Topographic Variation and Interocular Symmetry of Macular Choroidal Thickness Using Enhanced Depth Imaging Optical Coherence Tomography

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PURPOSE. To report and analyze factors influencing topographical and interocular variations in choroidal thickness (CT) in a healthy adult population.

METHODS. One hundred eyes of 50 healthy subjects underwent visual acuity and axial length measurements and optical coherence tomography (OCT) with enhanced depth imaging (EDI). CTs at the fovea and at 3 mm nasal, temporal, superior, and inferior to the fovea were measured manually. Topographic variation, relative interocular differences in CT and predictors of CT were analyzed. The relationships between interocular differences in CT and differences in age and interocular axial length were explored.

RESULTS. The mean (SD) foveal CT in the right and left eyes were 334 (95) and 333 (90) μm, respectively. For foveal CT, there was a high correlation between the two eyes (r = 0.90) with a relative interocular 95% limits of agreement of -80 to +83, and a median (range) absolute difference of 21 (0.4–135). There was no significant variation in the relative and absolute interocular differences in CT. Axial length was the main predictor of CT for nasal and foveal CT. Symmetry in CT in the horizontal and vertical meridians was seen in eyes with axial length shorter than 23.50 mm (P < 0.05).

CONCLUSIONS. There was no significant relative interocular difference in CT. Axial length contributes to some of the variances in CT but has a significant influence on the CT profile. Although relative interocular difference is not significant, absolute interocular differences in CT may reach 85 μm. (Invest Ophthalimol Vis Sci. 2012;55:975–985) DOI:10.1167/iovs.11-8771

Abnormal choroidal thickness (CT) has been implicated in the pathophysiology of several common ocular conditions including the disorders of emmetropization (hyperopia and myopia),1–5 central serous retinopathy,6–8 polypoidal choroidal vasculopathy,9 age-related macular degeneration,10 age-related choroidal sclerosis,11 inherited retinal dystrophy,12 inflammatory eye diseases13–15 diabetes,16 and glaucoma.17 Large variations in human CT has been reported in a histologic study18 and in several clinical studies using high-frequency ultrasound,19 magnetic resonance imaging,20 partial coherence tomography,21–23 spectral-domain optical coherence tomography (OCT)24 or swept-source OCT.25 Although 1-μm-probe spectral domain and swept-source OCT are probably more suitable for choroidal imaging because of the better penetration, these instruments are not widely available. Therefore, most centers use a combination of enhanced depth imaging (EDI) technique26 and/or averaging of high-density line scans26 to improve visualization of the choriocapillary interface on commercially available 800- to 850-nm spectral-domain OCT instruments.25

The first description of OCT choroidal imaging based on 17 healthy subjects demonstrated high interocular correlation of subfoveal24 CT with a nonsignificant relative interocular difference of 17 μm.24 Subsequent OCT studies assumed this interocular symmetry and explored the topographical variation of CT in one or both eyes of healthy subjects and demonstrated that the choroid is thickest at the fovea in the horizontal meridian in normal subjects.25,26,28,29 A recent study showed that the greatest CT is in a region superior to the fovea in highly myopic eyes.3 In three-dimensional reconstruction of OCT choroidal images, CT topography varies between eyes with longer and shorter axial lengths (AxLs).30–32 However, these studies showed various degrees of strength and significance of associations between paramacular CT, age, refractive error, and AxL. Furthermore, the assumption of interocular symmetry in CT topography has not yet been explored. This information is now becoming relevant for monitoring of conditions or treatments that may cause asymmetrical focal or generalized choroidal thickening or thinning.6,12,14,15 It has been reported that the thickness of the neuroretina in the macular region is remarkably symmetrical.33 However, it cannot be assumed that the CT in the macular region is also symmetrical, because other ocular parameters, such as AxL, peripapillary nerve fiber layer thickness, and cup–disc ratio have been shown to have significant relative and absolute asymmetry in large cohorts of healthy subjects.35

In addition to reporting the topographic variations and interocular differences of CT within and between eyes of a healthy adult population, we examined factors that may influence foveal and paramacular CT, horizontal and vertical CT profiles, and interocular differences in CT.

METHODS

Design and Subjects

This was a prospective study of EDI spectral-domain OCT choroidal imaging in healthy young adult volunteers. The study was approved by
the Ethics Review Board (10/H0722/6) and was conducted in compliance with the Declaration of Helsinki. Subjects were recruited into the study and had scanning data obtained between January and March 2010. Fifty-four healthy subjects between the ages of 30 to 50 years, with no known systemic or ocular disease, were recruited.36

To meet our criteria for normal, healthy eyes, the subjects had to have best corrected visual acuities of 0.00 logMAR or better, with AxLs between 22 and 27 mm measured with a partial coherence interferometer (IOL Master; Carl Zeiss Meditec, Dublin, CA), and normal maculas and optic disc nerve fiber layers in both eyes, when examined with a spectral-domain OCT scanner (Spectralis; Heidelberg Engineering, Heidelberg, Germany). Normal retinal structure was confirmed by two retinal specialists (JY, WR). Subjects were excluded if they were unable to give informed consent, if there was any media opacity, or if there was a history of eye disease, amblyopia, or previous ocular treatment, including past refractive surgery.

