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Eye Shape Using Partial Coherence Interferometry, Autorefractometry and SD OCT

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Abstract

Purpose—Peripheral refraction and retinal shape may influence refractive development. Peripheral refraction has been shown to have a high degree of variability and can take considerable time to perform. SD OCT and peripheral axial length measures may be more reliable, assuming that the retinal position is more important than the peripheral optics of the lens/cornea.

Methods—79 subjects right eyes were imaged for this study (age range: 22 to 34 yr, refractive error: −10 to +5.00.) Thirty deg SD OCT (Spectralis, Heidelberg) images were collected in a radial pattern along with peripheral refraction with an autorefractor (Shin-Nippon Auto-refractor) and peripheral axial length measurements with partial coherence interferometry (PCI) (IOLmaster, Zeiss). Statistics were performed using repeat measures ANOVA in SPSS (IBM), Bland-Altman analyses, and regression. All measures were converted to diopters to allow direct comparison.

Results—SD OCT showed a retinal shape with an increased curvature for myopes compared to emmetropes/hyperopes. This retinal shape change became significant around 5 deg. The SD OCT analysis for retinal shape provides a resolution of 0.026 diopters, which is about ten times more accurate than using autorefractometry or clinical refractive techniques. Bland-Altman analyses suggest that retinal shape measured by SD OCT and the PCI method were more consistent with one another than either was with AR.

Conclusions—With more accurate measures of retinal shape using SD OCT, consistent differences between emmetropes/hyperopes and myopes were found nearer to the fovea than previously reported. Retinal shape may be influenced by central refractive error, and not merely peripheral optics. Partial coherence interferometry and SD OCT appear to be more accurate than autorefractometry, which may be influenced other factors such as fixation and accommodation. Autorefractometry does measure the optics directly, which may be a strength of that method.

Keywords

myopia; emmetropization; retinal shape; SD OCT; peripheral refraction

The increase in myopia, both in the United States and worldwide, calls for increased study on the causes and potential methods of prevention.¹⁻³ Emmetropization appears to be highly associated with optical defocus during development.⁴ Essentially, the eye attempts to

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optimize vision by adjusting its length to the focal point of the eye's optics. These concepts have been demonstrated in chick and multiple mammal models, including primates.⁵⁻⁸ Compensatory eye growth appears to be locally controlled within the retina, since there are normal growth responses in animals when their optic nerves transected.⁹

Peripheral refractive error, which can provide a growth or stop signal, has been shown to influence refractive development, although the reliability of some of the first experiments has been questioned.^{10,11} Individuals with hyperopic peripheral refractive error across the horizontal visual field have been shown to be at a significantly higher risk of developing myopia. This peripheral hyperopic defocus in myopes has been demonstrated with a number of different techniques including autorefraction (AR), Hartmann-Shack aberrometry, retinoscopy, photorefraction, partial coherence interferometry (PCI), and magnetic resonance imaging.¹²⁻¹⁹ Over 60 papers have been written on peripheral refraction/retinal shape.²⁰ Hyperopic peripheral refractive error may be one indicator for myopia progression, as it would provide a continuous hyperopic signal that would allow eye growth past the optical length for achieving focus at the fovea.

Two of the more studied modern methods of measuring peripheral changes are PCI, and AR. PCI images have been sequentially taken off axis up to 30 deg, demonstrating that the retina is less oblate for myopes compared to emmetropes.^{16,20-23} However, there may be optical limitations of the experiments outside of 30 deg.²³ The more prolate retinal shape was associated with those likely to progress in myopia.²⁴ Obviously, PCI only measures the length of the eye, while AR is a combination of the anterior optics of the eye and retinal position. The current prevailing view, both for central myopia and peripheral refraction, is that the retinal position with respect to focus is the primary cause of refractive error. If that is the case, peripheral PCI and AR would be largely equivalent. There are potential confounding effects between these two devices though, such as what depth in the retina the two devices measure from (i.e. from the anterior limiting membrane or from the photoreceptor layer) and potential errors due to the presence of higher levels of astigmatism in off-axis autorefraction.

