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· Investigation ·

Image registration of the human accommodating eye demonstrates equivalent increases in lens equatorial radius and central thickness

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Abstract

● AIM: To compare the results of *in vivo* human high resolution image registration studies of the eye during accommodation to the predictions of mathematical and finite element models of accommodation.

● METHODS: Data from published high quality image registration studies of pilocarpine induced accommodative changes of equatorial lens radius (ELR) and central lens thickness (CLT) were statistically analyzed.

● RESULTS: The mean changes in ELR and CLT were 6.76 μm/diopter and 6.51 μm/diopter, respectively. The linear regressions, reflecting the association between ELR and accommodative amplitude (AA_{ELR}) was: slope=6.58 μm/diopter, r^2=0.98, P<0.0001 and between CLT and AA_{CLT} was: slope=6.75 μm/diopter, r^2=0.83, P<0.001. On the basis of these relationships, the CLT slope and the AA_{ELR} were used to predict the measured change in ELR ($ELR_{predicted}$). There was no statistical difference between $ELR_{predicted}$ and the measured ELR as demonstrated by a Student's paired *t*-test: P=0.96 and linear regression analysis: slope=0.97, r^2=0.98, P<0.00001.

● CONCLUSION: Image registration with invariant positional references demonstrates that ELR and CLT equivalently minimally increase ~7.0 μm/diopter during accommodation. The small equivalent increases in ELR and CLT are associated with a large accommodative amplitude. These findings are consistent with the predictions of mathematical and finite element models that specified the stiffness of the lens nucleus is the same or greater than the lens cortex and that accommodation involves a small force (<5 g).

● KEYWORDS: image registration; accommodation; equatorial lens radius; central lens thickness
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INTRODUCTION

After over 160 years, the mechanism of accommodation is still being examined. The Helmholtz theory predicts that during accommodation all zonular tension decreases causing reduced stability of the whole lens, a large decrease in equatorial lens radius (ELR; >35 μm/diopter) with rounding of the lens and a large increase in central optical power resulting in a shift of spherical aberration in the positive direction. In contrast, the Schachar mechanism of accommodation predicts that equatorial zonular tension increases causing the whole lens to remain stable, a small increase in ELR (≤20 μm/diopter), flattening of the peripheral lens surfaces with simultaneous steepening of the central lens surfaces resulting in a shift of spherical aberration in the negative direction. Both theories predict central lens thickness (CLT) will increase, however, Helmholtz predicts a much larger increase than Schachar. The fundamental differences between these two theories of accommodation are reflected by the magnitude of the change in CLT and the extent and direction of the change in ELR (Figure 1)[1].

It has been difficult to evaluate the mechanism of accommodation by observational techniques. Visualization of the edge of the lens during accommodation is not possible due to the presence of the iris. To overcome this obstacle,

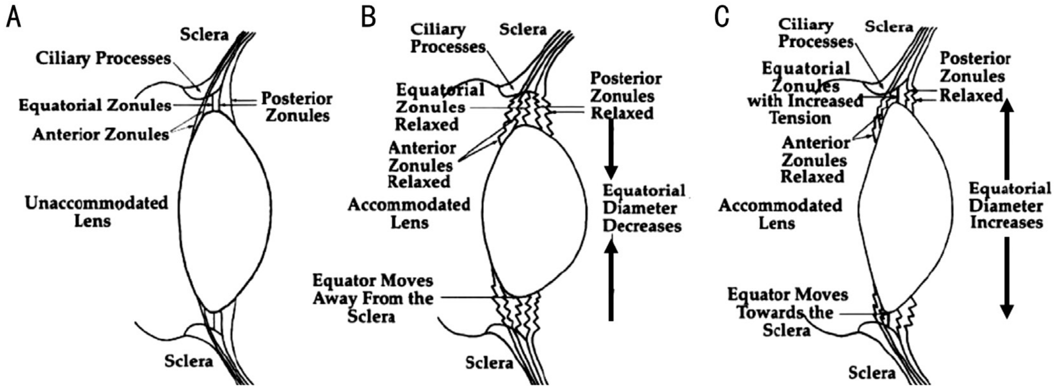

Figure 1 Schematic drawings of the lens according to the two theories of accommodation A: Unaccommodated state, viewing at distance; B: Accommodated states, focusing at near. Helmholtz mechanism of accommodation, note that the equatorial lens diameter decreases; C: Schachar mechanism of accommodation, note that the equatorial lens diameter increases. Reproduced with permission from the American Physiological Society.