Clinical Examination and OCT Scan Protocol

The subjects underwent visual acuity testing with Early Treatment of Diabetic Retinopathy Study (ETDRS) charts in both eyes to establish that they had visual acuity of 0.00 logMAR or better. This examination was followed by AxL measurements. Subjects who did not meet the AxL criteria were immediately excluded from the study. The submacular chorioids of both eyes in each patient were imaged without pupil dilatation by using the EDI technique, positioning the OCT device (Spectralis; Heidelberg Engineering) close enough to the eye to invert the image, as described elsewhere.54 The deeper structures were brought closer to zero-delay, which allowed better resolution and sensitivity. The scans were performed by two experienced operators (JY, WR).

Two best-quality horizontal and vertical 9-mm line scans through the foveal center (marked by bright foveal reflex and fovea externa) were obtained for each eye. To maximize signal-to-noise ratio and reduce speckle noise, the images were acquired in the high-resolution mode and after averaging 100 frames. In addition, a dense raster scan of the entire macular area was performed to confirm the absence of retinal or choroidal disease. A nerve fiber layer circle scan of the optic nerve head was also performed in all eyes, to ensure that the nerve fiber layer thickness was within normal limits and that there was no loss of thickness from an optic nerve disease such as glaucoma.

Foveal and Paramacular CT Measurements

With the manual calipers provided by the software of the proprietary device, two measurements of the CT at the foveal center (F-CT) were performed independently by the same operators (JY, WR), using the horizontal and vertical line scans obtained in each eye (i.e., F-CT data are derived from an average of eight measurements in each eye). F-CT was measured from the outer limit of the hyperreflective line (retinal pigment epithelium, RPE) next to the fovea externa, to the inner surface of the sclera, which is defined by a continuous hyporeflectivity line or defined boundary between the hyporeflective chorioid and the hyperreflective sclera. The caliper was drawn so that it was perpendicular to the RPE line. One observer (JY) also performed CT measurements at four paramacular loci: 3 mm superior (S-CT), inferior (I-CT), temporal (T-CT) and nasal (N-CT) to the foveal center in 100 vertical scans and 100 horizontal scans from both eyes of 50 subjects (i.e., 400 additional paramacular CT measurements). The horizontal and vertical section scans with the best definition of sclerochoroidal interface were used for these measurements. The second observer (WR) also performed measurements at the four paramacular loci in 10 randomly selected line scans (5 vertical and 5 horizontal; a total of 20 measurements) to assess interobserver agreement in paramacular CT measurement.

Statistical Analysis

The data are expressed as the mean (SD) and range. Data without normal distribution are also presented as the median and range. Interocular asymmetry was quantified by relative and absolute differences. The relative interocular difference in AxL and CT are summarized by the mean, SD, 95% limits of agreement,37 and range. The absolute interocular difference in CT is presented in the median with percentiles. The mean CT across five loci (location) between both eyes was evaluated using Pearson’s correlation coefficient.

As an exploratory analysis, we also examined the horizontal and vertical CT profiles in eyes belonging to the following four AxL groups: group A, 22.00 to 23.49 mm; group B, 23.50 to 24.49 mm; group C, 24.50 to 25.49 mm; and group D, 25.50 to 27.00 mm, using two-way ANOVA and Friedman’s test were used to compare the relative and absolute interocular differences across the five loci. The strengths of association in corresponding loci of CT measurements between the two eyes were analyzed by Pearson’s correlation coefficient.

Interobserver 95% limits of agreement in the foveal and paramacular CTs were calculated by the mean difference ±1.96 × the SD of the difference. CT measurements between the two observers were compared by the paired-sample t-test, and their association was analyzed by Pearson’s correlation.

Backward-elimination, multiple regression analysis was used to explore the contribution of the 4 independent variables age (in years), sex (male versus female), race (Caucasian versus non-Caucasian), and AxL (in millimeters) to the variance in CT at each of the five points across the macular region in each eye (10 separate dependent variables). The stepwise criterion for removal of a variable was set at an F ratio probability of 0.1.