Though many studies have measured peripheral refraction and retinal shape, most have focused on the horizontal plane. The studies that have examined the vertical plane have had mixed results. One study found that the inferior retina was relatively shorter in length, which corresponded to a relative hyperopic superior field in myopes relative to hyperope.²¹ The inferior retina in the same study showed no difference though the study only went out to fifteen deg. Others have shown relative myopia in the vertical meridian regardless of central refractive error.^{13,25}

There are multiple drawbacks to some of these methods of measuring peripheral differences, even though clear-cut individual differences have been demonstrated. First, the process generally is time consuming for the subject as it requires multiple fixation points or requires the device itself to rotate around the subject. As such, any system is then dependent upon how reliable the subject is at fixating. Research grade systems do exist to partially take care of the time and fixation problem by having scanning systems, though subject fixation can still vary.²⁶ Accommodation can also cause problems in AR and Hartmann-Shack based

systems which require cycloplegia to control.²⁸⁻³⁰ Finally, the data collected on many of these devices can have errors due to the location of the reflection off the retina in the axial direction, i.e. whether the reflection is off the photoreceptor/RPE interface or from the Inner Limiting Membrane (ILM),^{31,32} Thus, these drawbacks could obscure small but important differences between subjects. The lack of sensitivity for small changes could occur particularly for retinal locations that have large changes over a small retinal distance, such as locations nearer to the fovea.

In this paper, we compare a new method of collecting retinal shape data that uses Spectral Domain Optical Coherence Tomography (SD OCT) to methods previously used to demonstrate myopic changes in retinal shape. SD OCT controls for many of these problems as it allows for direct depth knowledge of the retina, using a diffraction limited laser spot that is minimally affected by accommodation, and offers high levels of lateral measurement. The retinal shape that we report is not necessarily the true retinal shape but rather the shape from the optical path length obtained from the SD OCT which is a combination of anterior segment optics and retinal position. This method allows us to measure much closer to the fovea with less variability. Thus, we also show that many retinal shape differences between myopes and emmetropes occur much closer to the fovea than previously shown. This method finding will help determine the potential effects of retinal shape on myopia development for more as opposed to fewer peripheral locations. This information may clarify whether myopia development mechanisms are dominated by rods, cones, or specific neural processes, and also the role of retinal regions nearer to or farther from the fovea dominates eye growth. Further, by using a technique that needs only a small sample size per group, the effects of environment and genetics can be more readily incorporated into the smaller studies. Finally, we examine the vertical and oblique angles (45 and 135 deg). The potential effects of aberrations beyond sphere, including individual differences in astigmatism or higher order aberrations, can eventually be incorporated into models of myopia development with small sample sizes. This will allow the study of unique groups of patients or individuals with unusual refractive errors.

METHODS

Informed consent was obtained after a full explanation of the procedures and consequences of the study. This research followed the tenets of the Declaration of Helsinki. The research was approved by the institutional review board (IRB) at Indiana University. All subjects signed informed consent forms.

Seventy-nine healthy subjects (ages 20-34 yr, mean = 26.7 yr) participated in this study. All subjects received a complete eye examination, including dilated fundus examination. All subjects had best corrected visual acuity of 20/20 or better. Any subjects with evidence of retinal pathology or systemic disease were excluded from this study. Spherical equivalent refractive errors ranged from +2.00 D to -10.00 D; mean = -2.69 D with astigmatism less than -2.00 D when referenced to the spectacle plane (mean astigmatism = -0.60 D). Central axial length measurements of each eye were made using an IOL Master (Carl Zeiss Meditec, Dublin, California) and were used to recalibrate for lateral magnification, as described previously.³³⁻³⁴ Only the right eye of each subject was tested in this study, although

extensive control conditions with left eyes indicated that the results were not due to asymmetries in the instrumentation. For data analysis, subjects were divided into two refractive groups based upon spherical equivalent. The groups were emmetropes/hyperopes (from -0.75 to $+2.00$ diopters, mean = 0.16 diopters, $N=34$), and myopes (-1.00 to -10.00 diopters, mean = -4.59 diopters, $N=45$.)

To obtain information about the retinal shape, infrared (870 nm) spectral domain OCT (SD OCT) imaging was performed, providing high resolution, cross-sectional measurements of the posterior pole (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) (Fig. 1). The axial and lateral resolutions of the SD OCT are approximately 7 μm and 14 μm , respectively. One eye of each subject was aligned to the instrument to achieve a bright, horizontal image of the b-scan and the S/N of at least 10. As the system is telecentric, the *en face* image provides a good target to allow the operator to achieve good pupil centration and focus. Thirty deg images in a radial star pattern were acquired with the SD OCT centered at the fovea for each subject, using the manufacturer supplied eye tracking feature (automatic real time, ART).²² For the purposes of this experiment, only the images along the 180, 135, 90 and 45 deg meridians were analyzed. Comparisons with AR and PCI were only analyzed along the 180 meridian. To reduce speckle noise in the SD OCT images, each b-scan was created by averaging 20 frames. The system aligns all images using true x, y, and rotation alignment which prevents artificial flattening and other artifacts. Figure 1 illustrates the segmentation and retinal profile for two subjects.

