ACCOMMODATIVE CHANGES OF THE REFRACTIVE INDEX OF THE CRYSTALLINE LENS IN THE HUMAN EYE

A thesis presented to the graduate faculty of
New England College of Optometry in partial
fulfillment of the requirements for the degree of
Master of Science.

Huayu Chai

May, 2024

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Huayu Chai

This manuscript has been read and accepted by the
Thesis Committee in satisfaction of the
thesis requirement for the degree of Master of Science.

6/4/2024
Date

DocuSigned by:
Ji He
9DAC3830219640A...
Ji Chang He, PhD
Graduate Faculty Advisor

DocuSigned by:
Chris Taylor
8C96C99C286D4CA...
Christopher Taylor, PhD
Thesis Committee Member

DocuSigned by:
ACB7B98939E24C0...
Teng Leng Ooi, PhD
Thesis Committee Member

DocuSigned by:
78A8AD9723D9447...
Thanasis Panorgias, MSc, PhD
Thesis Committee Member

6/4/2024
Date

DocuSigned by:
78A8AD9723D9447...
Thanasis Panorgias, MSc, PhD
Director of Graduate Studies

New England College of Optometry

Abstract

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Huayu Chai

New England College of Optometry, 2024

Purpose: Accommodation is the key to clear vision at various distances, but evaluating accommodative changes in the lens presents challenges due to the difficulties in assessing lenticular parameters. This study aimed to measure the changes in refractive index and lens biometry with accommodation *in vivo*.

Methods: A total of 12 subjects were recruited, but only the right eye data from 12 subjects aged between 22 and 26 were eventually included for data analysis. Spherical equivalent refraction ranges from -4.25 to + 0.50D. An anterior segment OCT (AS-OCT) equipped ray-traceable Scheimpflug imaging (RTSI) system was used to measure lens refractive index and lens biometry during accommodation. A Badal system was used to compensate for refractive error and induce accommodative stimulation of 0D, 2D, and 4D. The pupil was dilated with two doses of phenylephrine for RTSI imaging. The AS-OCT and RTSI images were processed by using a self-developed MATLAB program to trace the light ray and calculate the average lens refractive index (N_{av}), anterior chamber depth (ACD), lens thickness (LT), radius of the anterior lens surface (RALS), posterior lens surfaces (RPLS). A second-order polynomial function (A + B*x

+C*x^2) was later applied to fit the N_{av}, conveying the details of the central-ray refractive index (denoted by 'A') as well as the curvature of the function (denoted by 'C').

Results: As the accommodation stimuli changed from 0D to 4D in 2D steps, the mean N_{av} along the central ray increased from 1.401± 0.009, 1.406 ± 0.013 to 1.414 ± 0.014 accordingly. The mean C value was -0.0009±0.0012 (0D) and decreased to -0.0012±0.0009 (2D) and -0.0015 ± 0.0013 (4D). In the meantime, all lens biometrics changed. ACD decreased from 3.15 ± 0.14mm at baseline to 3.06 ± 0.15mm and 3.01 ± 0.16mm at 2.0D and 4.0D accommodation, respectively. RALS reduced from 10.72 ± 0.81mm to 9,64 ± 0.69 mm and 8.89 ± 0.68mm. LT increased from 3.72 ± 0.18mm to 3.83±0.21mm and 3.90 ± 0.20 mm with every 2D step. RPLS was 6.04 ± 0.22mm, 5.90 ± 0.32mm, and 5.80 ± 0.21mm at 0D, 2D, and 4D accommodative levels, respectively.

Conclusion: With accommodation, the N_{av} of the lens increases and undergoes more rapid changes from the center to the periphery across the equatorial axis, but substantial individual variations were revealed. At the same time, both the anterior and posterior surfaces of the lens steepen, while the lens thickens accompanied by shallowing of the anterior chamber.

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Chapter 1

INTRODUCTION

1.1 Accommodation

Accommodation is a dynamic process facilitated by the lens for maintaining a clear vision while adjusting the position of gazes from far to near. However, understanding the accommodation process has come a long way with the joint efforts of many scientists and philosophers.[1] Although the mechanism of accommodation still needs further investigation, Helmholtz proposed the most widely acknowledged theory. He suggested that the accommodation is induced by the ciliary muscle contraction and the reduction of tension applied by surrounding zonules to the lens, causing the increase of the lens thickness and the decrease of the radius of the curvature of the lens surface.[2,3] Therefore, the lens power increases. Later, based on Helmholtz's theory, Gullstrand suggested an 'exact eye' model to describe the accommodative changes of the lens quantitatively.[4] In this model, the relaxed and accommodated lens powers were provided. The new features in his model included (a) a two-shell structure to depict the lens; (b) a forward movement of the lens and a shallowing of the anterior chamber depth; (c) an intracapsular accommodation mechanism, emphasizing the capsular role in accommodation. More recent research has dug further and worked on establishing sophisticated eye models and lenticular biomechanics to help understand the physiological changes to the lens and predict the optical performance during the accommodation process.[5,6] Hence, there is a need for more accurate data collection and consideration of the physiological and anatomical features of the eyes, e.g., retina curvature and lens asphericity.

1.1.1 Change in the lens geometry

During the last forty years, various advanced techniques have been invented and employed to access the lens biometrics and visualize the accommodative changes of the lens, including OCT, magnetic resonance imaging (MRI), and Scheimpflug photography. Dubbelman et al. used Scheimflug imaging and found that the changes inside the lens were more due to the nucleus while the thickness of the cortex remained constant[7], and Xiang et al. SS-OCT with a capability to deeper imaging depth found a similar result.[8] During accommodation, the anterior surface moves forward, and the curvature decreases. The posterior surface will move backward, and the curvature steepens, thus causing increases in lens thickness and shallowing in anterior chamber depth (ACD).[8] Although researchers all agree that lens biometry changes during accommodation, subtle variations are noticed between measured parameters. For example, Gambra analyzed the results from 3-D OCT, and showed that the fluctuations of accommodation were driven by dynamic changes in the lens surfaces, particularly in the posterior lens surface.[9] In his research, he obtained a change rate of 0.20 mm/D for the radius of posterior curvature. With OCT, Xiang found that the posterior crystalline lens radius of the curvature decreased by an average magnitude (related to accommodative stimuli) of 0.09 mm/D.[8] With MRI, Kasthurirangan[10] found an average decrease of 0.58 ± 0.3mm in the radius of the posterior surface with accommodation, which is larger than Xiang's findings but smaller than Gambra's results.