the change in ELR following accommodation has been assessed photographically in patients with aniridic eyes and in normal subjects using magnetic resonance imaging (MRI). Unfortunately, the published MRI images in these studies are of low resolution (>100 μm/pixels), and did not include stable unchanging positional references for proper image registration. Even with one eye covered during accommodation, the eye translates and cyclotorts non-randomly inducing systematic bias that confounds data acquisition.

To minimize the effects of motion artifact, image registration is standard practice. It significantly improves measurement accuracy and detection of conformational changes. The advantages of image registration became apparent in ophthalmology when it was incorporated into commercially available optical coherent tomographic instruments designed for examining the posterior segment of the eye. Measurements of the change in retinal nerve fiber layer and central retinal thickness have become more accurate. Detection of subtle retinal pathologies, not visible in the past, are now routinely observed[2-3].

Currently, there is no commercially available instrument that incorporates image registration for assessing the anterior segment of the eye. If compared images are not precisely registered, any resulting observations cannot be assessed for small changes at the threshold required to determine the mechanism of accommodation. Because of the lack of accurate image registration, the literature is replete with exaggerated assessments of accommodative changes in the eye. For example, it has been contended that the cornea changes shape during accommodation. However, with image registration using limbal blood vessels, it has been documented that the cornea does not change shape during accommodation.

Mathematical and finite element analyses have been used to model the mechanism of accommodation. A basic requirement for these analyses is incorporation of realistic material properties, *e.g.*, is the lens nucleus harder (stiffer) or softer than the lens cortex. The physical parameters that characterize these properties of the lens are the elastic and shear moduli. Unfortunately, many published finite element analyses incorrectly assigned a lower elastic modulus for the lens nucleus than the lens cortex based on estimates from Fisher's spinning lens test, which has been shown to be incorrect. Or, by relying on the results from dynamic indentation on sections of previously frozen lenses, which makes the findings flawed because freezing alters the material properties of the lens.

An *in vivo* Brillouin light scattering study demonstrated that the longitudinal modulus, a measure of compressibility, is higher in the lens nucleus than the lens cortex at all ages and that the longitudinal modulus is linearly related to the shear modulus[4]. Consequently, the lens nucleus is less compressible and stiffer than the lens cortex. This is verified by multiple studies including *in vitro* conical probe indentation, shear rheometry, Brillouin light scattering and bubble acoustic radiation force. In addition, from clinical experience with clear lens phacoemulsification in patients <40 years of age, the nucleus has the same or greater hardness than the cortex.

When the stiffness of the nucleus was specified to be the same or greater than the lens cortex in mathematical models, only a small force, <5 g, is required to achieve accommodation. These models demonstrate that the central lens surfaces steepen; resulting in a large increase in central optical power with a very small increase in ELR (≤20 μm/diopter). Simultaneously, there is peripheral flattening of the lens surface with a consequential negative shift in spherical aberration while the whole lens remains stable. Importantly, these models predict that the small increase in ELR will essentially be equal to the change in CLT[1,5].

The purpose of this study is to statistically assess the validity of the mathematical and finite element predictions based upon clinically measured changes in ELR and CLT during accommodation. Data were obtained from published studies of ELR and CLT during accommodation, in which stable positional references for proper image registration were employed.

SUBJECTS AND METHODS

This is a retrospective analysis of data from two accommodation clinical studies that used high resolution techniques with strict image registration criteria. For the change in ELR during accommodation, data from a high resolution ultrasound biomicroscopic (UBM) publication was utilized[6]. For the change in CLT during accommodation, a high resolution, swept-source biometric (Zeiss IOLMaster 700) study of pilocarpine stimulated accommodation was utilized[7]. These studies were designed to provide data acquired by carefully executed image registration achieved with invariant positional references. These are the only two clinical studies in the current accommodative literature in which accommodation was stimulated with pilocarpine and invariant positional references were incorporated for image comparisons. Both of these studies had a small number of enrolled subjects, reflecting the difficulty in obtaining properly registered images (ELR study: n=7[6]; CLT study: n=8[7]).