Peripheral refraction measurements were taken using a Shin-Nippon Open Field Autorefractor SRW-5000 (Shin-Nippon, Tokyo, Japan). Subjects viewed a 20/60 letter “E” target viewed through a Badal Optometer set for infinity. Using a similar Badal Optometer and data collection, peripheral partial coherence interferometry data was collected using the IOLMaster (Carl Zeiss, Oberkochen, Germany). Both Badal Optometers were capable of rotating, which allowed the subject to change fixation up to 30 deg across the horizontal field. The Badal Optometers were external devices with the target “E” aligned to the measurement axis of the instrument when the target is at 0 deg rotation. Figure 2 shows a schematic of the Badal system and a photograph of the system on the IOLmaster. Measurements were limited to within the central ± 15 deg in 5 deg steps to allow comparison with the SD OCT data.

All b-scan images were exported as tiff files for further image processing, as previously described with custom software, (Matlab, Mathworks, Natick, MA).³⁵ To segment the cross-sectional images obtained from SD OCT, the posterior boundary of the RPE/Photoreceptor Outer Segment layer (OS) was segmented manually and read into additional custom software developed for this project (Matlab). As another control, two graders each segmented a set of five images. The manual segmentation of the RPE/OS interface had a test/retest repeatability of approximately 7 microns both between operators and within individual operators (Fig.3). An argument could be made that the superficial border of the OS may be a better measure, as it is where the phototransduction begins and may be closer to the cone apertures. However, the thickness of this layer varies significantly across the retina due to differences in OS length at the fovea vs. the periphery, and the overall quantal catch by the cones is potentially better characterized by quantifying their outer border

location. Retinal shape was then determined as the change in position from a flat plane from the center of the fovea.

As a control condition, we also investigated the effect of the SD OCT scanning through an axial location other than the nodal point of the eye. A series of images was taken for five subjects, acquiring the images at the maximum and minimum depth position allowed. In other words, the image was acquired as far in front and behind the nodal point as possible. While measurements from the maximal distance from the nodal point were measured, they account for less than a 5% difference from the average retinal shape. In addition, all data collected on subjects used to compare methods or subjects was aligned to the best of the operator's ability with the center of the capture screen to further reduce this error.

Following segmentation, a second custom Matlab program was developed to localize the fovea by measuring the change in sign for the first order derivative of the ILM. Otherwise, the location of the fovea would vary across subjects according to fixational differences, and the meridian data would have been influenced by the mislocalization of the fovea. This location was then used as the axis point for the peripheral measures of retinal shape. Tilt was calculated from the slope of the best fit line to the RPE shape. The tilt was then used to correct the retinal shape taken from the RPE/cone photoreceptor interface, as any tilt may induce a false asymmetry. The tilt of the retina in the SD OCT image can come from a number of sources. First, different angles between center of optics for the eye and the center of the fovea, typically called angle alpha, can induce these tilts in SD OCT data, which would not be a source of error due to the eye. A second source of error can come from acquiring the image while outside the center of the pupil, which would be an artificial source of error. Unfortunately, this technique can not differentiate between these two sources. To determine the magnitude and potential effects of tilt errors, multiple retinal images were acquired of each subject by inducing maximum tilt in different directions. After correcting for tilt using the slope of the RPE/OS, the average difference was approximately 7 microns, suggesting that tilt induces no change in the measurable curvature of the border between two layers on SD OCT, or retinal shape, as it is within our ability to segment that layer. Axial length was then used to correct for lateral magnification effects.³⁴

After correcting for tilt, the retinal shape in microns was calculated from the junction of OS and then converted into diopters by assuming 300 microns per diopter. This was done to allow comparisons between other techniques. Retinal shape was then taken at ± 14 deg along each meridian at 1 deg intervals of eccentricity, for both the nasal and temporal retina. This area of analysis was chosen as there is a possibility of image loss in some subjects outside of ± 14 deg that would make segmentation unreliable. In addition, only up to 10 deg nasal retina was analyzed due to the presence of the optic nerve. Data at the edge of the nasal retinal meridian was not analyzed due to individual differences in the shape of the optic nerve heads of individuals and for influences such as tilt of the nerve head, which are prevalent in myopic subjects.^{36,37} Also, the optic nerve head has no photoreceptors, and is not involved in the emmetropization process.