1.2 Lens refractive index

The human lens takes up approximately one-third of the power of the whole eye when no accommodation is needed, and it can provide up to 10D accommodation for young eyes. One major determinant of the lens power is the refractive index (RI), which depends on the inner structure of the lens. The crystalline lens has a lamellar structure with two major sections: the center nucleus and the peripheral cortex.[11] After birth, the crystalline lens is left with a monolayer of epithelial cells on the anterior pole, and the cells that have the mitotic ability in the germinative zone undergo continuous division and differentiation[12] Divided cells migrate inwards, simultaneously losing all their organelles, including the nucleus, and extending anteriorly and posteriorly. Consequentially, they turn into fiber cells and are tightly wrapped around the old lens fibers, accounting for lens growth throughout the life span. This pattern leads to the declination of the refractive index from the central nucleus to the peripheral cortex.[13]

Postnatally, the formation rate of new layers drops dramatically but the lens is still growing, and the refractive index is changing. By age of 6, the lens still hasn't achieved the peak index found in adults. Moreover, as mentioned above, since the mature secondary fiber cells lost their organelles, the turnover of lens proteins is disabled. In this sense, once the lens fiber is formed, it will last for a lifetime but gradually lose its water content. Therefore, the lens is not a structure with two distinctly different homogenous refractive indices but rather forms a gradient inside.[14] During accommodation, lens shape changes, undoubtedly leading to the redistribution of intracellular molecules and potentially the average refractive index change.

1.2.1 Change in refractive index with accommodation

One of the major challenges in experimental studies is the direct measurement of the lens. Various designs and advanced imaging techniques have been employed to overcome this

challenge. OCT is a widely used modality in lens studies. De Castrol[15] enucleated eyes from cynomolgus monkeys and only maintained the anterior segment structure to simulate disaccommodation by fixing eyes to stretchers. They also found a constant refractive index with accommodation. Another group of researchers studied isolated mouse lenses removed from their eyes. They found a genetic difference in the refractive index[16]. We have to consider the inter-species variability, but also provide a great insight into the genetic role of the lens refractive index. Although the consensus has been reached that the isolated lens is considered as consistent as a full-accommodated lens within the eyes, they are facing challenges, which are the potential tissue damage like the ruptured capsule and whether it could truly represent the in vivo state even with the stretch mimicking ciliary muscle activity. Besides, whether and how the animal experiments can be extrapolated to humans is a conundrum. Also donated eyes but from humans, Uhlhorn[17] with customized OCT found that the full-accommodated lens has an average refractive index of 1.408 at 589 nm and a peak refractive index in the nucleus closer to 1.420. Later, De Freitas et al. applied the OCT system in vivo for three subjects, and the average RI was 1.41, 1.43, and 1.38 at 835nm, respectively.

Using MRI research, Kasthurirangan[18] measured RI in vivo and found that the central refractive index is 1.409, which agrees with Uhlhorn's study. Their results also showed that RI would stay constant with accommodation. Jones et al. [19] used isolated lenses and found the central RI was 1.4181 ± 0.075 and the surface RI was 1.37 ± 0.0039. The difference between Jones' study and Uhlhorn's study seems small, but if the assumed index is 0.001 in error in OCT measurement, the error in the estimated lens thickness will be about 3 μm. While this may seem small, it is of about the magnitude that is found by OCT for the changes in the total axial length of the eye when it accommodates. Later, the same group conducted the in vivo experiments and

found a decrease in the central refractive index with accommodation. So far, no agreement on the refractive index has been reached, even with the same imaging tools.

Theoretical models take a holistic view of ocular function optically. Besides the Gullstrand eye model mentioned above, substantial schematic eye models incorporating accommodative features have been proposed. To introduce lens accommodation ability into eye models, their features must be quantified by numerical methods. However, different models adapt to different values, with the refractive index being an important parameter. Gullstrand used 1.386 and 1.406 for the cortex and nucleus for both unaccommodated and accommodated states. Le Grand built 1.42 for nonaccommodative RI and 1.427 for accommodated RI into his model. [20]

The debate on the refractive index of the lens is longstanding. Most studies that evolved around the refractive index can be divided into theoretical and experimental categories, but they complement each other. We are trying to fit our findings into an applicable model, but in reverse, the model can benefit further research experimentally and clinically

1.3 Statement of the problem

Knowing the refractive index of the lens, together with other lens biometry, is crucial for determining the power of the whole eye. Having a better understanding of accommodative changes qualitatively and quantitively in the crystalline lens plays a vital role in many aspects, such as assisting in the determination of the axial length increase as a contributor to myopia development. Hughes et al. found myopic children had a significantly greater accommodation-induced axial elongation than nonmyopic children at 3, 6, and 9 D accommodation stimuli with IOL master. By Swept-source OCT, Shoji[21] found that the axial length independently contributed to the shape of the lens. However, the commercial instrument assumes the same refractive index

for different accommodation states, which could lead to pseudo-axial elongation and inaccurate measurements.

From previous studies, each type of equipment alone has the limitation in revealing the actual value of lens RI. The Scheimpflug imaging system diverges from traditional imaging systems by altering the geometric relationship between the lens plane and the image plane. Instead of keeping them parallel, the lens is tilted in relation to the image plane. This deliberate tilt allows for a sharp focus on planar subjects rather than just a single point, such as a transverse section of the anterior segment of our eyes. Additionally, before the light beam hits the lens, it travels through the cornea, which can cause the bending of the light at two interfaces where the cornea is in contact: the air and aqueous humor. Therefore, the two types of distortion necessitate appropriate corrections to be applied to the Scheimpflug image to ensure the right measurements.

A ray tracing method was used by applying Snell's law, which involves the lens refractive index to correct image distortion. Therefore, to derive the posterior lens shape, an assumption regarding the refractive index of the lens was required to process the image. However, the assumption of the lens refractive index can introduce measurement errors in the posterior lens shape. On the other hand, if Scheimpflug imaging is used to measure the refractive index of a lens, the lens thickness or posterior lens shape must be known for image processing. In previous studies, lens thickness was indirectly calculated from other measurements, such as eye’s axial length combined with refraction measurements. However, other measurements still suffer from the influence of the lens refractive index; therefore, the indirectly derived lens thickness might not be accurate. Thus, the derived lens refractive index could also be affected by measurement errors.

MRI images show different contrasts based on the density of nuclear spins of protons within a tissue. Subjects are usually instructed to lie supine within the MRI machine and view the near and far targets through a hole reflected back from a mirror angled at 45 degrees. The approximate time of acquiring an image is 2 minutes, , so it's necessary to consider that the subjects have to refocus after every blink throughout the imaging process and the motion artifacts it might cause. Besides, accommodation typically occurs under natural viewing conditions, where subjects are seated upright. The supine position can induce eye rotation, thereby causing lens tilt which requires applying algorithms to estimate the degree of rotation.

MRI does not directly measure the refractive index of the lens; rather, it measures the water content of the lens. The local refractive index is calculated assuming that it is proportional to the corresponding water content. In addition, the resolution of MRI is low compared with that of optical imaging techniques; therefore, MRI is not a highly accurate method for testing lens refractive index.

OCT is a quick, noncontact, and noninvasive imaging modality that has been used to image lens dimensions and access lens refractive index. An OCT image is formed by interference of the test light reflected from the lens surfaces with the reference light. The measurements directly derived from the OCT image are the optical path lengths between the anterior and posterior lens surfaces. A lens refractive index must be assumed to derive the true lens dimensions from these optical path lengths. On the other hand, if true lens thickness can be independently obtained by using other methods, it is possible to derive the average lens refractive index from the optical path values.

