Highly Precise Eye Length Measurements in Children Aged 3 Through 12 Years

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Objective: To determine the feasibility, reliability, and validity of using partial coherence interferometry, a non-contact method that detects interference patterns from various layers of the eye, to measure axial length in young children.

Methods: The right eye of 64 subjects (mean age, 8.4 y; age range, 3.4-12.9 y; best-corrected visual acuity /H11350 20/30) was measured. Subjects fixated monocularly on the collimated light pattern from a laser diode (the alignment beam) and the operator used a video monitor to align the corneal reflection in the optical path. Axial length was measured during an 0.8-second scan using interference patterns from a collimated short coherence superluminescence diode aligned coaxially with the laser diode. Five series of 16 readings each were obtained. The average axial length for each of the 5 series of readings was calculated.

Main Outcome Measure: Axial length.

Results: Within-subject precision of axial length measurements was high, with an overall SE of measurement of 8 µm for individual subjects across the 5 sessions (95% confidence interval, ±16 µm). Subgroup analysis showed that sex, age, spherical equivalent, and refractive error exerted statistically significant effects on precision, but all of the differences among subgroups were 3 µm or less and likely to be insignificant clinically. Axial length measured by partial coherence interferometry varied systematically, with factors known to influence eye length (ie, age and refractive error), further validating the measurement method.

Conclusion: The partial coherence interferometry technique provides reproducible, extraordinarily precise eye length measurements in young children and should enable novel approaches to study eye growth and refractive development.

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PARTIAL COHERENCE interferometry (PCI)1-6 is a safe, non-contact, and highly precise technique to measure eye length, which has been used in both human adults and animals. The present study, applying this technology in young children, was undertaken to determine the feasibility and reliability of PCI axial length (AL) measurements in children aged 3 through 12 years, and further validated this technology by correlating the results with such factors as age and refractive error.

The standard clinical technique for determining eye length is ultrasonography.7 Conventional ultrasonographic measuring devices have, at best, an SD of ±100 µm in measuring eye length, depending on the frequency and diameter of the transducer. Ultrasonographic measurements frequently are confounded by potential misalignments, corneal indentation during measurement, and artifacts from the fluid meniscus between the probe and cornea.7,8 In optimum research settings, the expected SD can be greater, that is, between 150 and 200 µm, and in clinical settings, more than 250-µm SD should be expected (Cynthia J. Kendall, BMET, Innovative Imagery Inc, oral communication, April 8, 2003). The empirical variability of ultrasonography for children is even less certain, as studies commonly take repeated measurements and discard those that are inadequate measurements subjectively, thus biasing the findings toward lower variability. For instance, the technique reported in the COMET (Correction of Myopia Evaluation Trial)9 involved attempting 5 individual scans and, if any of these scans showed poor component definition or anterior chamber flattening, they were excluded. Then, additional scans were obtained to achieve an AL reading with a within-subject SD less than 100 µm.

In contrast to routine clinical ultrasonography, PCI is both noncontact and
more precise for AL measurements. In a small series of adults, PCI demonstrated excellent agreement with clinical ultrasonography, supporting its accuracy with the 2 methods showing average within-subject differences of 0 to 190 μm. However, PCI measurements were more precise, with an SD less than 30 μm, compared with 200 μm by ultrasonography in the same series.2 By extending the use of PCI to young children, such highly precise measurements could potentially provide novel insights into eye growth and refractive development and would have considerable value in evaluating methods of reducing the progression of myopia by shortening the time needed for a study.

METHODS

SUBJECTS

Children aged from 3 through 12 years were recruited from among the patients seen in the Division of Pediatric Ophthalmology, The Children’s Hospital of Philadelphia, Philadelphia, Pa. All subjects had a best-corrected visual acuity of 20/30 or better in the eye to be tested. Eyes with nystagmus or amblyopia were excluded. Each subject’s test date, birth date, sex, race, and refraction under cycloplegia (sphere, cylinder, or axis) were recorded. Partial coherence interferometry measurements were made in the subject’s right eye, except in subjects with unequal vision, in which case the eye with the better visual acuity was measured. The protocol was reviewed and approved by the institutional review board of The Children’s Hospital of Philadelphia.