All statistics were performed using SPSS (IBM, Armonk, NY) by using repeat measures ANOVA, Bland-Altman analysis, and multivariate regression, to compare between

refractive groups. ANOVA was chosen with refractive error as the classifying variable, so that we could perform powerful, parametric statistics. This allows relatively small sample sizes to be used, while reaching statistical significance. This statistical method, along with relatively low variability of the measures with SD OCT, allowed analysis near the fovea. The analysis did not use linear regression of the results of one method on another because all three methods produced independent variables, and none would be considered as the dependent variable. Thus, partial correlation analysis of the three types of results from the different refractive techniques was not performed.

RESULTS

Figure 3 shows the data from five subjects, demonstrating the intra-grader reliability of segmentation for the OS/RPE interface using SD OCT. The 95% confidence interval for repeatability for this layer was around one pixel or 7.7 microns. This would translate into a resolution of approximately 0.026 diopters. It would be nearly a tenfold improvement from the traditional resolution of refractive techniques at 0.25 diopters. Even at the maximum difference between graders, it was only two pixels or 0.052 diopters of resolution which exceed other refractive techniques.

Figure 4 shows the regression (1A) and Bland-Altman (1B) plots comparing PCI and autorefraction for 10 deg temporal retina. This region is outside the fovea, where peripheral measurements of PCI and AR have been taken previously by other studies, but not in the retinal region (nasal retina) where variability in the optic nerve head size and position across subjects would influence relative retinal shapes. The two measures were correlated ($R^2 = 0.203$, $P = 0.005$, difference 95% confidence interval = 0.41 diopters). Again, the PCI and SD OCT were converted to diopters by using 300 microns per diopter. Figure 5 shows the same plots for PCI and SD OCT. These two measures were the least correlated between the three ($R^2 = 0.106$, $P = 0.03$, difference 95% confidence interval = 0.49 diopters). Autorefraction compared to the other two measures showed the greater variability. SD OCT and PCI (Fig. 6) were the most correlated ($R^2 = 0.4928$, $P < 0.000$, difference 95% confidence interval = 0.48 diopters.) Using an F-test, ($F = 1.43$) the R^2 was significantly different for the SD OCT/PCI data ($F = 3.65$) compared to the PCI/AR (F value = 1.42) and the SD OCT/AR (F value = 0.92).

Figure 7 shows the difference in retinal shape for SD OCT between the myopic and emmetropic/hyperopic group across the horizontal, vertical, and two oblique retinal planes. The myopic group showed greater curvature of the retinal shape than the emmetropic/hyperopic group in all four planes, which was statistically significant ($P < 0.0001$). The difference between refractive groups, from the fovea to more eccentric locations, became statistically significant at 7 deg on average, using the Student T-Test. Seventy-seven percent of the myopic subjects exhibited greater curvature of the retinal shape than the upper 95% confidence interval of the emmetropic/hyperopic group at 14 deg, i.e. the greater curvature seen on SD OCT is typical among myopic subjects. The coefficient of variation, which is the standard deviation normalized by the mean magnitude of the effects, examines whether variability between groups is actual variability or due to changes in the mean of a population (i.e. a larger mean would have larger potential variability. Using an F-test to test (F -statistic

cutoff = 1.84), the coefficient of variability was only significant within ± 4 deg, which was not significant for curvature change. All other locations had non-significant differences in variability between myopes and hyperopes/emmetropes.

