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Reproducibility and variation of corneal thickness in different locations in the cornea as measured by an ultrasonic pachymeter

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ABSTRACT
Corneal thickness was measured in nine positions of nineteen normal eyes with an ultrasonic pachymeter. A standardized protocol was used to examine for intraobserver and interobserver variation, day to day variation, and time of day variation in the measurement of corneal thickness. No statistically significant difference was noted for most points in intraobserver, interobserver, day to day, or different time of day variation measurements. However, it was noted that central measurements of corneal thickness tended to be less variable (more reproducible) than paracentral (p=.0366) and peripheral (.0032) measurements. Paracentral measurements were less variable than peripheral measurements (p=.0323).

While this was a small study, 95% confidence intervals were also calculated for each of the nine corneal positions where measurements were performed.

Ultrasound pachymetry is an important technique for the measurement of corneal thickness. It is used by the ophthalmologist in many clinical situations including prior to radial keratotomy and other refractive surgery procedures, for following patients with Fuch's dystrophy and pseudophakic bullous keratopathy, for monitoring the adaptation of the cornea to contact lens wear, and for checking corneal thickness in keratoconus. Salz, Azen, Berstein, Caroline, Villasenor, and Schanzlin (1983) have shown central measurements of corneal thickness with three different ultrasonic pachymeters to have little intersession or intrasession variation, but a statistically significant interobserver variation. [Ed. note: "inter" is used to mean "different" sessions and observers, "intra" to mean the "same" session and observer.] They also noted no significant right/left eye variation with the ultrasonic pachymeters. No statistically significant difference was noted between preoperative and intraoperative central corneal thickness measurements of 395 eyes of patients in the Prospective Evaluation of Radial Keratotomy (PERK) study (Villasenor, Santos, Cox, Harris, Lynn, and Waring, 1986). However, there was a variation of .03 to .08mm in 12.7% of these patients with 3.3% being .03 to .06mm thicker intraoperatively and 9.4% being .03 to .08mm thicker intraoperatively. This would suggest that there is not a statistically significant day to day variation in central corneal thickness in most patients. Fujita (1980) used an optical pachymeter to show a diurnal variation in corneal thickness which follows a circadian periodicity. In that study, the cornea was noted to be relatively thick in early morning followed by a gradual thinning in daytime until late afternoon and a subsequent thickening during the night.

Two studies (Insler and Cooper, 1986) and (Holland, Willis, and Krachmer, 1986) have been done in patients with keratoconus which compare peripheral, paracentral, and central corneal thickness measurements obtained with an ultrasonic pachymeter. An additional study was performed which examined the average corneal thickness in nine different positions in 48 eyes of patients in the PERK study (Steinberg, Waring, and Lynn, 1986). The reproducibility and variation of paracentral and peripheral measurements of corneal thickness obtained with an ultrasonic pachymeter has not been studied previously.

This present study was undertaken to determine the interobserver, intraobserver, day to day...
day, and time of day variation and reproducibility of measurements of corneal thickness in nine different locations (one central, four paracentral, and four peripheral) in the cornea. In addition, 95% confidence intervals around the mean for a single measurement were calculated.

**Materials and methods**

Nineteen eyes (10 right eyes, 9 left eyes) of 10 employees of the University of Iowa Department of Ophthalmology (4 male, 6 female) were studied over a two week period. Each had a normal slit lamp examination, no history of ocular disease, and had not worn contact lenses for at least one week prior to entry into the study. Four eyes of two people wore soft contact lenses less than three days per month. The other fifteen eyes of eight people had never worn contact lenses. One eye of one subject was excluded because the subject was a continuous user of a daily wear soft contact lens for monovision.

The Pachysonic II ultrasonic pachymeter (Teknar Inc., St. Louis, MO) was used to measure corneal thickness in nine positions on five separate occasions following a standardized protocol. The patient was placed in a sitting position and given a distant object for fixation. The right eye was always measured first in each patient, followed by the left eye. The instrument was set to use a velocity of sound through the cornea of 1630 meters/second in its calculations. Each reading is the average of three measurements at that position. The design of the pachymeter is such that any reading >10u from the previous reading is disregarded by the machine before averaging three good measurements. The operator knows when the probe is in the proper orientation because the machine makes an audible sound to indicate this. Prior to each patient being tested, the ultrasonic pachymeter was calibrated for accuracy with the standardized test fixture accompanying the machine. All measurements were made by one of two ophthalmic nurses who are well-trained and experienced in this technique.