As an exploratory analysis, we also examined the horizontal and vertical CT profiles in eyes belonging to the following four AxL groups: group A, 22.00 to 23.49 mm; group B, 23.50 to 24.49 mm; group C, 24.50 to 25.49 mm; and group D, 25.50 to 27.00 mm, using two-way

<p>| Table 1. CT and AxL Variation and Relative Interocular Difference |
|-------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Topographic Variation   |                       |                       | Relative Interocular Differences |
|                         | Right Eye (µm)        | Left Eye (µm)         |                         | Right Eye - Left Eye (µm) | 95% Limits of Agreement (µm) | Interocular Correlation Pearson’s Coefficient |</p>
<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean (SD)</th>
<th>Median (Min, Max)</th>
<th>Mean (SD)</th>
<th>Median (Min, Max)</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Foveal CT</td>
<td>334 (94)</td>
<td>310 (172, 568)</td>
<td>335 (90)</td>
<td>321 (133, 555)</td>
<td>1.0 (42)</td>
<td>–87, 135</td>
<td>–80</td>
</tr>
<tr>
<td>Nasal CT</td>
<td>188 (76)</td>
<td>181 (78, 447)</td>
<td>174 (71)</td>
<td>154 (65, 398)</td>
<td>13.6 (45)</td>
<td>–100, 153</td>
<td>–71</td>
</tr>
<tr>
<td>Temporal CT</td>
<td>282 (62)</td>
<td>266 (153, 488)</td>
<td>285 (60)</td>
<td>270 (121, 429)</td>
<td>–2.9 (61)</td>
<td>–177, 139</td>
<td>–123</td>
</tr>
<tr>
<td>Superior CT</td>
<td>518 (67)</td>
<td>518 (209, 480)</td>
<td>308 (68)</td>
<td>512 (176, 472)</td>
<td>9.7 (38)</td>
<td>–65, 98</td>
<td>–65</td>
</tr>
<tr>
<td>Inferior CT</td>
<td>295 (74)</td>
<td>293 (119, 431)</td>
<td>285 (74)</td>
<td>290 (154, 444)</td>
<td>10.0 (46)</td>
<td>–120, 105</td>
<td>–81</td>
</tr>
<tr>
<td>AxL</td>
<td>24.46 (1.12)</td>
<td>24.49 (22.24, 26.96)</td>
<td>24.45 (1.09)</td>
<td>24.41 (22.09, 26.89)</td>
<td>0.01 (0.32)</td>
<td>–1.11, +1.57</td>
<td>–0.61</td>
</tr>
</tbody>
</table>

CT is in micrometers and AxL is in millimeters.
* P < 0.001.
(five repeated-measure × four between-subject variables) mixed ANOVA with post hoc Bonferroni adjustment for multiple corrections in each eye. The same analysis was performed to determine whether the CT profile varied between the four age-group cohorts: 30 to 34, 35 to 39, 40 to 44, and 45 to 49 years.

The relationship between the absolute interocular differences of each loci and each of the variables (1) mean CT measurements from both eyes and (2) the subject’s age were examined with the nonparametric Randall’s correlation. The relationship between the relative interocular difference in CT and the relative interocular difference in AxL was analyzed by Pearson’s correlation.

All effects are reported as significant at $P < 0.05$, incorporating the Bonferroni correction within multiple regression analyses and ANOVA post hoc tests (SPSS 12.0.1; SPSS Inc, Chicago, IL).

**RESULTS**

Fifty-four subjects were recruited. Four were subsequently excluded: two because their AxLs were greater than 27 mm, one with AxL less than 22 mm, and one who was not cooperative enough to fixate steadily, resulting in a poor-quality scan. Fifty subjects (100 eyes) were scanned and completed the study.

The mean and median ages (in years) were 38 and 36.5 (SD 5; range, 30 – 49), respectively. Of the 50 participants, there were 26 men and 24 women from the following racial backgrounds; 38 Caucasian (22 white European and 16 Indian subcontinent) and 12 non-Caucasian (8 Chinese or Southeast Asian and 4 African Caribbean). The mean AxL (in millimeters) of the subjects’ eyes was 24.46 (SD, 1.12; range, 22.24 –26.96) and 24.45 (SD: 1.50; range, 22.09 –26.89) in the right and left eyes, respectively (Tables 1, 2).

### Choroidal Thickness

Mean (SD) and median F-CT (in micrometers) were 334 and 310 (94; range, 172–568) in the right eyes and 333 and 321 (90; range, 133–555) in the left eyes. CTs at 3 mm nasal (N-CT), temporal (T-CT), superior (S-CT), and inferior (I-CT) to the foveal center and the mean differences are summarized in Table 1. The mean (SD) relative (right minus left) interocular difference in F-CT was 1.0 (42) μm. The median (range) and the 95th percentile for the absolute interocular difference in F-CT were 21 (0.38 –135.13) and 85 μm (Table 2, Fig. 1).