Both OCT and Scheimpflug imaging have limitations in accessing the refractive index of the lens when used alone. However, a novel technique combining ray-traceable Scheimpflug

imaging with the AS-OCT system successfully measured the radial refractive index, the lens thickness, and the posterior lens surface of the human eye in vivo. This technique, therefore, provides an interesting method to access the accommodation response in the lens. This study aims to measure accommodative changes in the refractive index of the lens and the lens shape for a group of young adults by using the new technique.

Chapter 2

Methods

2.1 Participants

A total of 20 subjects were recruited. Eight were excluded due to the difficulty of obtaining the image of the back of the lens while maintaining the response to keep the target clear. Thus, a total of 12 subjects aged between 22 and 26 were eventually included, and the average spherical equivalent refraction was -4.25 to +0.50D. There were 10 females and 2 males in the study.

2.1.1 Inclusion Criteria

Refractive error was screened using an autorefractor to determine if a subject was eligible for the study. To be eligible for the study the subject's non-cycloplegic objective refraction (measured with the autorefractor) must have an equivalent sphere in the range from -8.00D to +0.50 D. Additionally, the cylinder must be less than or equal to 1.50 D in each eye. The subjects could not have a large amount of anisometropia (i.e., the difference in spherical equivalent between OD and OS had to be less than 1.00D.) Finally, the best corrected monocular VA using the ETDRS chart must be 20/20 or better in each eye.

2.1.2 Exclusion Criteria

Additionally, the subjects were asked to fill out an information sheet that included their systemic and ocular history. Subjects with a history of ocular pathology, ocular injury, or ocular surgery were excluded from the study. The subject could not have any lid, pupil, or infections in either eye. The patient could not be aphakic in either eye. Additionally, the subject could have no history of any ocular condition that could affect the retinal image (ex. cataracts, vitreous hemorrhages, and retinal diseases). Strabismus or amblyopia in either eye was excluded from the study. The subject could not be using medication or eye drops that affect accommodation and pupil size. The subject could not be a current rigid contact lens wearer or Ortho-K wearer. Subjects could not exceed myopia greater than -8.75 D in each eye and cylinder greater than 1.50 D in each eye. Subjects could not have a systemic disease that could affect the eye, such as diabetes or HIV. Finally, the age of the subjects had to be between 18 years old to 30 years old.

2.2 Scheduling

Subjects were asked to participate in the study at NECO for one session of two hours to complete the experiment. All procedures took place at the New England College of Optometry.

2.3 Informed Consent

To be enrolled, each subject read, understood, and signed the Statement of Informed Consent (see Appendix A) before enrollment into the study, and a witness must sign the documents, as must the investigator or a designee. The subject was given a copy of the signed documents.

2.4 Case History

A limited case history (see Appendix B) was taken to ensure the subject meets the inclusion and exclusion criteria. We also inquired about eye strain and headaches in the case history form, as these symptoms are most commonly associated with patients experiencing accommodative and convergence dysfunction.[22] None of our participants reported those symptoms to us.

2.5 Apparatus

A slit-lamp platform was used to mount the AS-OCT scanning probe. Figure 1 illustrates the principal sketch of the AS-OCT (red channel) equipped RTSI system (red- and blue channels), where the same illumination source, that is, the super-luminescent light emitting diode (SLED), is shared for both AS-OCT and RTSI systems. The peak wavelength of SLED is 840nm with a bandwidth of 50nm (IPSDD0808, InPhenix Inc, CA, USA). Then a dichroic mirror (DM) (DMSP805R, Thorlabs Inc, NJ, USA) is used to reduce the noise light to each system since it can reflect more than 90% for wavelengths longer than 820nm and transmit more than 90% for wavelengths shorter than 790nm.

The main components of the RTSI system include the illumination light shared with the AS-OCT system, an SI lens (L3), and a CCD camera connected to a computer. The camera lens was set at 45° sideway from the optical axis of the illumination channel along the vertical axis, so it takes the RTSI image of the eye at the horizontal section across the pupil center. Since the RTSI system shared the same illumination light as the AS-OCT system, both systems image the exact same section of the eye. For the RTSI imaging, the light beam was scanned at 9Hz, which

makes the ray-to-ray distance of 0.11mm. So, according to this setup, about 54 rays could be imaged in the lens for a 6.0mm pupil. The RTSI image was captured by a high-speed and high-resolution CCD (Raspberry Pi HQ camera module) through the OBS studio software on the computer.

The angle of the CCD surface normal is not set at 45° from the optical axis of the SI lens, as in the case of the conventional SI setup, because the magnification of the RTSI camera is not 1, which means the lateral magnification is not equal to longitudinal magnification, and thus the best image will be on a plane with an angle different from the conventional 45°. The angle for the best image plane could be derived by taking a ratio between the lateral and longitudinal magnifications. In this study, the angle between the SI lens's optical axis and the CCD surface's normal was about 22°.

The AS-OCT system has 24,000 A-scans per second, a 12.00mm scan depth and an axial resolution of ~10 μm. To compensate for the drop in the signal-to-noise ratio with image depth, two reference arms were used alternatively to shorten the image depth in each arm. Two images were acquired separately with these two arms. The two OCT images can be merged accurately into one cross-sectional image of the whole anterior segment of the eye.

To stimulate accommodation for the same eye, a visual stimulation channel with a Badal system (BDS) (green channel) is employed, and the details are described in the previous study.[23] BDS consists of two lenses (L5 and L6), which were so arranged that lights from the accommodative stimulation target (ST) formed an image by the lenses L6 and L5 at the focal plane of the lens L5. The image of ST was movable with respect to the lens L4. A transparent slide was printed as the ST and conjugated to the retina. The ST can be divided into two sections.

The lower section features a ruler-like structure with notches separated by 1mm increments. The upper section presents targets with numbers that increase in size from left to right.

2.6 Procedure

For each subject, only the right eye was dilated with two doses of 2.5% phenylephrine at 10-minute intervals and then examined within a two-hour session. Prior to the beginning of our image acquisition, the case history form and consent form were provided to ensure that they met the inclusion and exclusion criteria and fully understood the operation of our experiment. Besides that, auto-refraction and Lenstar measurements were also scheduled to verify their refraction and ocular biometrics.

After the preparation, the subject was asked to sit in front of our slit-lamp-mounted examination system with the chin and forehead rest. The room light was dimmed. The 840nm AS-OCT system was co-axially aligned with the RTSI shown in Figure 2-2. At the beginning of the test, the Badal system was adjusted to align with the subject's far point. The subject's task was to fixate on the ST with the right eye while the left eye was patched. When the AS-OCT system was aligned with the cornea vertex and the RTSI system was in good focus, four image acquisitions were performed for both systems. Then, the fixation target in the Badal system was pushed 10mm and 20mm forward from the original position to induce 2D and 4D accommodation separately, and the same image acquisition process was repeated.