Equatorial Lens Radius During Accommodation A UBM 50 MHz probe was used to measure the positional change of the lens equator during pharmacologically controlled accommodation in 12 young healthy volunteer subjects (mean age 26y; range: 20 to 34y) with correctable visual acuity of 20/20 and mean near point of 9.5 diopters, which was within normal limits for the 12 enrolled subjects. Tropicamide 1% was used to induce cycloplegia for the baseline measurements. Then pilocarpine 2% was applied to induce accommodation and the near point was measured 1h later with the pupils no smaller than 2 mm to avoid any pinhole effect. The accommodative amplitude was defined as the difference between the pilocarpine and the tropicamide near points. The cornea and sclera were used as non-changing positional references for image registration of the unaccommodated and accommodated images. Seven of the 12 subjects met the strict image registration requirements to be included in the ELR study. Image registration of the cornea and scleral profiles were achieved by obtaining the absolute difference of the superimposed images. Bitmap analysis was performed to ensure that the corneal and scleral profiles were precisely aligned. The identification of precisely aligned images, although not masked, was performed as an independent process, prior to any other comparisons or measurements. The precision of the measurements fell between the time base resolution of the UBM, which was 5 μm, and the pixel size of the image, which was 11.5 μm. The data for the ELR change during accommodation were obtained from the original publication[6].

Central Lens Thickness During Accommodation The data for the CLT change during accommodation was obtained from the original swept-source biometric publication[7]. For inclusion in the CLT study, the subjects had to be aged ≥18y and ≤25y. Each had a normal ophthalmological examination with best corrected visual acuity of 20/20 in the right eye with spherical equivalent refractive error between -5.00 diopters and +2.50 diopters and a cylindrical error <+1.50 diopters.

The following dosing regimen was used to maximize accommodation while minimizing miosis[8]. Phenylephrine does not affect accommodative amplitude[9]. Thirty minutes after instillation of 10% phenylephrine, one drop every minute for five applications in the right eye, the refraction of the right eye was obtained while it was fixating on a non-accommodative target within an auto-refractor. Then the CLT of the right eye was measured using a Zeiss IOL700 Master swept-source biometer. The left eye of the subject was occluded during all measurements. Following these baseline measurements, pilocarpine 4%, one drop every minute times 3, and after 5min phenylephrine 10%, one drop every minute times 5, were instilled in the cul-de-sac of the right eye. One hour later, auto-refraction was repeated and three additional biometric measurements of the CLT were obtained. The change in the spherical equivalent, auto-refraction measurement before and after pilocarpine was defined as the accommodative amplitude.

Foveal registration was determined by magnifying the biometric foveal images 400% and precisely superimposing the post-pilocarpine image on the pre-pilocarpine image. Only 8 of 25 subjects satisfied the inclusion criteria of registerable foveal images, central corneal shifts ≤100 μm and ≥7 diopters of change in accommodative amplitude post-pilocarpine. For enrollment, the foveal images had to be visually registerable by superimposition and the subtracted images had to have a mean gray scale value <25.

Statistical Analysis Descriptive statistics and linear regression were performed to assess the change in ELR and CLT associated with accommodation[10]. This was based upon prior clinical studies that have established a linear relationship between accommodative amplitude and the change in CLT and ELR[11-13]. A zero intercept was used for the linear regressions because any change in CLT only occurs when there is an accommodative change and the P-value of the intercept of the ordinary linear regression was not statistically significant.