Repeated-measures ANOVA showed a significant main effect of the location of CT measured ($F_{(4,196)} = 94.46$, $P < 0.001$). Comparisons between CT measured at the various locations showed that F-CT was thicker than N-CT ($F_{(1,49)} = 30.3, r = 0.93, P < 0.001$), T-CT ($F_{(1,49)} = 25.9, r = 0.59, P < 0.001$), S-CT ($F_{(1,49)} = 4.97, r = 0.50, P = 0.030$), and I-CT ($F_{(1,49)} = 33.0, r = 0.65, P < 0.001$). There was no significant difference between the eyes ($F_{(1,49)} = 1.70, P = 0.11$), nor was there a significant interaction effect between laterality and location ($F_{(4,196)} = 1.30, P = 0.27$).

### FIGURE 1.

The distribution of foveal thicknesses with normal curves. (A) F-C CT in the right eye was not normally distributed. (B) Relative (right–left) interocular difference in CT at the fovea was close to normal distribution. (C) The distribution of absolute interocular difference in CT at the fovea was positively skewed.

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**TABLE 2.** Absolute Interocular Difference in CT and AxL

<table>
<thead>
<tr>
<th>Parametric Summary Statistics</th>
<th>Nonparametric Summary Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Foveal CT</td>
<td>29.88</td>
</tr>
<tr>
<td>Nasal CT</td>
<td>31.30</td>
</tr>
<tr>
<td>Temporal CT</td>
<td>42.86</td>
</tr>
<tr>
<td>Superior CT</td>
<td>30.80</td>
</tr>
<tr>
<td>Inferior CT</td>
<td>39.10</td>
</tr>
<tr>
<td>AxL</td>
<td>0.168</td>
</tr>
</tbody>
</table>

CT is in micrometers, and AxL is in millimeters.

CT is in micrometers, and AxL is in millimeters.
For relative interocular difference, there was no significant variation between the five loci ($F_{(3, 14)} = 1.31, P = 0.27$) although there was a trend toward thicker N-CT (14 µm) and thinner T-CT ($3$ µm) in the right eye than in the left eye (Table 1, Fig. 2). The Friedman test showed that the median absolute interocular difference in CT was also similar across the five loci ($x^2_{(4)} = 3.30, P = 0.51$), ranging from 21 µm (F-CT) to 34 µm (I-CT; Table 2). The correlation between the eyes was strongest for F-CT ($r = 0.90, P < 0.001$) and weakest for T-CT ($r = 0.49, P < 0.001$).

**Interobserver Agreement in Paramacular CT Measurement**

The interobserver 95% limits of agreement in all horizontal and the vertical F-CT measurements were $-34$ and $31$ µm and the mean (SD) difference was $1.3$ (16.6) µm. The mean (SD) difference in paramacular CT was $-4$ (22) µm and the 95% limits of agreement were $-26$ and $+19$ µm. A paired-sample $t$-test showed no significant differences in CT measurements between the two observers in the F-CT ($P = 0.285$) or the paramacular CT ($P = 0.149$) measurements. Pearson’s correlation showed strong association in F-CT ($r = 0.98, P < 0.001$) and paramacular CT measurements ($r = 0.99, P < 0.001$) between the two observers.

**Factors Influencing Foveal and Paramacular CT Measurements**

In the initial regression from entering all variables (Table 3), AxL had correlation coefficients ranging from $-0.05$ to $-0.48$. In contrast, correlation coefficients for age ranged from $-0.24$ for T-CT to $+0.18$ for N-CT.

**Factors Influencing Horizontal and Vertical CT Profile**

Since age and AxLs have been reported to be significant predictors of CT measurements, we further explored the differences in CT profile between four AxL and age range subgroups.

The number of subjects in AxL categories A, B, C, and D were 9, 16, 17, and 8 for the right eye and 10, 18, 15, and 7 for the left eye, respectively. There was a significant effect of AxL category on CT profile in the right eye ($F_{(3, 46)} = 3.84, P = 0.016$, but not in the left eye ($F_{(3, 46)} = 2.01, P = 0.126$). There was a significant interaction effect between CT profile and AxL groups (right eye: $F_{(12, 156.7)} = 2.08, P = 0.028$; left eye: $F_{(12, 184.3}) = 2.03, P = 0.024$). In the horizontal meridian, N-CT was similar to T-CT in short eyes (category A) whereas N-CT was significantly thinner than T-CT in longer eyes (right eye: $F_{(3, 46)} = 2.82, r = 0.39, P = 0.049$; left eye: $F_{(3, 46)} = 2.87, r = 0.40, P = 0.046$). In the vertical meridian, significant interaction was also found in S-CT compared with F-CT across differ-