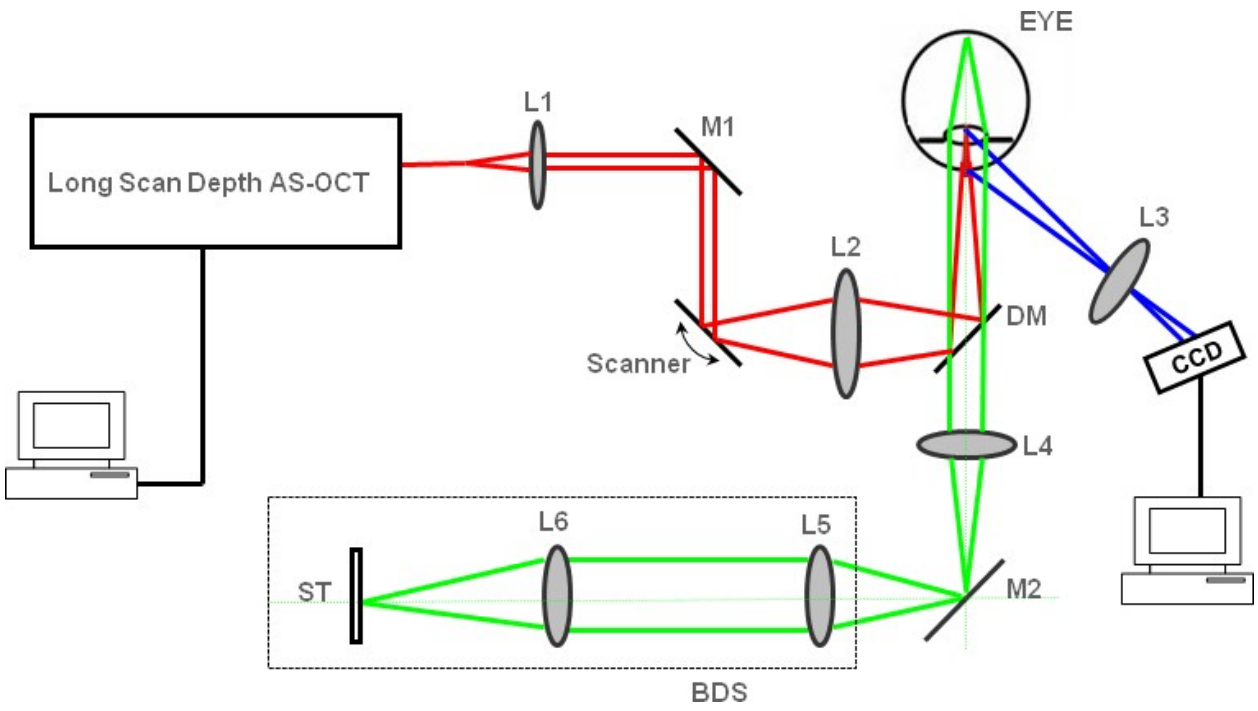


Figure 1 Principal sketch of the optical coherence tomography systems equipped with a ray-traceable Scheimpflug imaging system

2.7 Image Process

OCT and RTSI images were obtained from the horizontal scan. Both AS-OCT and RTSI images were processed using customized MATLAB programs in which the boundaries of the cornea and lens were semi-segmented to obtain the morphometric dimensions of the eye. To process the AS-OCT image, an algorithm was developed based on Snell's law to optically correct image distortion and yield the values of the ocular morphometric dimensions in three steps: (1) the positions of all interfaces in the original AS-OCT image were semi-segmented, (2) the surface extraction algorithm was used to produce a set of positions for well-defined interfaces,

and (3) the refraction correction algorithm was applied using Snell's law ray tracing algorithm. The RTSI image was first corrected for its projection error, and a program based on Snell's law was then used to correct the refractive distortion in the RTSI image.

During the image processing of the posterior lens surface in both the AS-OCT and RTSI measurements, a N_{av} of 1.40 was used as the first trial to calculate the lens thickness. Because the true Nav for a real eye might differ from the trial Nav, the lens thickness calculated from the AS-OCT measurement could differ from the lens thickness from the RTSI estimate. The difference between the two lens thicknesses was then used to guide the adjustment of the trial Nav to reach a minimum difference of less than 0.001 mm. The estimates of the Nav and the posterior lens surface position were then fitted. After deriving the N_{av} and the position of the lens surface for each ray across the pupil, a second-order polynomial function was applied to fit the Nav across the lens diameter. This fitted N_{av} was a function of the distance from the lens center.

2.8 Data Analysis

Four measurements were averaged to derive the mean estimate for each session, and the means from the two sessions were used to calculate the refractive index and anterior segment parameters. Statistical analyses were performed to test the significance of the measurements.

Chapter 3

Results

3.1 OCT and Scheimflug images of the anterior segments of the eye

OCT and Scheimflug images were collected in all subjects at 0-4D (every 2D step) accommodative demands. Figure 2-1 shows examples of uncorrected OCT images for subject #1 for accommodative demands at 0D(left) and 4D(right). OCT scans taken from 2 different foci have been manually merged for representation purposes. Figure 2-2 shows the RTSI images for the same subject for accommodative demand at 0D (left) and 4D(right). It's apparent from the images that the front surface is moved forward while the posterior surface is moved back.