The nurses were given a written protocol in how to perform the pachymetry for the study. Instructions were as follows:

1. One drop of proparacaine 0.5% should be placed in each eye prior to performing the measurements.
2. The ultrasonic probe will be used to measure corneal thickness in nine positions. The reported measurement for each position should be the average of three consecutive measurements made at each position without moving the probe. If three consecutive measurements cannot be made without moving the probe, then the probe should be replaced in the same spot and the measurements repeated until three consecutive measurements without probe movement are obtained.
3. The ultrasonic probe should be applied perpendicular to the corneal surface where the measurement is being made.
4. The ultrasonic probe should be applied gently to the corneal surface such that it is in contact with the cornea, but does not indent the cornea where the measurement is being made.
5. The nine position measurements, which should be measured in the same order each time, are to be made by applying the probe to the cornea as follows:
   - #1—to the center of the cornea as determined by visualizing a point on the cornea equidistant from the 12:00 and 6:00 corneal limbus, and equidistant from the 3:00 and 9:00 corneal limbs.
   - #2—to a position at the 12:00 limbus such that the outer edge of the probe is tangential to and flush with the corneal limbus. The limbus will be determined visually by the examiner as the point where clear cornea terminates,
   - #3—to a position halfway between points #1 and #2.
   - #4—same as #2, but at 6:00
   - #5—same as #3, but halfway between #1 and #4.
   - #6—same as #2, but at 3:00 in left eyes or 9:00 in right eyes such that the point is temporal in location.
   - #7—same as #3, but halfway between #1 and #6
   - #8—same as #2, but at 9:00 in left eyes or 3:00 in right eyes such that the point is nasal in location.
   - #9—same as #3, but halfway between #1 and #8.

Position 1 will be referred to as the central corneal thickness measurement. Positions 3, 5, 7, and 9 will be referred to as paracentral measurements, and position 2, 4, 6, and 8 as peripheral measurements of corneal thickness. See Figure 1.

Study 1: Intraobserver Variation—All nine corneal positions were measured according to the standardized protocol, first in the right eye and then in the left eye, by a first observer.

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The same observer then immediately repeated these same eighteen measurements in the same order. These two sets of measurements were then compared to each other.

Study 2: Interobserver Variation—Immediately after the two sets of measurements were made for study 1, a second observer performed the same nine corneal thickness measurements in each eye following the standardized protocol. Again, the right eye was measured prior to the left eye. This set of measurements was compared to the first set of measurements made by the first observer.

Computation of 95% confidence intervals of a single measurement was then performed using the total variance including intraobserver, interobserver, time of day, and day to day variation. The standard deviation was then multiplied by 1.96 to determine the 95% confidence intervals.

For the statistical analysis, data was analyzed using the analysis of variance for random effects model. Sources of variance included observer, eye, day, and time of day.

Results
Statistical analysis of the data was performed using the analysis of variance for random effects model, with p<0.05 as the level of significance.

Study 1: Intraobserver Variation—The standard deviations for each of the nine positions were analyzed using the two sets of results obtained by the first observer. No significant difference in eyes was noted in any of the nine positions, and no significant interaction difference between eyes was noted.

Study 2: Interobserver Variation—No significant difference was noted in eight of the nine positions between observers. There was a significant difference noted in position 4 (p=0.0452). Position 2 (p=0.0638) and position 3 (p=0.0659) did approach a significant interobserver variation.

Study 3: Day to Day Variation—On a second day, two to five days after the initial measurements, and within one hour of the time of day of the initial measurements, the first observer repeated the nine corneal thickness measurements in each eye. The right eye was again measured first. These measurements were compared to the first set of measurements made by this same observer on day one of the study.

Study 4: Time of Day Variation—The first observer repeated the nine corneal thickness measurements in each eye following the standardized protocol, right eye before left eye, and five to seven hours after the first set of measurements made on the second study day. These two sets of measurements made on the second day were then compared.

Computation of 95% confidence intervals of a single measurement was then performed using the total variance including intraobserver, interobserver, time of day, and day to day variation. The square root of the total variance was taken to determine the standard deviation. See Table 1.