Table 1 ELR study[6]

Subject	Age (y)	Iris color	Baseline pupil (mm)	Post-pilocarpine		
				△Pupil (mm)	△ELR (μm)	AA_{ELR} (diopters)
1	29	Blue	7	-2	40	5.5
2	34	Brown	8	-2.5	45	6.0
3	27	Brown	8	-3	43	6.0
4	30	Brown	7.5	-2.5	42	6.5
5	20	Brown	8	-2	66	8.5
6	23	Blue	7.5	-2	66	10.0
7	20	Blue	9	-2.5	58	11.0
Mean	26.1		7.9	-2.4	51.4	7.6
SD	5.3		0.6	0.4	11.5	2.2

ELR: Equatorial lens radius; AA_{ELR}: Accommodative amplitude; △Pupil: Change in pupil; △ELR: Change in ELR; SD: Standard deviation.

Table 2 CLT study[7]

Subject	Age (y)	Iris color	Baseline			Post-pilocarpine		
			SER (diopters)	Pupil (mm)	CLT (mm)	△Pupil (mm)	△CLT (μm)	AA_{CLT} (diopters)
1	20	Blue	1.5	7.2	3.77	-0.1	100	11.25
2	20	Blue	-0.62	8.4	3.59	-1.1	120	15.38
3	20	Green	-4.25	7.8	3.33	-0.1	50	10.50
4	20	Hazel	-0.75	8.3	3.26	-2.5	10	13.12
5	20	Green	-0.37	8.5	3.45	-2.1	110	16.88
6	22	Brown	-3.12	8.9	3.47	-2.5	170	16.25
7	22	Brown	-1.25	7.7	3.45	-1.7	20	8.50
8	20	Blue	-1.37	8.6	3.58	-1.2	70	7.75
Mean	20.5		-1.28	8.2	3.49	-1.4	81	12.45
SD	0.9		1.75	0.6	0.16	1.0	54	3.51

SER: Spherical equivalent refraction; CLT: Central lens thickness; AA_{CLT}: Absolute value of post- minus pre-pilocarpine SER; △Pupil: Change in pupil; △CLT: Change in CLT; SD: Standard deviation.

RESULTS

The mean increase in ELR and CLT associated with accommodation were 6.76 μm/diopter and 6.51 μm/diopter, respectively (Tables 1 and 2).

Linear regression analyses of the changes in ELR and CLT were plotted as two independent linear regressions on the same graph (Figure 2). For the change in ELR, the slope was 6.58 μm/diopter [95% confidence interval (CI): 5.67 to 7.49 μm/diopter], $r^2=0.98$ and the $P<0.0001$, and for the change in CLT, the slope was 6.75 μm/diopter (95%CI: 3.97 to 9.53 μm/diopter), $r^2=0.83$ and the $P<0.001$.

The mean change and slopes of the regression lines for ELR and CLT were essentially the same. Based on this commonality, accommodative amplitude can be used to predict the associated change in CLT or ELR. The CLT slope and the AA_{ELR} were used to predict the change in ELR. No statistical difference was found between $ELR_{predicted}$ ($CLT \times AA_{ELR}$) and the measured ELR as demonstrated by a Student's paired *t*-test: $P=0.96$ and linear regression: slope =0.97, $r^2=0.98$ with $P<0.00001$ (Figure 3).

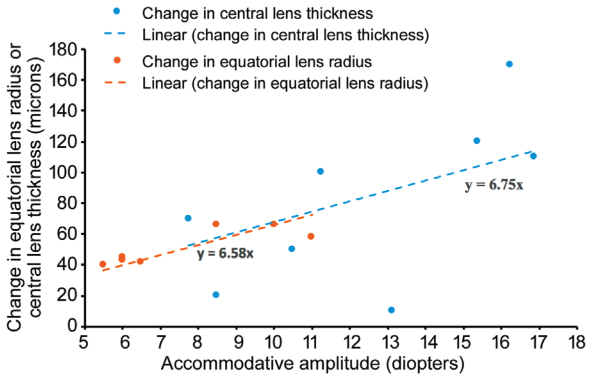

Figure 2 The change in ELR and CLT versus the change in accommodative amplitude for each subject Linear regression lines are shown for ELR and CLT *vs* accommodative amplitude.

DISCUSSION

Statistical analysis of lens changes during accommodation, from the two, independent image registration studies, indicates that for each diopter of change in accommodation there is only a 6.58 μm increase in ELR and a 6.75 μm increase in CLT. Accommodation is clearly a small displacement phenomenon.