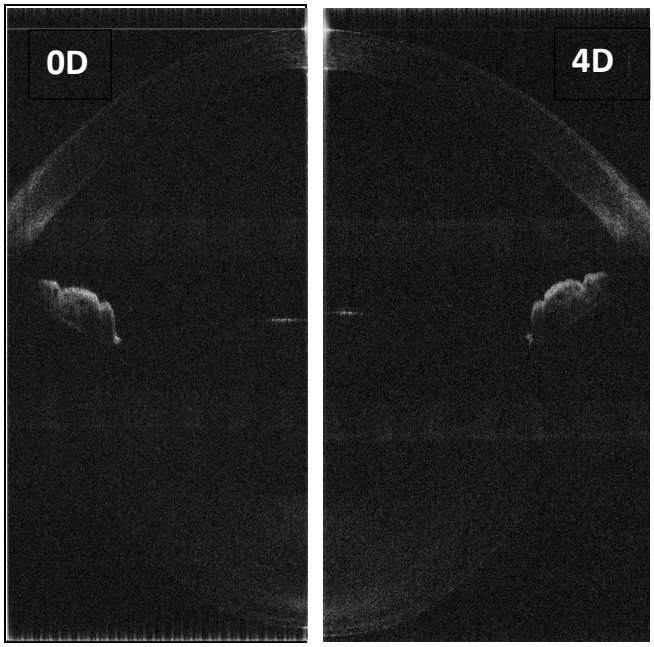


Figure2-1. Raw AS-OCT images at 0D (left) and 4D (right) accommodative level

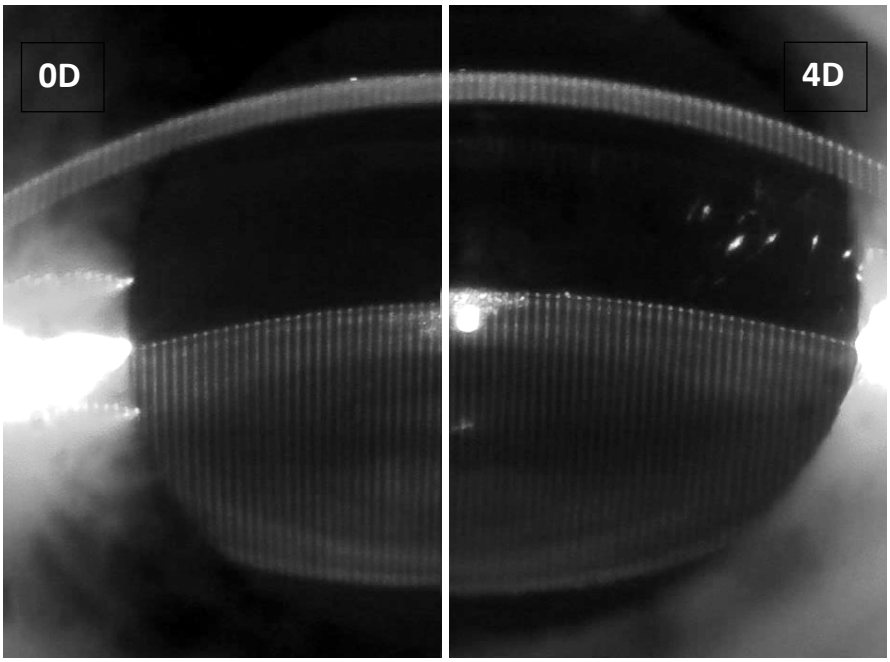


Figure 2.2. The RTSI images at 0D (left) and 4D (right) accommodative level

3.2 The Average lens refractive index change

The N_{av} under each accommodation level is plotted below in Figure 2.3. From 0D to 4D accommodation, the mean N_{av} along the central ray for this group of subjects was found to change from 1.401±0.009, 1.406±0.013 to 1.414 ±0.014 and varies in the range of 0.013. One example of refractive index distribution across the horizontal axis for one subject is shown in Figure 2.4. As the zero point in the x-axis corresponds to the lens vertex, it has the highest refractive index value, and the refractive index gradually decreases towards the periphery. The lens refractive index was fitted into a second-order polynomial function ($A + B*x + C*x^2$), where 'A' represents the refractive index of the central ray, and 'C' indicates the degree of curvature. As shown in Figure 2.5, the mean C value was -0.0009±0.0012 for 0D

accommodation. It decreased to -0.0012±0.0009 and -0.0015±0.0013 when the accommodation demand was at 2D and 4D separately.

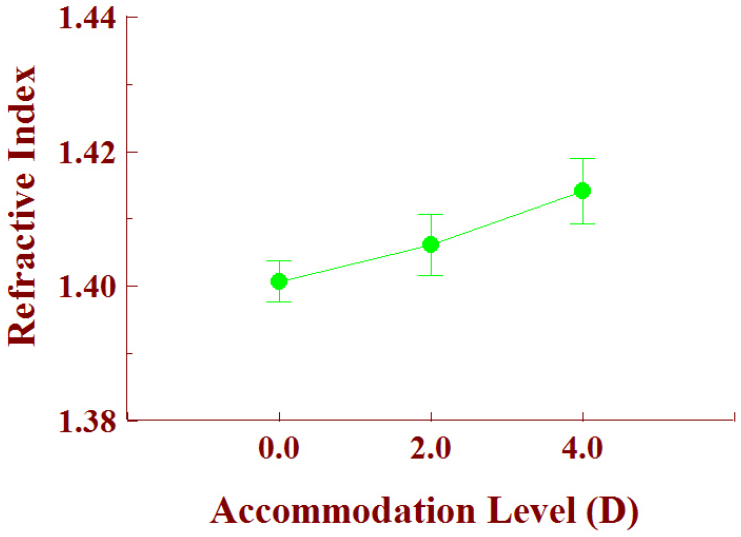


Figure 2.3. The changes in mean N_{av} with accommodation

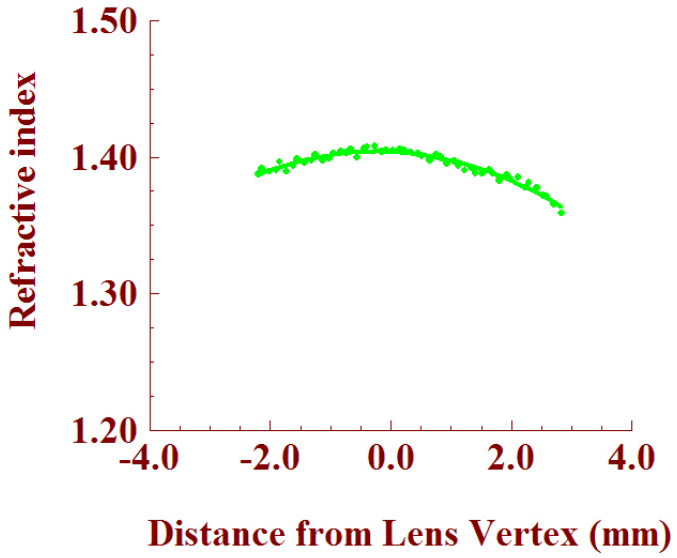


Figure 2.4. The average refractive indices along the lens diameter

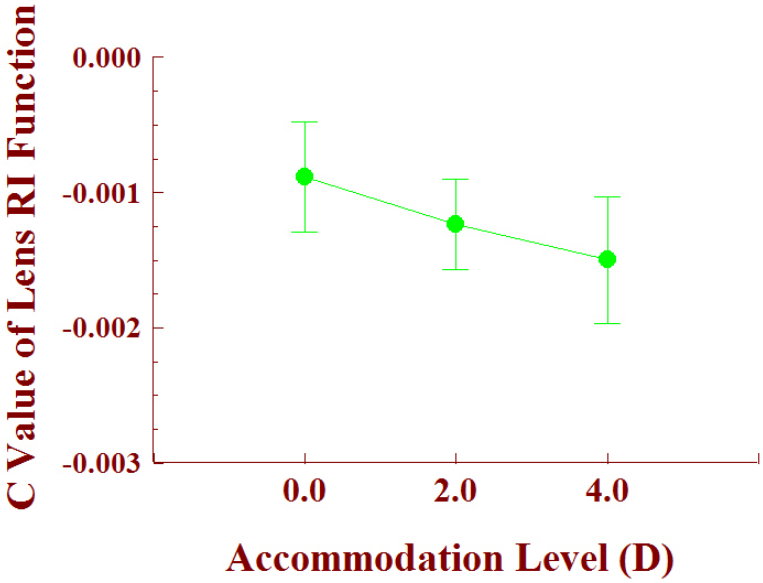


Figure 2.5 The C value of the lens refractive index function at different accommodation levels

3.3 Mean accommodative changes of lens shape and position

The average anterior chamber depth (ACD) was 3.15±0.14mm at the baseline and slightly decreased to 3.06±0.15mm and 3.01±0.16mm at 2.0D and 4.0D accommodation, respectively. The radius of the anterior lens surface (RALS) at baseline was 10.72±0.81mm and became 9,64±0.69mm and 8.89±0.68mm at 2.0D and 4.0D.