**Table 3. Correlations between CT with Four Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Right Eye</th>
<th>Left Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Foveal</td>
<td>Nasal</td>
</tr>
<tr>
<td>Age, y</td>
<td>-0.014</td>
<td>0.112</td>
</tr>
<tr>
<td>AxL mm</td>
<td>-0.450†</td>
<td>-0.470‡</td>
</tr>
<tr>
<td>Female vs. male</td>
<td>0.179</td>
<td>0.067</td>
</tr>
<tr>
<td>Caucasian vs. NC</td>
<td>0.191</td>
<td>0.225</td>
</tr>
</tbody>
</table>

Data are correlation coefficients. NC, non-Caucasian. $P$ values incorporate the Bonferroni correction: † $P < 0.05$; ‡ $P < 0.01$; †† $P < 0.001$. 

After backward elimination, a significant final model for predicting CT was found at all locations measured except S-CT in the right eye and T-CT, S-CT, and I-CT in the left eye (Table 4). The most significant models found were those predicting N-CT in both the right and left eyes ($F_{(12, 47)} = 10.01, P < 0.001$, and $F_{(1, 46)} = 14.46, P < 0.001$, respectively) with the variables explaining 27% (RE) and 22% (LE) of the variance in N-CT, AxL was the most significant variable but it reached a $P < 0.001$ significance level only in the N-CT of both eyes (Fig. 3). Age and race were incorporated in some of the final models, but they were not major predictors of CT (Table 4, Fig. 3).
TABLE 4. Final Regression Model Derived from Backward Selection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Right Eye</th>
<th>Left Eye</th>
<th>Right Eye</th>
<th>Left Eye</th>
<th>Right Eye</th>
<th>Left Eye</th>
<th>Right Eye</th>
<th>Left Eye</th>
<th>Right Eye</th>
<th>Left Eye</th>
<th>Right Eye</th>
<th>Left Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>1252 (723 to 1782)*</td>
<td>1007 (598 to 1416)*</td>
<td>933 (527 to 1340)*</td>
<td>318 (299 to 337)*</td>
<td>875 (440 to 1310)*</td>
<td>1019 (464 to 1574)*</td>
<td>940 (535 to 1346)*</td>
<td>285 (268 to 302)*</td>
<td>308 (289 to 328)*</td>
<td>285 (264 to 306)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>6.9, 0.6‡</td>
<td>6.9, 0.6‡</td>
<td>6.9, 0.6‡</td>
<td>6.9, 0.6‡</td>
<td>6.9, 0.6‡</td>
<td>6.9, 0.6‡</td>
<td>6.9, 0.6‡</td>
<td>6.9, 0.6‡</td>
<td>6.9, 0.6‡</td>
<td>6.9, 0.6‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AxL, mm</td>
<td>37.5 (59.2 to 15.9)†</td>
<td>34.0 (50.7 to 17.2)*</td>
<td>30.9 (41.5 to 6.0)‡</td>
<td>23.7 (41.5 to 6.0)‡</td>
<td>12.3 (41.5 to 6.0)‡</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian vs. NC</td>
<td>49.3 (5.7 to 92.9)‡</td>
<td>20.2 (0.2 to 40.0)‡</td>
<td>4.2 (0.2 to 20.0)‡</td>
<td>0.2 (0.0 to 0.4)‡</td>
<td>0.1 (0.0 to 0.2)‡</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<td></td>
</tr>
</tbody>
</table>

Data are standardized coefficients (95% CI). Multiple regression was performed for each of the 10 CT measurements (five loci for each eye) using the variables shown. Variables with F ratio of 0.1 or greater were eliminated during modelling. $P$-values incorporate the Bonferroni correction: *$P < 0.05$; ‡$P < 0.01$. 

Factors Influencing Interocular Differences in CT

Absolute interocular differences in CT did not increase with the average of CT measurements between the two eyes in the fovea (Kendall’s $\tau = 0.03$, $P = 0.738$) or any of the paramacular loci (Fig. 5, Table 5). However, there was a weak inverse relationship between absolute interocular difference in CT at the fovea and age (Kendall’s $\tau = -0.20$, $P = 0.048$).

Moderate correlation was found between relative interocular difference in AxL and relative interocular differences in F-CT ($r = -0.433$, $P = 0.002$) and N-CT ($r = -0.281$, $P = 0.048$). However, a scatterplot showed that two subjects with extremes of interocular difference in AxL were driving this relationship. This conclusion was confirmed by a sensitivity analysis after these two subjects were removed (Fig. 5, Table 5).

