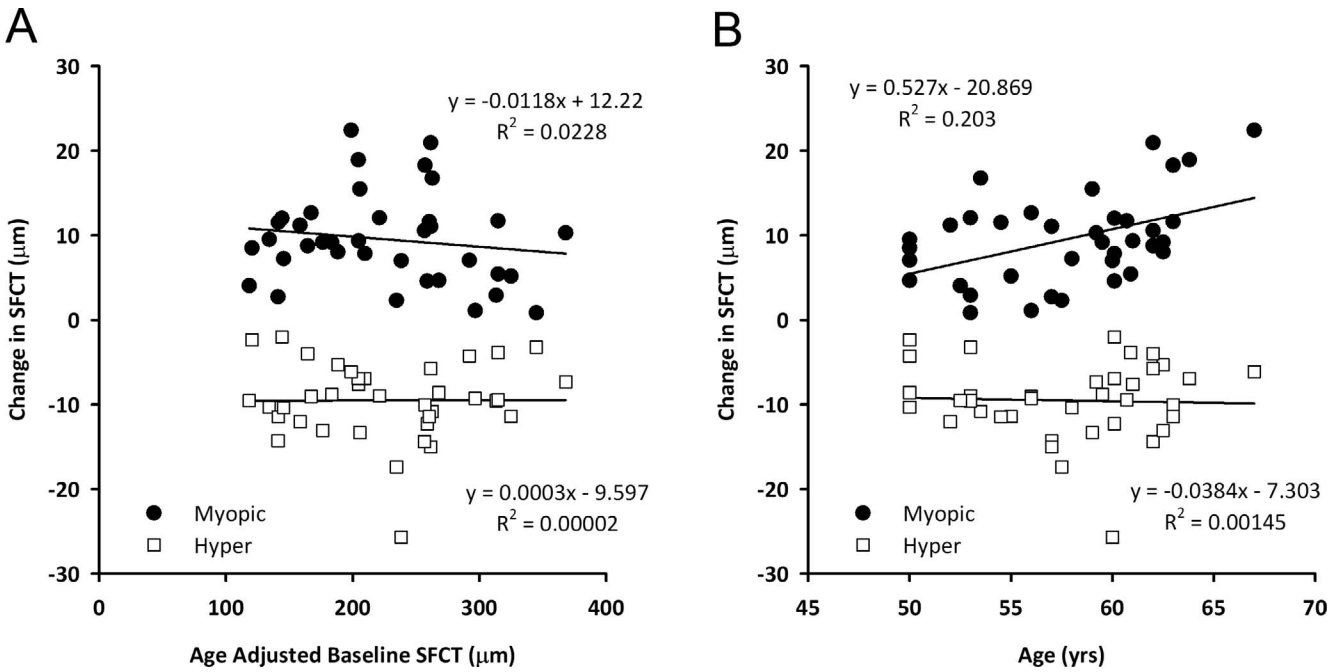

FIGURE 5. Change in SFCT after 60 minutes of 2.00 D of hyperopic (*open squares*) and myopic (*filled circle*) retinal defocus (**A**) versus (age-corrected) baseline SFCT of the experimental eyes and (**B**) versus participant age.

Again, the thinning associated with hyperopic defocus was approximately 10 μm, independent of age. The thickening associated with myopic defocus appeared to increase somewhat with age.

Among subjects, there was a wide range in the magnitude of changes in SFCT induced by myopic and hyperopic defocus (at time 60 minutes, myopic range: 1 to 22 μm; hyperopic range: −2 to −26 μm); however, there was no correlation between the magnitude of change induced by myopic defocus and that induced by hyperopic defocus (Pearson correlation coefficient = 0.12, $P = 0.47$).

DISCUSSION

This study found that small but significant bi-directional changes in SFCT were caused by retinal defocus in healthy presbyopic subjects aged 50 to 67 years of age. Significant thickening of SFCT was observed after 20 minutes of retinal exposure to 2.00 D of myopic defocus, and by 60 minutes, SFCT had increased by +10 ± 5 μm. Conversely, significant thinning of SFCT was observed after 20 minutes of retinal exposure to 2.00 D of hyperopic defocus, and by 60 minutes, SFCT had decreased by −10 ± 5 μm. The amplitude of these changes was approximately half those we have reported previously in young adults (thickening and thinning of approximately 20 μm for 2.00 D of myopic and hyperopic defocus, respectively).[10] Defocus-induced changes in choroidal thickness were somewhat unexpected in presbyopic subjects because in developing eyes they have been regarded as indicative of precursor signals to decreases and increases in subsequent eye growth,[15] mediated by changes in the sclera. Because there is little evidence of changes in eye growth in presbyopia, the presence of these sign-of-defocus–dependent choroidal thickness changes suggests either that the sclera in presbyopic eyes no longer responds to these signals, or that the choroidal thickness changes are associated with some other function.