Once the corrected average refractive index is applied to each lens, we can obtain a precise quantitative profile of the lens shape parameters. Figure 2.6 (b) shows the change in average lens thickness and radius of the posterior surface of the lens. The central lens thickness (LT) increased from 3.72 ±0.18mm to 3.83±0.21mm and 3.90±0.20mm in response

to the accommodation change in every 2D step. The radius of the posterior lens surface (RPLS) was 6.04±0.22mm, 5.90±0.32mm, and 5.80±0.21mm at 0D, 2D, and 4D accommodative levels, respectively. Table 1 presents the result of changes in anterior segment biometry altogether at three different accommodative stages and the rate of change from 0D to 4D.

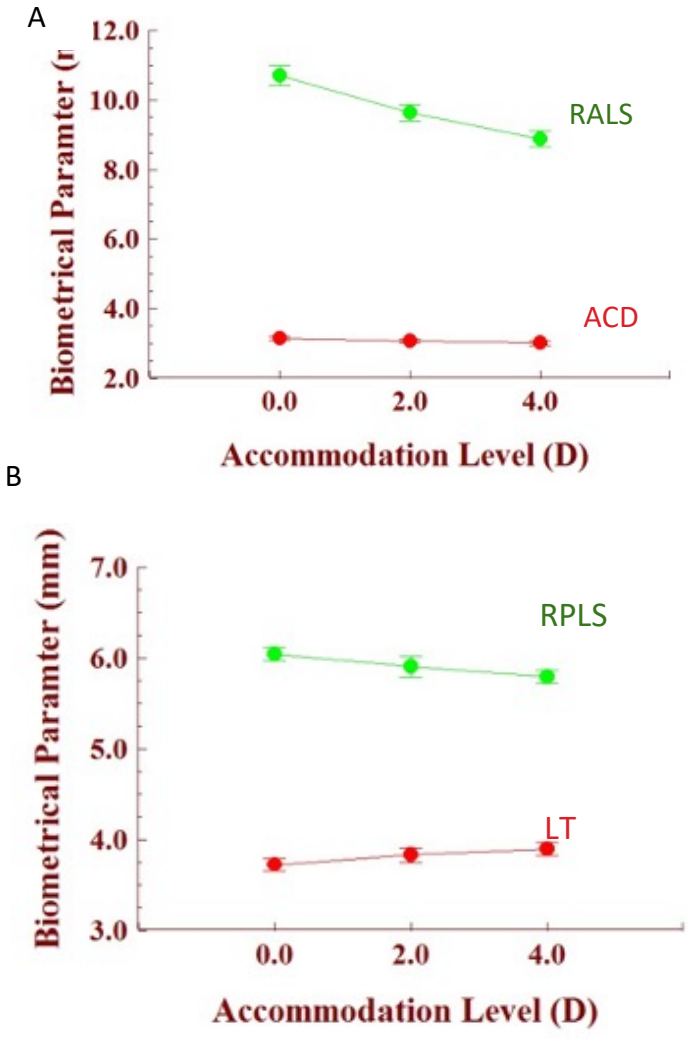


Figure 2.6 The changes in the lens (A) the changes in anterior chamber depth (red line) and the radius of the anterior lens surface (green line) for different accommodation stimuli

(B)The changes of lens thickness (red line) and radius of the posterior lens surface (green line).

	Resting state (Mean ± SD)	**2D accommodation** (Mean ± SD)	**4D accommodation** (Mean ± SD)	**Rate of change**
Refractive index	1.401 ± 0.009	1.406 ± 0.013	1.414 ± 0.014*	0.0032/D
'C' value	-0.0009 ± 0.0012	-0.0012 ± 0.0009	-0.0015 ± 0.0013*	
Anterior chamber depth	3.15 ± 0.14mm	3.06 ± 0.15*	3.01 ± 0.16*	-0.035 mm/D
The radius of anterior lens surface	10.72 ± 0.81mm	9.64 ± 0.69mm	8.89 ± 0.68mm*	-0.456 mm/D
Lens thickness	3.72 ± 0.18mm	3.83 ± 0.21mm	3.90 ± 0.20mm *	0.045 mm/D
The radius of posterior lens surface	6.04 ± 0.22mm	5.90 ± 0.32mm	5.80 ± 0.21mm*	-0.06 mm/D

Table 1.1 Changes in the anterior segment biometry with accommodation

Chapter 4

Discussion

Accommodation is well-recognized as a crucial player that aids the eye in changing the refractive power on a short-term basis. Scholars have strived for decades to resolve the challenge of achieving precise measurements to describe lenticular changes, but accurate *in vivo* experimental data are very rare. In the present study, by combining the AS-OCT with ray-traceable Scheimpflug imaging methods, we were able to successfully assess the refractive index of the lens and lens biometrics *in vivo*. We found that N_{av} increased with accommodation, but a huge inter-person variation was noticed. Additionally, with the accommodation level increasing, the 'C' value became increasingly negative, suggesting that the N_{av} underwent a more rapid change along the equatorial axis. We also found that both the radius of the anterior surface and the posterior surface of the lens steepened and thickened with accommodation. However, the alteration in the radius of the anterior surface was more pronounced than its posterior counterpart. The observed trends of all the morphological changes in the lens agree with the existing literature.[24,25] However, many studies on the lens suffer from a small sample size or focus solely on either the refractive index or lens shape. Additionally, different accommodative demands were used across studies. Furthermore, each method has shortcomings. For instance, even though MRI is considered a distortion-free method, it's difficult to utilize it on the anterior surface of the lens due to its overlap with the iris. Consequently, most measurements are from alternative techniques such as OCT and

Scheimflug image, or ultrasound biomicroscopy.[25–27] These methodological differences pose challenges in comparing the findings directly in a quantitative way.

The ACD results are generally less controversial. In this study, the change rate per diopter is 0.035 mm/D, which aligns with most previous studies.[24,28] However, Ramasubramanian's study used ultrasound biometry and reported universally higher measurements, including an ACD changing rate of 0.049 mm/D.[29] Regarding RALS, we found at the relaxing state, it was 10.72 mm ± 0.81mm, and the changing rate was 0.456mm/D. Although the changing speed is similar to Xiang's study, specific values under each accommodative state are generally smaller than those of other studies, including Xiang's. These discrepancies might be explained by the differences in population characteristics, imaging techniques, and sample sizes.

LT and RPLS usually require a relatively accurate RI when optical algorithms are involved in obtaining the values. After applying the individualized N_{av} on each subject, we found that the increase in LT magnitude exceeds the decrease in ACD, which is consistent with the findings from Martinez-Enriquez's research[24], where custom spectral OCT was used to reconstruct the RI map in 3D dimension. The results indicated that the posterior surface of the lens moved toward the vitreous upon accommodation. However, a few years ago, Pérez-Merino[25] used OCT-based lens topography and found that the rate of ACD decrease and LT increase were the same. The underlying reason for the discrepancies in LT and RPLS may be stem from the fact that most OCT equipment employs a uniform refractive index for all individuals.