Discussion

In this study, we found that EDI of the choroid is feasible through undilated pupils and that CT measurements are reproducible. Although there was a significant topographic variation in CT between the foveal center and the four paramacular loci, there was no significant relative interocular difference, and the corresponding CTs in the two eyes were highly correlated. Among the four factors examined, the strongest predictor for F-CT was AxL. Furthermore, AxL, but not age group, contributed to the unique horizontal and vertical CT profiles.

Foveal and Paramacular CT

A wide range of F-CT has been reported in several reports using various OCT instruments, including Spectralis OCT (Heidelberg Engineering), Cirrus HD OCT (Carl Zeiss Meditec), Copernicus SOCT (Optopol Technology, Zawiercie, Poland), and a noncommercial prototype, swept-source OCT. The differences in F-CT reported by the previous studies may be attributed to differences in age, refractive error, AxL, manual segmentation criteria, OCT instrumentation, and the use of CT from both eyes in a variable subset of the study cohort in the final analysis (Fig. 6). We reported a similar F-CT (354 μm) compared with that reported by other studies that examined only one eye per subject (F-CT ranging from 204 μm, with a mean age of 65 years, to 342 μm, with a mean age of 25 years).

Significant topographic variation in CT was found within the submacular region. In the horizontal meridian, we found F-CT > T-CT > N-CT. However, in previous studies of myopic eyes, the T-CT was thicker than both the F-CT and N-CT (Fig. 6). In the vertical meridian, the trend was F-CT > S-CT > I-CT, with F-CT only marginally thicker than S-CT. In contrast, a previous study reported no significant CT variation in the vertical meridian. Therefore, in contrast to retinal thickness profile in the macular region, there is no consensus in the current literature on the normal CT profile. Therefore, we chose to analyze this further by examining the impact of AxL and age on CT at each of the five loci and CT profile in the...
horizontal and vertical meridians (see Fig. 6 and discussions below).

Spaide et al.\textsuperscript{24} reported a relative interocular difference of 17 µm between the two eyes with the left thicker than the right. We found that F-CT on the right was thicker than the left by 1 µm (SD 42). There was also a trend for the paramacular choroid on the right to be thicker than that on the left except for T-CT. Although relative interocular differences at the foveal center and across four paramacular loci were not statistically significant, up to 95% of individuals may have an absolute difference of 85 µm at the fovea. A proportion of this difference may be explained by intrasession interscan variability (see below). Irrespective of the source of this variation, the reported threshold may be useful in future studies for identification of patients with unilateral pathologic change in subfoveal CT.

**Interobserver Variability in CT Measurements**

Current segmentation software can detect only the boundary between the choroid and RPE. Our manual segmentation pro-

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**FIGURE 3.** Scatterplots showing relationship between CT at each of the five loci and AXL and age. Relationship between CT and AXL in (A) the right eye and (B) the left eye. Relationship between CT and age in (C) the right eye and (D) the left eye.
tocol is similar to that used in other studies, but there may be interobserver differences in identifying boundaries. We previously reported the 95% limit of interscan agreement in CT measurement as \(35\text{ to } 39\) μm (interval: 74 μm), when one observer obtained two measurements from two separate horizontal scans performed in the same session.\(^{36}\) We used four measurements of the F-CT from two observers and two best vertical and horizontal scans to minimize the impact of interobserver and interscan variability. The reported 95% limits of agreement for F-CT (\(34\text{ to } 31\) μm) were similar to those for paramacular CT (\(26\text{ to } 19\) μm). This suggests that chorio-scleral boundaries in the paramacular regions are no more difficult or easier to detect than those at the foveal center.

### Predictors of CT in the Foveal and Paramacular Regions

We found that AxL was the only significant predictor of F-CT in the final regression model with a reduction of 38 or 28 μm in choroidal thickness per millimeter increase in AxL in the right and left eyes, respectively. Conversely, age, sex, and race had only weak correlations with F-CT.

Only one study showed that men have a thicker choroid than do women, when adjustment is made for age and AxL.\(^{38}\) but race does not influence F-CT.\(^{29,30,39}\) The lack of significant relationship between the sex of the subject and F-CT in our study may be related to the larger range and older age group in our cohort and the smaller sample size.

Similar to Agawa et al.,\(^{5}\) Ouyang et al.,\(^{30}\) Esmaeelpour et al.,\(^{31}\) and Hirata et al.,\(^{32}\) we also found that AxL was the most significant predictor for F-CT. Other studies that reported age as the most significant predictor of F-CT had older subjects with mean age ranging from 50 to 65 years.\(^{26,28,29,32}\) Both Agawa et al.\(^{5}\) and Esmaeelpour et al.\(^{31}\) showed that the relationship between foveal CT and age becomes significant only in a subset of eyes with longer AxL. This analysis was not performed in our study because of the small sample size in the subset of longer eyes. Therefore, the lack of relationship between F-CT and age in our study is probably due to the younger age subjects and the relatively few eyes with longer AxL in our cohort. The implication is that age-related choroidal thinning may occur at an earlier age in myopes.