PCI APPARATUS

Partial coherence interferometry is a noncontact, noninvasive method for the precise measurement of axial ocular dimensions. Near infrared light (850 nm in our instrument) from a low-coherence light source is delivered to the eye through a Michelson interferometer that has 2 independent optical paths.2,6 The mirror in 1 path is moved with a constant speed of 6 mm/s, changing the optical path lengths between the 2 arms of the interferometer. At the mirror position where the difference between these 2 optical paths matches the optical distance from the cornea to the retina, the light reflected from the anterior corneal surface and that from the individual reflective surfaces in the retina interfere and produce concentric interference fringes in front of the eye. The intensity of the reflected interference fringe is measured with a photograph detector and recorded with a computer as a function of mirror position. Between each series, the child was asked to move away from the chin rest and headrest to take a break. The child then returned for additional series of 16 readings. A complete measurement session consisted of 5 series of 16 readings each and required 20 to 30 minutes to complete.

PEAK IDENTIFICATION AND LOCALIZATION

As previous reports using PCI by our group and others have shown,2,3,6 the retinal reflections of the PCI signal generally comprise 3 or, in optimum tracings, 4 peaks. The largest of these, and the one most consistently visualized, is a peak that likely originates from the retinal pigment epithelium–Bruch membrane interface and corresponds to the third retinal peak (P3) from the internal limiting peak (first retinal peak or P1) in optimum tracings when 4 peaks are visualized. Axial length, in this article, is defined as the distance between the anterior corneal reflection and P3.

While the retinal pigment epithelium–Bruch membrane interface (P3) was the tallest peak in most readings, this was not a consistent finding between subjects or even between readings from a single subject. For this reason, the following analysis technique was developed to enhance identification of P3.

To analyze the interference fringe intensity data, customized software was written using MatLab (The Math Works Inc, Natick, Mass) to (1) eliminate aberrant waveforms, (2) average all valid readings from the 16 tracings of each measurement series, and (3) identify and locate the 4 peaks in the averaged waveforms.

Briefly, the automated algorithm involved examining the individual waveforms within each series to determine whether eye movements (characterized by large amplitude signal transients) were present, whether reflections were in a generally consistent location, and whether there was a high signal-noise ratio. The automated algorithm excluded an individual waveform (results of a single scan) from the analysis if it (1) contained any peak with an amplitude greater than a predefined threshold (set as the upper limit for uncontaminated waveforms) to exclude eye movements and blinks that produce high-amplitude signal artifacts, (2) did not contain any peaks higher than 4 SDs above the mean (values calculated from the entire trace), or (3) contained an apparent peak located more than 500 μm away from the median peak position calculated from the 16 waveforms for that series, to exclude occasional spurious peaks in locations outside the retina.

Validated waveforms were then low-pass filtered using a 10th order Butterworth filter to eliminate high-frequency noise and averaged to yield, ideally, 5 averaged waveforms for each subject, 1 from each measurement series. Digital filtering techniques were applied to prevent the influence of this filtering on peak location. Peaks representing reflective surfaces within the retina were identified in the averaged waveforms using an automated peak identification algorithm to assist in consistent identification of P3.

All averaged waveforms and automated peak identifications for each subject were reviewed by 2 observers (G.E.Q.,
and E.L.F.) in collaboration. Of the total of 304 averaged waveforms evaluated by the automated algorithm, only 7 averaged waveforms from 5 subjects appeared to have erroneously identified P3. The following 3 types of misidentification were encountered:

1. **Confusion with other retinal peaks**—The identified peak appeared, when all waveforms for that subject were compared, to represent either the first peak (P1) that is thought to represent the internal limiting membrane or the fourth peak (P4) that is thought to represent interfaces within the choroid-sclera (n = 1 excluded as P1 and no P3 could be identified in the averaged waveform, and n = 1 included as P3 could be identified on the averaged waveform though P4 was the maximum peak).