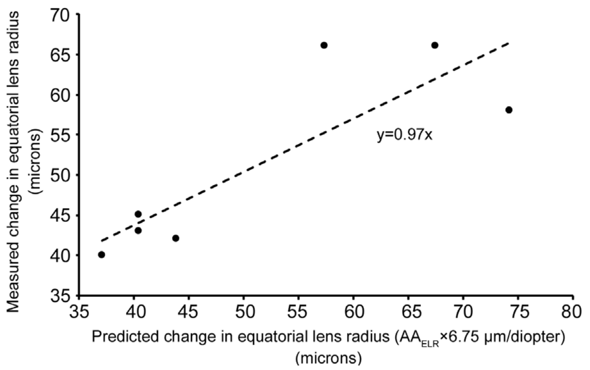

Figure 3 The measured change in ELR versus the predicted change in ELR The predicted change in ELR was obtained by multiplying accommodative amplitude, AA_{ELR} given in Table 1, by the change/diopter in CLT, 6.75 μm/diopter.

To assess the robustness of the analysis of the CLT data, the regression was evaluated with and without outliers. The regression analysis of CLT yielded a slope =6.75 μm/diopter with a 95%CI of 3.97 to 9.53 μm/diopter. The change/diopter of subjects 4 and 6 were both outside this 95%CI. However, when these two subjects were removed from the analysis, the regression yielded essentially the same slope =6.80 μm/diopter. In addition, the median for the subjects was 7.16 μm/diopter. When the two outliers, subjects 4 and 6 are removed from the analysis, the median is identical, 7.16 μm/diopter. Even if only subject 4, the largest outlier, is removed, the median =7.80 μm/diopter and the regression yields a comparable slope =7.64 μm/diopter. These analyses demonstrate that the outliers in the CLT data did not significantly affect the outcome.

Consistent with these observations, a swept-source biometric study of CLT found the accommodative change in CLT was 16 μm/diopter during voluntary stimulated accommodation[14]. In addition, an anterior segment optical coherence tomographic (OCT) clinical study found that CLT changed less than 5% during accommodation[15]. Independently, another OCT study found that the mean decrease in anterior chamber depth for 10 diopters of accommodation was 130 μm. This decrease in anterior chamber depth is directly related to and similar in magnitude to the change in CLT[7].

In further support of these findings, published *in vivo* UBM nonhuman primate image registration studies also demonstrated that accommodation was associated with a small increase in ELR and a large increase in central lens optical power[1]. In addition, symmetrical stretching of the non-human primate lens *in vitro* revealed that in response to a small force, <5 g, an increase in equatorial lens diameter was associated with a large increase in central lens optical power (Figures 7, 9-11 of Ehrmann *et al*[16]).

For the lens equatorial radius to increase, zonular tension must increase. This is caused by contraction of the ciliary muscle. As OCT has demonstrated during human accommodation, the anterior ciliary muscle fibers move toward the sclera, forming a notch in the anterior ciliary muscle fibers (Figure 3C of Ke *et al*[17] and Schachar[18]). A similar outward notching of the anterior ciliary muscle fibers has also been demonstrated during non-human primate pilocarpine stimulated accommodation[1]. This small outward movement of the anterior ciliary muscle fibers causes an outward force, <5 g, to be transmitted through the anterior ciliary body stromal collagen fibers to the equatorial zonules[1]. The small force minimally increases equatorial lens radius, flattens the peripheral lens surface with a consequential negative shift in spherical aberration[19] and increases the stress on the lens capsule[20] resulting in significant central lens steepening associated with only a small increase CLT. Since zonular tension is increased during accommodation, the whole lens remains stable and gravity does not affect accommodative amplitude[1,7,21-22].