In the present study, we observed a mild/moderate negative correlation between baseline SFCT and age, an association that has been reported previously[34] and that appears to be accounted for by thinning of the large-vessel sublayer (Haller's layer) of the choroid with age, rather than with changes to Sattler's layer or the choriocapillaris.[35] In our study, the choroidal changes induced by defocus amounted to approximately ±10 μm regardless of baseline SFCT (range, 396–117 μm). These changes are relatively small compared with overall SFCT (2%–8%), but as with age changes, they may be restricted to a sublayer of the choroid. A recent study of healthy subjects (n = 1992) from the Beijing Eye Study[36] found that the thickness of the subfoveal small-vessel layer (including the choriocapillaris) was 30.5 ± 9.8 μm, whereas the thickness of the medium- and large-sized vessel layers (Sattler's and Haller's layers) were 91.6 ± 39.0 μm and 155.2 ± 65.7 μm, respectively.[36] The Beijing study subjects had characteristics (age 62.7 ± 9.3 years; SFCT 277 ± 102 μm) similar to the subjects in the present study (age 57.4 ± 4.07 years; SFCT of experimental eyes 226 ± 72 μm), suggesting that the thickness of the choroidal sublayers in our study would be similar. Thus, although the changes of ±10 μm that we observed are modest when compared with the overall choroidal thickness, they are much more significant when compared with the reported thickness of the small-vessel sublayer (approximately 30 μm) or Sattler's layer (approximately 90 μm).[36]

Although the degree of choroidal thinning induced by hyperopic defocus amounted to approximately 10 μm regardless of baseline SFCT or age, the degree of choroidal thickening induced by myopic defocus was weakly and inversely correlated with baseline SFCT. The degree of choroidal thickening appeared to be moderately correlated with age within the age range of our subjects. This was the opposite of the expected result, as our previous study[10] showed a much greater degree of thickening in young adults than found in the older adults of the present study. This suggests that the correlation found within the age group 50 to 67 years does not extend to all ages. The finding that choroidal thickening showed some association with SFCT and with age, but

choroidal thinning was not associated with either SFCT or age, is consistent with previous proposals that choroidal thickening and thinning are mediated by different mechanisms.[37,38]

One consequence of our findings is that uncorrected presbyopia, which results in hyperopic retinal defocus at near, would be expected to cause choroidal thinning during sustained near tasks or while spending time in a near environment. Because choroidal thinning has been associated with reduced choroidal blood flow in healthy subjects,[18] our findings suggest that adults with uncorrected presbyopia who spend prolonged periods engaged in near work may experience reduced choroidal blood flow.

Evidence of a role for choroidal blood flow in the pathogenesis of early AMD has initiated several investigations aimed at discovering drug therapies for increasing choroidal blood flow to prevent progression of the disease in its early stages.[39] Our finding that sustained myopic defocus causes choroidal thickening in healthy adults aged 50 to 67 years, suggests the possibility that blood flow might be increased under conditions of myopic defocus in this group. Whether the findings of the present study hold true in adults with early ischemic retinal disease remains to be ascertained.

There are several limitations to our study. The first is that defocus of only ±2.00 D was investigated. The rationale was that ±2.00 D has been used in previous studies in younger age groups, but it remains unclear whether this is an optimal power to cause changes in choroidal thickness. Of more relevance to this study is whether lesser degrees of hyperopic defocus might still cause choroidal thinning, with the possibility that objects within a normal indoor environment, for example, at 2 m distance (0.5 D hyperopic defocus), might also reduce choroidal thickness. A further limitation is that the recovery time for the choroid to regain its baseline thickness following removal of retinal defocus was not studied, so it is not known how long the effects may last once defocus is removed. Although optical defocus was presented under low light levels (in order to facilitate OCT measures), pupil size was not monitored in this study. It is possible that choroidal thickness changes seen with defocus are also influenced by pupil size, either via effects of blur-circle size on the retina, or possibly via retinal illuminance.

In conclusion, we found that myopic retinal defocus caused thickening, and hyperopic defocus caused thinning of SFCT in presbyopic subjects. Consequently, uncorrected presbyopia, which is associated with hyperopic retinal defocus for near objects, and which is highly prevalent in the developing world, would likely be associated with choroidal thinning and possibly reduced choroidal blood flow with prolonged periods in a near visual environment.

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