2. **Outlying peaks**—Automated peak detection identified a maximum peak several hundred micrometers removed from the region of the retina, likely due to poor fixation or an artifactual peak caused by aberrant reflections within the eye (n = 2 excluded).

3. **Noisy waveform**—Automated peak detection identified P3, but, on inspection, the averaged waveform was excessively noisy, having many peaks and no clear pattern of the usual 4-peak configuration (n = 3 excluded).

In the first 2 types of misidentification, if P3 was identified based on comparison with the other averaged waveforms from that subject, its location was established using a Matlab peak detector and was entered in the data set as P3 (n = 1). In the other cases, the averaged waveform was excluded from further analysis.

Optical length of an eye was converted to geometric AL by dividing optical AL by an empirically established average index of refraction for the human eye of 1.364. This value was derived by comparing the results of AL measurements in our laboratory using contact ophthalmic ultrasonography (model AB-5500; Sonomed, Lake Success, NY) and PCI in 39 adult subjects. This average index of refraction conforms to prior estimates used for PCI measurements of eye length.14

**DATA ANALYSIS**

Axial length for individual subjects is reported as the mean (SEM) of the location of P3 calculated from the averaged waveforms of each measurement series; thus each subject has up to 5 AL measurements that contributed to their mean value. Analysis of variance, intraclass correlations, and linear regressions were performed using SAS Version 8.2 (SAS Institute Inc, Cary, NC). F tests were used to compare variance estimates between subgroups of participants. The precision of the PCI measurement series was used as the basis for the 95% confidence interval (CI) of the AL measurement.

Errors were considered significant at a p value of less than 0.05. The generalized estimating equation approach was used in the regression analysis involving measurements from several series for each subject. In addition, ocular and demographic characteristics of each subject were considered in univariate and multivariate analyses.

The intensity of the measurement beam of the current instrument, 240 µW, corresponds to an incident radiation power of 600 µW/cm² assuming a 7-mm pupil. According to American National Standards Institute Z136 safety standards, this level of power at a wavelength of 850 nm is allowably continuous for longer than 20 minutes. Because the measurement beam illuminates the retina during the 0.8-second scan only, a total of about 1500 consecutive scans could be obtained and still be within safety standards. Considering that not more than 80 scans are obtained in a typical session and that the subjects take several breaks, the retinal light exposure with this instrument is well below the maximum permissible exposure levels as defined by the Food and Drug Administration requirements, as set forth in 21 §CFR 1040.10 and 1040.11.

**RESULTS**

Sixty-four subjects, 29 males and 35 females, participated in this study. The mean age of the subjects was 8.4 years (age range, 3.4–12.9 years). There were 33 white, 25 African American, 3 Asian, and 3 Hispanic children. Visual acuity ranged from 20/15 to 20/30 best corrected (mean, 20/21.9). Mean spherical equivalent was ±0.8 diopter (D) (range, −5.0 to +6.0 D); mean astigmatic error was 0.4 D (range, 0 to +2.5 D).

Representative PCI waveforms are provided for one reading in a series (Figure 2A) and for the waveform determined by the automated algorithm for a single series of 16 readings from the same subject (Figure 2B). All recruited subjects provided a measure of AL. Sixty of the 64 subjects provided data for 5 series of waveforms. Three subjects (aged, 4 years 3 months, 6 years 2 months, and 9 years 3 months) provided only 3 series of 16 waveforms; 1 subject, aged 3 years 4 months, provided only 1 series. Therefore, there were 305 series of individual waveforms obtained in the 64 subjects. The automated algorithm for identifying peaks excluded 13 series of waveforms. Six series were ultimately excluded subjectively. (One series in which P3 had been erroneously identified by the algorithm was included after P3 was identified on reevaluation). In the end, at least one P3 reading was obtained on all 64 subjects (n = 48 with...
5 series, n=8 subjects with 4 series, n=1 with 3 series, n=4 with 2 series, and n=3 with only 1 series).