In another study that aimed to investigate internal changes in the eyes of myopic children, Hughes et al.[30] theorized that the accommodation-induced axial length elongation could contribute to myopia development. However, the commercially available instrument they used was the IOL Master, which, as mentioned before, uses the same RI to apply to all. Concerning the critical role the RI plays in determining the axial length, the finding is questionable.[31]

The measurement of RPLS is under much more debate, as demonstrated in a study conducted by Koretz[32] , which sought to compare MRI and Scheimpflug data. Despite the excellent statistical agreement found between the ACD, LT, and RALS, the RPLS was less well-defined in the Scheimpflug images. The lack of definition may come from the need to input the refractive index to derive the RPLS from Scheimflug images, and potential errors in the refractive index could also confound the evaluation of the posterior surface. For RPLS, our reported rate of change (0.06 mm/D) showed a substantial difference from what was reported in Sheppard's (0.15 ± 0.23 mm/D)[33], Dubbelman's (0.13 mm/D)[34], and Martinez-Enriquez (0.22mm/D)[24].

The average refractive index value showed greater differences among different research. Our study found that the mean average RI along the central ray increases with the accommodation from 1.401±0.009, 1.406±0.013 to 1.414 ±0.014. Nevertheless, with MRI, Kasthurirangan[10] suggested that the refractive index of the lenticular central region does not change significantly with accommodation but rather stays constant at 1.409 ±0.008. On the contrary, Jones et al. found a decrease in the central refractive index but no statistical difference using MRI. A previous study conducted by Hermans [35] and his group utilized

Schiemflug imaging and found that the equivalent refractive index does not change with accommodation.

We also found that the average RI decreased as the distance of the ray from the lens vertex increased. However, unlike other studies utilizing MRI[18,19,26], we did not observe a central reflective index plateau. Nevertheless, these MRI studies reported that the diameter of the central area of the plateau decreases accommodation. These results agree with our finding based on the C value decreasing to more negative values as the accommodation levels go up, indicating that the N_{av} profile will have much more rapid changes.

One of the limitations of our study is that the precision of this study is constrained by the axial resolution of the OCT system and our subjects' responses to the dilating agent and ability to accommodate. We strive to find a balance between maintaining the accommodative power for each participant and keeping the pupil as large as possible. According to previous studies, the ciliary muscle, which controls accommodation, has both sympathetic and parasympathetic components. And by using phenylephrine, a sympathomimetic drug, has no effects on patients' accommodation response at least up to 4 diopters[36–39]. However, after applying phenylephrine, we noticed the presence of accommodation-induced pupil constriction because the pupil size was fluctuating in the process, which limited our ability to obtain the full extent of the posterior surface of the lens with RTSI, which is also indicative of the accommodation oscillation. However, during the daytime, the pupils are relatively small; even though we don't have the subjects' pupils dilated to a full extent, the average refractive index should predict the optical performance very well.

A second limitation that needs to be considered is that 2-D OCT imaging can also introduce errors. The image plane needs to be carefully aligned with the corneal reflex every time to ensure the same slice of lens cross-section image is acquired throughout the test. The same person processed the front and back of lens OCT images to minimize the inter-examiner variations. Furthermore, the lens is not homogenous and has a gradient refractive index along the visual axis. In our study, we were able to measure the refractive index from the central to the periphery across the lens; however, more advanced techniques and eye models are required to calculate the changes in the lens refractive index from front to back.

In summary, using an OCT-equipped ray-traceable Shiemflug imaging system, we have derived the refractive index for a group of young adults who can accommodate at least 4D with no effort. The average refractive index increases with accommodation, and the decreasing pattern of refractive index from the lens vertex along the equatorial axis occurs faster when the eyes are under greater accommodative stress. Yet, notable variation was observed across individuals. Meanwhile, the changes in the anterior segments are consistent with those in previous studies: RALS and PALS decrease with accommodation alongside observations of thickening in the lens and shortening of the ACD.

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Appendix A: INFORMED CONSENT FORM

Title of Project: ACCOMMODATIVE CHANGES OF THE REFRACTIVE INDEX OF THE CRYSTALLINE LENS IN THE HUMAN EYE

Principal Investigator: Ji-Chang He, Ph.D.

Participant's Printed Name: Huayu Chai, Xiang Zhang

Introduction

We invite you to volunteer for our study. This is being conducted by some of the New England College of Optometry (NECO) faculty. This study will examine structures of the eye, including cornea and lens gradient refractive index (GRIN) in accommodated eyes. We encourage you to discuss any questions about this study with us. Take your time to make your decision. If you decide to participate, you must sign this form.

There will be up to 20 normal subjects aged 18 and over but under the age of 30 in the study. Exclusion criteria are as follows: history of ocular pathology, eye injury or surgery, present ocular medications, cataracts, or other media opacity, fixational instability (e.g., nystagmus), or restricted eye movement. The equivalent sphere must be between or equal to +0.50 D and -8.00 D, and the cylinder must be less than or equal to 1.50 D in each eye. In addition, we plan to exclude users of rigid contact lenses.

Purpose of the Study

The purpose of the research is to examine what role crystalline lens plays in accommodation and explore the underlying mechanism by measuring lens GRIN and relevant parameters.

Procedures of the Study

You are required to come to Dr. He's optical laboratory at NECO for approximately 2 hours to participate in this study.

You will be asked to:

- Tell us general information about yourself, your eye history, and your health history.
- Be screened for eligibility to participate in the study. Spherical equivalent refraction must fall within the range from +0.50 to -8.00 D sphere and up to 1.50 D cylinder.
- Be as still as possible when the investigator is taking measurements from your eyes.

We will do the following with you:

- We will collect data from your right eye with an optical coherent tomography (OCT) equipped with a Ray-tracing Scheimpflug imaging (RTSI) optical system. The machines WILL NOT touch your eyes or cause any harm to your eyes.
- This procedure will take approximately 2 hours to complete.

- The 2.5% phenylephrine will be used for pupil dilation.

Description of Tests

Lens GRIN test: The lens GRIN and lens shape will be imaged with the OCT and RTSI system. You will be seated and positioned at a chinrest and forehead restraint in front of the device and asked to fixate various targets. Multiple pictures will be taken of your eye, in various positions of fixation.

Risks and Discomfort

You will experience minimal risk throughout the study. The risks involved are minor. Though highly unlikely, you may experience eye strain, dry eyes, watery eyes, tired eyes, blurry vision, and headache. These symptoms will resolve over about one hour with rest.

Potential Benefits

You will not benefit directly from the research. However, it may affect the future of eye research and help develop a treatment to prevent or intervene with the development of presbyopia and cataracts.

Compensation

You will receive $15 of reimbursement for the one hour of participation in this research experiment.