The analyses in the present study confirm the predictions of both mathematical and finite element models of accommodation[1]. In order for the models to be valid, the mathematical and finite element analyses must incorporate realistic material properties, with the stiffness of the lens nucleus the same or greater than the lens cortex. That the nucleus must be less compressible and stiffer than the cortex is confirmed by *in vivo* Brillouin light scattering[4] and the gradient refractive index (GRIN) of the lens. The lens refractive index progressively increases from the surface of the cortex to the nucleus. Within the nucleus the refractive index is maximum with a relatively constant value. The lens GRIN is due to the progressive increase in protein concentration from the surface of the cortex to the nucleus. Similar to other protein solutions, the elastic modulus of the lens would be expected to be directly related to its protein concentration. Therefore, it is not a coincidence that the *in vivo* measurement of the longitudinal modulus within the lens increases from a softer periphery toward a stiffer central (nuclear) plateau at all ages[4] just like the lens refractive index changes from a lower index to a higher index with a central (nuclear) plateau. When the stiffness of the lens nucleus is the same or greater than the lens cortex, these models accurately predict the small magnitude of increase in the ELR and CLT associated with accommodation. As further evidence that the designation of lens material properties is critical in finite element analysis, some of the finite element models varied the cortical and nuclear elastic moduli without changing the baseline lens geometry[1]. When the elastic modulus of the nucleus was the same or greater than the cortex, the predictions of these finite element models were consistent with those in the present study.

In contradiction to the results of the present study, clinical studies[10-12] and finite element models[1,23] have found that the zonular tension causes both CLT and central optical power to decrease, that a change in ELR is less than the change in CLT and that changes in ELR and CLT are 3 to 10 times greater than found in the present study. These clinical studies are subject to flawed conclusions, since they did not utilize proper image registration, with invariant positional references for image comparison. Extraocular movements can affect the accurate measurement of ocular parameters during accommodation. Similarly, multiple finite element models were in error because of the incorrect assumption that the lens cortex was stiffer than the lens nucleus.

The present study has limitations. Accommodative amplitude was calculated from the near point in the ELR study and measured with an auto-refractor in the CLR study. However, a study of young subjects[8] demonstrated that following pilocarpine, accommodative amplitude measured with an auto-refractor is comparable to reported near point accommodative amplitude. Clearly, the mean accommodative amplitudes in the ELR and CLR studies were different. This can be attributed to the mean age difference between the studies, the use of tropicamide in the ELR study (which reduced the effect of pilocarpine), the use of phenylephrine in the CLR study (which had no effect on accommodation) and the much higher pilocarpine dose in the CLR study. Although the amplitudes were different in the two studies, this would did not affect the results, since the change in accommodative amplitude is linearly related to the changes in ELR and CLR. As a consequence of the strict image registration requirements, data from only a small number of subjects were available to both the UBM and CLT studies. This small number of subjects is a limitation of the present analysis. Future studies of accommodative lens changes from a large population of subjects are needed, that incorporate high resolution techniques, with automatic registration of the limbal and retinal vessels and fovea/optic nerve to facilitate accurate, precise and repeatable measurements.

In conclusion, for accurate mathematical and finite element modeling of accommodation, the elastic and shear moduli of the lens nucleus must be specified as the same or greater than the lens cortex. Valid measurements in accommodative experiments demand the use of invariant positional references for proper image registration. When these requisite methodologies are employed, as in this analysis of the mechanism of accommodation, large increases in central lens optical power are associated with small similar increases in ELR and CLT. These findings are consistent with the Schachar mechanism of accommodation that the lens forms a "steep profile" in response to equatorial tension similar to other negligibly compressible objects, such as water/gel filled mylar/rubber balloons that have an aspect ratio (minor/major) ≤ 0.6[1].

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REFERENCES

1 Schachar RA. *The Mechanism of Accommodation and Presbyopia*. Amsterdam: Kugler Publications; 2012.

2 Mendez N, Kommana SS, Szirth B, Khouri AS. Structural changes by spectral domain optical coherence tomography in patients with type 1 diabetes mellitus. *J Diabetes Sci Technol* 2015;10(2):271-276.

3 Ramsey DJ, Sunness JS, Malviya P, Applegate C, Hager GD, Handa JT. Automated image alignment and segmentation to follow progression of geographic atrophy in age-related macular degeneration. *Retina* 2014;34(7):1296-1307.

4 Besner S, Scarcelli G, Pineda R, Yun SH. *In vivo* Brillouin analysis of the aging crystalline lens. *Invest Ophthalmol Vis Sci* 2016;57(13): 5093-5100.