VARIABILITY OF MEASUREMENT

A random-effects repeated-measures analysis of variance model was fit to the data to estimate AL measurement error using the PCI. The estimated component of variance within children due to measurement error was 67.4 µm², providing an SEmeasurement of 8.2 µm for individual children across 5 sessions. Thus, for an individual child, a single PCI AL measurement series of 16 readings has a 95% CI of 16 µm. The low variability between successive measurement series is shown in Figure 3 as boxplots of the differences between the first series and each of the 4 subsequent series. The distributions of differences are all centered around 0 and are similar in shape.

F tests were performed to determine whether the magnitude of measurement error varied with the demographic characteristics of the child (Table 1). There were several statistically significant comparisons: the SEmeasurement was larger in females, in children younger than 8 years, in eyes with a spherical equivalent refraction with an absolute value of greater than 0.5 D, and in eyes with an AL less than or equal to the median value of 23.08 mm. Importantly, none of these statistically significant differences in measurement precision between demographic groups were greater than 3.0 µm and, thus, none are likely to be of clinical importance. The highest estimate of variance was 9.5 µm (95% CI, 19.0 µm) for children younger than 8 years. Race did not significantly influence the SEmeasurement.

FACTORS INFLUENCING AL

Multivariate linear regression models were fitted to AL measurements to examine the relative contribution to AL of refractive error, various demographic characteristics (age, sex, and race), and position of the measurement series in the session. Four of the models are given in Table 2, beginning with a simple model with only age and spherical equivalent (model 1) and progressing to the more complete model with all factors (model 4).

As expected from the results of previous studies of refractive error, increased spherical equivalent myopic refraction (P<.001) and increased age (all P<.001) were strongly associated with longer AL in each model. Also as expected from previous studies, the average AL was about 650 µm longer for male than for female subjects of the same ages and having the same refractive error (P<.001). Axial length measured using the PCI did not vary significantly by race or for series position in a measurement session.

Table 1. Comparison of Reliability of Measurement Between Various Subgroups of Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Participants</th>
<th>SEmeasurement*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>29</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>35</td>
<td>9.4</td>
<td>.001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>33</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>25</td>
<td>8.3</td>
<td>.92</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>7.8</td>
<td>.80</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤8</td>
<td>29</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>&gt;8</td>
<td>35</td>
<td>7.1</td>
<td>.003</td>
</tr>
<tr>
<td>Spherical equivalent, D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.5</td>
<td>25</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>&gt;0.5</td>
<td>39</td>
<td>9.3</td>
<td>.005</td>
</tr>
<tr>
<td>Axial length, µm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Median</td>
<td>33</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>&gt;Median</td>
<td>31</td>
<td>7.3</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviation: D, diopter.
*Values calculated from the analysis of variance.
†Values calculated from F test of equal variances between subgroups.
comes $8.2/\sqrt{5} = 3.6 \mu m$, with a 95% CI of 7 \mu m. De-

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mated signal processing strategy described here in chil-
dren aged 3 through 12 years yields an SEmeasurement of \pm 8.2 
\mu m and a 95% CI of \pm 16 \mu m. This 95% CI estimate ap-
pplies to a single measurement series—that is, 16 indi-
vidual tracings. The precision was unaffected by race; there 
were statistically significant, but clinically trivial, influ-
ences of sex, age, spherical equivalent, and AL on mea-
surement precision, ranging between 1.7 and 3.0 \mu m for 

**Axial length as measured by the PCI significantly 
correlated with age and increasing negative spherical 
equivalent refractive error. Because both of these factors 
are known to correlate with AL as measured by other 
techniques,\(^4\) these relationships support the validity of 
the PCI technology and signal analysis for measuring 
ocular length. Additional support is provided by the re-

tuiton among series measurements were adjusted by GEE method. 
\(\dagger\)\(P\) value for the test of overall statistical significance of the factor.