In the horizontal meridian, AxL was also a significant predictor for N-CT. In contrast, AxL was predictive of T-CT only in the right eye but not the left. Previous studies also showed that AxL was related to both N-CT and T-CT or the mean CT in the horizontal meridian.\(^{5,29–52,40}\) In the vertical meridian, backward elimination did not find a significant regression model except for the right eye, in which 11% of the variance in I-CT was explained by AxL. There is inconsistency in reported contributors to paramacular CT.\(^{5,31}\) The disparity may be related to the differences in study population with respect to AxL distribution (see below) and the distance from foveal center at which the N-CT and T-CT were measured (i.e., \(2.25\) mm in other studies compared to \(3.00\) mm in our study).

AxL and refractive error are related variables, but they are not interchangeable, because of the considerable variation in the size of emmetropic eyes.\(^{41}\) Axial length does not tend to change after the second decade of life, except in cases of posterior staphyloma, ocular hypotony, shrinking eye syndrome, or scleral buckling. In contrast, refractive error can fluctuate or change in the settings of contact lens wear, hyperglycemia, aging of the lens, serous macular detachment, posterior staphyloma progression, and ocular surgery such as cataract, glaucoma, refractive, and retinal procedures. Previous
studies suggest that CT is inversely related to the axial eye dimension and is positively correlated with refractive error. Given the relationship between these two variables, they contributed to no more than 30% of the variance in foveal CT. The disagreement in the importance of the various predictors of paramacular CT suggests that the relationships between CT and various demographic and biometric variables are likely to be more complex, as shown below.

Predictors of Horizontal and Vertical CT Profiles

Our results showed that horizontal and vertical CT profiles are unique and often asymmetrical. In the horizontal meridian, previous studies showed that CT decreased faster in the nasal direction than in the temporal direction (see Fig. 6). We found that this nasal–temporal asymmetry was almost absent in eyes with AxLs shorter than 23.5 mm. Conversely, this asymmetry

![Figure 5](http://tvst.arvojournals.org/)

**FIGURE 5.** Factors influencing interocular difference in foveal center CT. Absolute interocular difference of (A) CT against the mean, showing a slight trend for increasing asymmetry with magnitude ($\tau = 0.03, P = 0.738$), and (B) against age, showing a marginally significant trend for reduced difference with increasing age ($\tau = -0.20, P = 0.048$). Relative interocular difference in CT against (C) AxL differences, showing two subjects driving the negative correlation and (D) against AxL differences after two extreme outliers were removed, showing minimal correlation.

<table>
<thead>
<tr>
<th>Location</th>
<th>Absolute Difference in CT</th>
<th>Relative Difference in CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean CT from Both Eyes (n = 50)</td>
<td>Age (n = 50)</td>
</tr>
<tr>
<td></td>
<td>Location Coefficient</td>
<td>P</td>
</tr>
<tr>
<td>Foveal CT</td>
<td>0.033</td>
<td>0.738</td>
</tr>
<tr>
<td>Nasal CT</td>
<td>0.120</td>
<td>0.222</td>
</tr>
<tr>
<td>Temporal CT</td>
<td>-0.043</td>
<td>0.663</td>
</tr>
<tr>
<td>Superior CT</td>
<td>0.150</td>
<td>0.128</td>
</tr>
<tr>
<td>Inferior CT</td>
<td>0.061</td>
<td>0.536</td>
</tr>
</tbody>
</table>

CT is in micrometers. Absolute interocular CT difference was correlated with age and mean interocular CT using Kendall’s $\tau$. Relative interocular CT difference was correlated with relative interocular axial length difference with and without removal of extreme outliers using Pearson’s correlation.
was exaggerated in eyes with longer AXLs, as shown in previous studies.\textsuperscript{3,5,31,32} When examining the CT profile in the vertical meridian, we also found a similar superior-inferior asymmetry where the CT decreases faster in the inferior direction than in the superior direction. The asymmetry was virtually absent in shorter eyes but was exaggerated in longer eyes. These findings are consistent with the observation by Esmaeilpour et al.,\textsuperscript{31} in that greater topographic variations are found in the submacular region of longer eyes than in shorter eyes.\textsuperscript{33} Shorter eyes had a maximum CT at the foveal center with fairly symmetrical choroidal thinning in the horizontal and vertical meridians, away from the foveal center. In contrast, longer eyes had gradual thickening of the choroid in the nasal-to-temporal and inferior-to-superior directions. Therefore, maximum CT in longer eyes may be located superotemporally to the fovea, but further studies are needed for confirmation.