5 Wang K, Venetsanos D, Wang J, Pierscionek BK. Gradient moduli lens models: how material properties and application of forces can affect deformation and distributions of stress. *Sci Rep* 2016;6:31171.

6 Schachar RA, Tello C, Cudmore DP, Liebmann JM, Black TD, Ritch R. *In vivo* increase of the human lens equatorial diameter during accommodation. *Am J Physiol* 1996;271(3 Pt 2):R670-R676.

7 Grzybowski A, Schachar RA, Gaca-Wysocka M, Schachar IH, Kamangar F, Pierscionek BK. Mechanism of accommodation assessed by change in precisely registered ocular images associated with concurrent change in auto-refraction. *Graefes Arch Clin Exp Ophthalmol* 2018;256(2):395-402.

8 Grzybowski A, Schachar RA, Gaca-Wysocka M, Schachar IH, Pierscionek BK. Maximum human objectively measured pharmacologically stimulated accommodative amplitude. *Clin Ophthalmol* 2018;12:201-205.

9 Esteve-Taboada JJ, del Águila-Carrasco AJ, Bernal-Molina P, Ferrer-Blasco T, López-Gil N, Montés-Micó R. Effect of phenylephrine on the accommodative system. *J Ophthalmol* 2016;2016:1-13.

10 R Core Team. *A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2018.

11 Neri A, Ruggeri M, Protti A, Leaci R, Gandolfi SA, Macaluso C. Dynamic imaging of accommodation by swept-source anterior segment optical coherence tomography. *J Cataract Refract Surg* 2015;41(3):501-510.

12 Martinez-Enriquez E, Pérez-Merino P, Velasco-Ocana M, Marcos S. OCT-based full crystalline lens shape change during accommodation *in vivo*. *Biomed Opt Express* 2017;8(2):918-933.

13 Ramasubramanian V, Glasser A. Prediction of accommodative optical response in prepresbyopic subjects using ultrasound biomicroscopy. *J Cataract Refract Surg* 2015;41(5):964-980.

14 Schachar RA, Mani M, Schachar IH. Image registration reveals central lens thickness minimally increases during accommodation. *Clin Ophthalmol* 2017;11(9):1625-1636.

15 Moulakaki AI, Monsálvez-Romín D, Domínguez-Vicent A, Esteve-Taboada JJ, Montés-Micó R. Semiautomatic procedure to assess changes in the eye accommodative system. *Int Ophthalmol* 2018;38(6):2451-2462.

16 Ehrmann K, Ho A, Parel JM. Biomechanical analysis of the accommodative apparatus in primates. *Clin Exp Optom* 2008;91(3):302-312.

17 Ke B, Mao X, Jiang H, He J, Liu C, Li M, Yuan Y, Wang J. The relationship between high-order aberration and anterior ocular biometry during accommodation in young healthy adults. *Invest Ophthalmol Vis Sci* 2017;58(13):5628-5635.

18 Schachar RA. Human accommodative ciliary muscle configuration changes are consistent with schachar's mechanism of accommodation. *Invest Ophthalmol Vis Sci* 2015;56(10):6075.

19 Zhou XY, Wang L, Zhou XT, Yu ZQ. Wavefront aberration changes caused by a gradient of increasing accommodation stimuli. *Eye (Lond)* 2015;29(1):115-121.

20 Schachar RA, Koivula A. The stress on the anterior lens surface during human *in vivo* accommodation. *Br J Ophthalmol* 2008;92(3):348-350.

21 Augousti AT, Pierscionek BK. Gravity does not affect accommodative amplitude. *Invest Ophthalmol Vis Sci* 2016;57(11):4570.

22 Schachar RA. Gravity does not affect lens position during accommodation. *Invest Ophthalmol Vis Sci* 2016;57(11):4566.

23 Pour HM, Kanapathipillai S, Zarrabi K, Manns F, Ho A. Stretch-dependent changes in surface profiles of the human crystalline lens during accommodation: a finite element study. *Clin Exp Optom* 2015;98(2):126-137.