In order to compare variance of position (i.e., central vs. paracentral vs. peripheral measurements), analysis was applied to the mean of the standard deviation of the five measurements.
taken at each position from each eye enrolled in the study. It was noted that there was less variation in central than paracentral measurements (p = .0366), in central than peripheral measurements (p = .0032), and in paracentral than peripheral measurements (p = .0323).

Discussion
Our study showed no statistically significant variation in the measurement of corneal thickness by ultrasonic pachymetry, in the majority of positions in the cornea, between observers, from day to day, or at different times of day. Position 4 (an inferior peripheral position) was noted to show statistically significant day to day and interobserver variation. Position 5 (an inferior paracentral position) also showed day to day variation which was significant. Perhaps this is due to difficulty in accurately positioning the ultrasonic probe inferiorly, since there was no statistically significant variation in the other positions tested. Our results indicate that there is little variation in the measurement of corneal thickness by ultrasonic pachymetry induced by different observers, different days, or different times of day. The lack of statistically significant interobserver variation is contrary to the findings of Salz et al. (1983).

Our finding of no statistically significant day to day variation is similar to the findings of Villasenor, et al. (1986) when they analyzed preoperative and intraoperative central corneal thickness measurements of 395 eyes in the PERK Study. We have extended this lack of statistically significant variation to include time of day variation. This is in contrast to the findings of Fujita (1980) who found a diurnal variation in central corneal thickness with an optical pachymeter. Our study limitations of two sets of measurements made five to seven hours apart may have masked a significant variation if one exists. Following Fujita's cosine curve for daily corneal thickness variation, our measurements were made at such times that the first measurements were made in the middle of the descending curve of corneal thickness and the second measurements were made at the trough of corneal thickness. The limited numbers of measurements and timing may have masked a statistically significant time of day variation.

Examination of the calculated 95% confidence intervals for each of the nine positions that we tested shows that a fair amount of the variation can occur in the measurement of the same position on the cornea. These confidence intervals, although they may vary slightly from machine to machine and observer to observer, will hopefully prove helpful in analysis of corneal thickness measurements obtained prior to refractive corneal procedures, in following patients with Fuch's dystrophy and pseudophakic bullous keratopathy or other disorders with corneal decompensation, and also in monitoring the adaptation of the cornea to contact lens wear. Previously, there has been no reliable and consistent method for comparing measurements of corneal thickness made at different examinations to see if there is a significant difference.

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Mean, Standard Deviation, Range, and 95% Confidence Intervals of corneal thickness measurements of nine corneal positions (microns)

<table>
<thead>
<tr>
<th>Point</th>
<th>Mean±S.D.</th>
<th>Range</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>506±21</td>
<td>435-561</td>
<td>±41</td>
</tr>
<tr>
<td>2</td>
<td>678±41</td>
<td>520-788</td>
<td>±80</td>
</tr>
<tr>
<td>3</td>
<td>570±46</td>
<td>484-676</td>
<td>±90</td>
</tr>
<tr>
<td>4</td>
<td>651±28</td>
<td>565-730</td>
<td>±55</td>
</tr>
<tr>
<td>5</td>
<td>529±26</td>
<td>455-616</td>
<td>±51</td>
</tr>
<tr>
<td>6</td>
<td>656±29</td>
<td>536-768</td>
<td>±57</td>
</tr>
<tr>
<td>7</td>
<td>543±16</td>
<td>464-639</td>
<td>±32</td>
</tr>
<tr>
<td>8</td>
<td>657±31</td>
<td>522-760</td>
<td>±60</td>
</tr>
<tr>
<td>9</td>
<td>539±19</td>
<td>439-617</td>
<td>±38</td>
</tr>
</tbody>
</table>

We used only one brand of ultrasonic pachymeter. It is possible that other brands show more or less variation and might demonstrate different confidence intervals.

Analysis was also performed to see if measurements at certain corneal positions were more reproducible and showed less variation than other positions. It appears from our data that central corneal thickness measurements showed less variability than paracentral (p = .0366) and peripheral (p = .0032) measurements. Paracentral measurements were in turn less variable than peripheral measurements (p = .0323). This would suggest that caution be exercised in analysis of data in studies com-
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Comparing central, paracentral, and peripheral corneal thickness measurements such as those by Insler and Cooper (1986) and Holland et al. (1986). Peripheral and paracentral positions may be more difficult to measure reproducibility because of increasing difficulties in positioning the ultrasonic probe in exactly the same spot and perpendicular to the corneal surface as one moves away from the center of the cornea.

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References