What could explain these contrasting submacular CT topographies in eyes of extremes of AXL? It has been hypothesized that the process of emmetropization involves close interaction between the choroid and sclera mediated through retinal signaling of defocus; secretion of growth factors, matrix metalloproteases, and their tissue inhibitors; and the release of dopamine, acetylcholine, and nitric oxide.\textsuperscript{3} Animal models have shown that short-term thickening of choroid induced by myopic defocus (image focused in front of the retina) results in long-term inhibition of eye growth.\textsuperscript{3} It is not known whether this transient change in CT occurs in human during development. Even if CT change occurs, we do not know whether it persists into adulthood. One explanation for our observation is that the default developmental endpoint is to have maximum CT at the fovea acting as a heat and metabolic sink. However, in eyes with progressive elongation as seen in myopia, there may be asymmetrical stretching and thinning of the choroid leading to asymmetry in CT relative to the foveal center. The alternative hypothesis is that asymmetrical CT relative to the fovea in addition to generalized choroidal thinning contributes to excessive eye growth, leading to myopia.

It has been shown that CT and possibly the CT profile can vary with systemic variables, such as diurnal rhythm,\textsuperscript{21} use of phosphodiesterase inhibitors,\textsuperscript{42} ocular perfusion pressure,\textsuperscript{40} and diabetes mellitus.\textsuperscript{10} The introduction of longer wavelength OCT, the examination of the peripapillary CT profile in conjunction with submacular CT profile, and the use of automated choroidal segmentation software will help in further studies examining factors affecting topographic variation in posterior pole CT.\textsuperscript{30}

**Predictors of Intercocular Differences in CT**

Until now, the relative interocular difference in CT has not been studied in detail. We found CT at the fovea to be highly symmetrical, but there was a trend for a thicker choroid on the left, except for the loci at 3 mm temporal to the fovea. Although there was no significant difference in the overall CT, it may be masked by the greater variability in T-CT measurement, as indicated by its lower correlation coefficient, greater SD in the differences and limits of agreement. Another possibility is that asymmetry is region specific, similar to that found in nerve fiber layer asymmetry in which left eyes had a thicker superior nerve fiber layer, but the right eyes had thicker temporal and nasal nerve fiber layers.\textsuperscript{5} We found that the relationship between relative interocular difference in AXL and relative interocular difference in F-CT was driven by two subjects with large interocular differences in these variables. Although we did not examine refractive error, previous animal studies found this to be a predictor of interocular CT difference in marmosets, guinea pigs, and macaques.\textsuperscript{1}

Absolute interocular difference in CT showed that large differences of up to 135 μm in the F-CT or 180 μm in the paramacular loci can be observed. This did not increase significantly with the magnitude of the average CT between the two eyes and may decrease with age for F-CT. The absolute interocular difference in CT is considerably larger than that reported for macular thickness.\textsuperscript{34} The differences in CT may be due to errors in (1) segmentation, (2) localization of the paramacular loci due to curvature of the RPE layer, or (3) head tilt during fundus imaging.

**Limitations**

The main limitations in this study are the small sample size and the lack of refractive error data. We chose to record only four variables (age, sex, race, and AXL) to enter into the CT prediction model because of the small sample size and because AXL is a more clinically useful biometric measure than refractive error, as the former is less likely to be confounded by other systemic and ocular variables. No adjustment was made for...
other variables such as central corneal thickness, intraocular pressure, systemic medication, blood pressure, and the time of acquiring OCT (diurnal rhythm). We did not study the three-dimensional CT profile, because current commercially available OCT instruments do not provide automated segmentation, manual segmentation is time intensive, and the current proprietary software does not measure the true CT, adjusted for the concave curvature of the posterior pole RPE surface.

CONCLUSIONS

To summarize, EDI OCT is feasible and reproducible through undilated pupils in a cohort of healthy subjects. We reported a significant topographic variation in CT in the paramacular region and no significant relative interocular difference in CT. However, absolute interocular CT differences can be large in healthy individuals. CT variations in horizontal and vertical meridians appear to be related to the AxL. CT variations between the two eyes are not strongly related to age, average CT, or AxL differences. Future studies are needed to identify other factors that may contribute to topographic and interocular variations in CT in healthy individuals so that physiological thresholds of intraocular variations and interocular differences can be individualized for identifying early pathologic changes in the choroid.

References

7. Manjunath V, Fujimoto JG, Duker JS. Circus HD-OCT high definition imaging is another tool available for visualization of the choroid and provides agreement with the finding that the choroidal thickness is increased in central serous chorioretinopathy in comparison to normal eyes. Retina. 2010;30:1520–1521.