Drop Out or Early Withdrawal from the Study

You may choose to drop out of the study at any time with no consequences physically, emotionally, socially, or legally.

Privacy and Confidentiality

Your medical records will be kept as confidential as possible within the limitations of state or federal law.

If you decide to be a subject in this study, both demographic and technical information about you will be collected. Demographic information will include, but will not be limited to such things as, your name, date of birth, address, gender, ethnicity, etc.

Technical information will include elements of your personal health history and results of all the tests and measurements related to the study. This information is collected in order to determine whether you are eligible to be a subject in the study; that is, to meet the inclusion/exclusion criteria, and, if so, to allow the study investigators to gather the data from you that is necessary to support the study's purpose. The results from all of the subjects in the study can then be analyzed to develop the study's conclusion

All study-related information will remain confidential with the investigators and administrative staff at NECO. However, any regulatory authority or the Institutional Review Board may inspect the investigator's records pertaining to you as a subject. But they too should maintain confidentiality.

The result of the study may be used in health care education or in scientific publications. Neither your name nor any information that specifically could identify you will be used in any such presentation or publication.

Personal Health Information

Your personal health information (PHI), as related to this study, is described in the "Confidentiality" section above. If you sign this informed consent form, it grants permission to use your PHI as specifically discussed. This permission does not have an expiration date, but you can cancel it at any time by writing to the principal investigator(s) at the address below.

If you cancel your permission to use your PHI after you have started the study but before your participation is generally concluded, you will not be allowed to continue in the study, and the investigators will stop collecting data. However, they retain the right to use the information they have already collected to evaluate the study's results.

Privacy Practices and Your Rights

Healthcare providers are required by law to keep private any health information that identifies people. Federal Privacy Regulations require that you authorize the release of any health information that may reveal your identity. The persons entities that you authorize to use or inspect all of the health information generated or collected about you during this study include the study doctor(s), the study staff, the institution, and the study Sponsor (or the authorized agents of the sponsor), the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS) agencies, and the institutional Review Board. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. Once your personal health information is released, it may be re-disclosed, at which point your health information may no longer be protected by federal privacy regulations.

You may ask the study investigator to see a copy of your PHI related to the study. You may also request the study investigator to correct any information that you feel is incorrect. However, you may have to wait until the end of the study to see your records so that the study can be organized and conducted scientifically.

You must be given notice of your investigator's privacy policies. The Confidentiality, Personal Health Information, and Privacy Practices and Your Rights sections of this form fulfill this requirement.

Unless you authorize the use and disclosure of your personal health information, you cannot participate in this research study. If you refuse to give your authorization, your medical care will not be affected.

Voluntary Participation/Withdrawal from the study

Participation in this study is voluntary and you may withdraw at any time. Refusal to participate or withdrawal from the study will not involve any penalty or loss of benefits to which you are otherwise entitled. If you are a student at NECO, your participation or withdrawal will not affect your position at the College. We will disclose to you in a timely manner any significant new findings that may influence your willingness to participate in this study.

The investigators or the Institutional Review Board may terminate your participation in the study (with or without your consent) if it is believed to be in your best interest.

Questions

Any questions you may have about this study or about your rights as a study participant may be directed to the investigator, Dr. Ji-Chang He (617 318 8993). You may also contact Dr. Alan Lewis (617-448-7576), Chairman of the Institutional Review Board of the New England College of Optometry, 424 Beacon Street, Boston MA 02115

When results of a research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. We will not release any information about your research involvement without your written permission. If you sign a release of information form, for example, for an insurance company, we will provide the information.

All your personal information will be kept confidential. Your identity will not be revealed except through numbered codes. Your identity by numbered code and any computer data related to you will be password-protected and stored on the investigator's computer. Only personnel involved directly in the study will have access to it. All written data will be stored in a locked cabinet.

Voluntary Consent

I have read this consent form and I understand it. Any questions concerning this study have been answered to my satisfaction and I have been offered a copy of this consent form. By signing this form, I voluntarily agree to participate in this study.

I understand the potential risks and benefits involved in this study and that I may withdraw at any time without penalty. I understand that I must notify the study investigator immediately if I notice any medical problems that may be related to my participation in the study. I also understand that my participation in the study may be terminated at any time if the investigators or the Institutional Review Board feel that it in my best interest or if I fail to keep the required study appointment(s) or follow the study instructions.

I understand that the study records may be inspected by the Institutional Review Board.

Subject's Name (PRINT)

Signature of the Subject Date

Signature of the Witness Date

Signature of the Investigator Date

APPENDIX B: CASE HISTORY FORM

DEMOGRAPHIC

Subject's Name: _____
Last First

Subject's ID:_____ **Age:**____ **Date of Birth:** _____/_____/____
Month Day Year

Gender (Please Circle): M / F

OCULAR HISTORY

Date of last complete eye examination: __/ _____ / _____
Month Day Year

History of Present Illness (Please check all the symptoms the subject is currently experiencing)**:**

☐ None	☐ Headaches	☐ Eye injuries
☐ Double vision	☐ Dizziness	☐ Eye surgeries
☐ Loss of vision	☐ Eyestrain	☐ Lazy eye
☐ Gritty or sandy feeling	☐ Eye patch	☐ Eye turn

Ocular Diseases (Please list all the ocular diseases the subject currently has)**:**

_____

_____

_____

History of Ocular Correction:

Have you ever wore:

a. Rigid Gas Permeable Lenses? No Yes From _____to_____

b. Orthokeratology Lenses? No Yes From _____to _____

Current Contact Lenses
Prescription: OD _____

OS _____

CL
Replacement Schedule: ☐ Daily ☐ Bi-weekly ☐ Monthly ☐ Conventional
(Please place and check for the current lens replacement schedule)

CL Brand: _____

Wearing Schedule: ___hours/day; ___days/week

The date that the current contact lenses were prescribed: _____/_____/_____ **By**: _____
Mon Day Year

MEDICAL HISTORY

The date of last medical examination: _____/_____/_____ **By**: _____
Mon Day Year

Review of Health (Describe any systemic diseases the subject currently has)**:**

_____

_____

_____

MEDICATIONS

List of Current medications/supplements

_____ _____ _____

ELIGIBILITY

Exclusion List

- Ocular Pathology
- Eye injury or surgery (e.g. LASIK)
- History of any systemic disease that can affect the eye (e.g., Diabetes, HIV)
- Use of medication or eye drops that affect accommodation and pupil size
- Pupil or lid abnormality or infection in either eye
- Aphakia in either eye
- Any ocular condition that may affect the retinal image (e.g., vitreous hemorrhages, retinal diseases).
- Strabismus or amblyopia in either eye
- Rigid contact lens wearer
- Refraction is hyperopic (more than +0.50D, or myopic greater than -8.00 D, and/or cylinder greater than 1.50 D in each eye.
- Best corrected monocular visual acuity worse than 20/20 using the ETDRS chart

Screening Rx: _____

Eligible _____Yes __No

Signature:_____ Date:_____