DISCUSSION

It is not surprising that the SD OCT and PCI measures were the most correlated with one another, as PCI is essentially a B-scan from an OCT over a longer range to incorporate interference patterns from the lens. SD OCT, when done correctly, scans through the nodal point with a series of B-scans to create the composite image. It is important to note that the PCI technique uses dual-beam interferometry rather than the single beam used in the SD OCT. All subjects were tested in all conditions without cycloplegia, which may account for some of the variability in the AR data. The SD OCT and PCI are less influenced by accommodation than autorefractometry, which would suggest an improvement for the AR data when using cycloplegia.²⁶ It is also a strength of the other two measurements that it is not required. Another limitation of the AR method is that current commercially available instruments, as were used in this study, are limited to 0.25 diopter steps. Even with averaging over five measurements for each location, the sensitivity was far less than either SD OCT and PCI. SD OCT appears to measure finer changes near the fovea than other techniques, though outside of 15 deg the differences may decrease. No input on corneal curvature was used in the calculations for the SD OCT and as such, is a potential confounding variable. Without cornea curvature, it is possible that the incidence of the scanning beam is not perpendicular to the corneal surface. Developing a full optical model that includes corneal curvature, and potentially lens, may further improve measures of retinal curvature using SD OCT.

It is interesting that the SD OCT measurements did demonstrate a difference between myopic and emmetropic groups in the vertical meridian. This would agree with the results of previous studies in that the retina is relatively more curved for myopes.¹⁶ This may not be surprising as they used PCI compared to AR in other vertical meridian studies. As previously stated above, PCI and SD OCT appear to have greater agreement. Also, Schmid (2003) only examined the central 15 deg similar to this study. It is possible that the change found could reverse further out, though it appears unlikely looking at the data. Another possible explanation is that the vertical meridian is being affected more than the horizontal by anterior optics effects like astigmatism, which would only effect the AR measurements.

The use of new technologies, such as SD OCT in this study, may improve treatment studies (whether optical or luminance based) in the future by determining which patients respond better.³⁸⁻³⁹ SD OCT allows for more accurate measures nearer to the fovea than other devices such as autorefractometry and PCI. Current literature suggests that these differences between SD OCT and PCI do not appear to be due to changes from eye muscles during eye movement, or from head position.⁴⁰⁻⁴¹

Similar to previously reported literature, the SD OCT data showed a more prolate retina curvature for the myopes. An interesting finding of this data is that SD OCT shows retinal profile differences between groups at nearly five deg eccentricity. This is significantly closer

than previously reported work which usually only find differences at 15 deg or greater. The nasal retina showed the least curvature between either group, though it was still statistically different between the myopic and hyperopic/emmetropic groups. This may be due to a physical restriction by the optic nerve within the orbit.

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Figure 1.

Two examples of segmentation. The top image is of a 0.00 Diopter emmetrope. The middle image is of a -3.50 Diopter myope. White lines show the segmentation between the RPE/Photoreceptor interface. The bottom image is the two segmented subjects plotted together illustrating the individual differences between the two. The black dashed line represents the reference plane from which the retinal profile is measured.

Figure 2. Schematic and photo of the Badal system used in these experiments to change the target position and also to provide a stimulus for accommodation and fixation for the subject. Example shown is for the IOLmaster. An identical one was used for the autorefractor with a different attachment base.

Figure 3. Test-retest of segmentation for the Outer Segment (OS)/Retinal Pigmented Epithelium (RPE) layer. Two blinded graders (segmenters) compared the five different subjects. Figure A shows the difference between graders. Figure B shows the mean difference between graders for all subjects. Figure C shows the Bland-Altman for all subjects. It appears to be a solid line, but is in actuality 1536 data point for each pixel. This was accomplished by using a spline function as used in the data analysis to interpolate between graders for all pixels in the image. One pixel is 7.7 microns.

Figure 4.

Comparison of autorefraction and partial coherence interferometry. Figure A shows the regression of the two ($P = 0.005$). Figure B shows the Bland-Altman. All data points were for 10 deg temporal retina. The slope of the Bland-Altman was not significant.

Figure 5. Comparison of autorefraction and SD OCT. Figure A shows the regression of the two ($P = 0.02$). Figure B shows the Bland-Altman. All data points were for 10 deg temporal retina. The slope of the Bland-Altman was not significant.

Figure 6. Comparison of partial coherence interferometry and SD OCT. Figure A shows the regression of the two ($P < 0.000$). Figure B shows the Bland-Altman. All data points were for 10 deg temporal retina. The slope of the Bland-Altman was not significant.

Figure 7.

Myopic vs Emmetropic/Hyperopic retinal shape. The two groups were statistically different using repeat measures ANOVA ($P = 0.001$.) Error bars represent 95% confidence interval.

Retinal shape is the change in retinal position from a theoretical the theoretical curve.

Squares represent emmetropes/hyperopes. Circles represent myopes.