**Table 2. Factors Associated With the Axial Length of Eyes From Multivariate Model\(^*\)**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Model 1: Estimate (95% CI), (\mu m); (P) Value</th>
<th>Model 2: Estimate (95% CI), (\mu m); (P) Value</th>
<th>Model 3: Estimate (95% CI), (\mu m); (P) Value</th>
<th>Model 4: Estimate (95% CI), (\mu m); (P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherical equivalent, 1 D  (^\dagger)</td>
<td>(-245.7 (\pm 357.5 to \pm 135.7)) (&lt;.0001)</td>
<td>(-240.2 (\pm 324.6 to \pm 155.8)) (&lt;.0001)</td>
<td>(-244.2 (\pm 329.5 to \pm 158.8)) (&lt;.0001)</td>
<td>(-244.2 (\pm 329.5 to \pm 158.8)) (&lt;.0001)</td>
</tr>
<tr>
<td>Age, 1 y  (^\uparrow)</td>
<td>129.1 (58.9 to 199.2) (&lt;.0003)</td>
<td>103.8 (41.6 to 166.0) (&lt;.001)</td>
<td>101.5 (39.9 to 163.1) (&lt;.001)</td>
<td>101.4 (39.8 to 162.9) (&lt;.001)</td>
</tr>
<tr>
<td>Sex, M vs F</td>
<td>637.7 (338.8 to 936.6) (&lt;.0001)</td>
<td>653.8 (361.2 to 946.4) (&lt;.0001)</td>
<td>653.9 (361.4 to 946.3) (&lt;.0001)</td>
<td>653.9 (361.4 to 946.3) (&lt;.0001)</td>
</tr>
<tr>
<td>Race</td>
<td>African American vs white</td>
<td>63.5 (\pm 220.6 to 347.5) (66)</td>
<td>63.8 (\pm 220.2 to 347.8) (66)</td>
<td>63.8 (\pm 220.2 to 347.8) (66)</td>
</tr>
<tr>
<td>Other vs white</td>
<td>74.0 (\pm 401.7 to 549.7) (.76)</td>
<td>74.2 (\pm 401.6 to 550.0) (.76)</td>
<td>74.2 (\pm 401.6 to 550.0) (.76)</td>
<td>74.2 (\pm 401.6 to 550.0) (.76)</td>
</tr>
<tr>
<td>Series</td>
<td>2 vs 1</td>
<td>37.0 (\pm 24.3 to 98.3) (.24)</td>
<td>37.0 (\pm 24.3 to 98.3) (.24)</td>
<td>37.0 (\pm 24.3 to 98.3) (.24)</td>
</tr>
<tr>
<td>Series</td>
<td>3 vs 1</td>
<td>36.8 (\pm 37.4 to 110.9) (.33)</td>
<td>36.8 (\pm 37.4 to 110.9) (.33)</td>
<td>36.8 (\pm 37.4 to 110.9) (.33)</td>
</tr>
<tr>
<td>Series</td>
<td>4 vs 1</td>
<td>35.4 (\pm 40.2 to 111.0) (.36)</td>
<td>35.4 (\pm 40.2 to 111.0) (.36)</td>
<td>35.4 (\pm 40.2 to 111.0) (.36)</td>
</tr>
<tr>
<td>Series</td>
<td>5 vs 1</td>
<td>38.3 (\pm 36.2 to 112.7) (.31)</td>
<td>38.3 (\pm 36.2 to 112.7) (.31)</td>
<td>38.3 (\pm 36.2 to 112.7) (.31)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GEE, generalized estimating equation.

\(\*\) The intercorrelation among series measurements were adjusted by GEE method.
\(\dagger\) \(P\) value for the test of overall statistical significance of the factor.

**COMMENT**

Partial coherence interferometry with the semiauto-
mated signal processing strategy described here in chil-
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Both instrument-related and computational issues may explain the improved precision of our PCI technique over the commercially available IOLMaster. From the instrument perspective, the low-coherence light sources differ. First, the super luminescence diode (emission at 850 nm) in our instrument emits at a longer wavelength than the multimode laser diode (emission at 780 nm) in the IOLMaster. Longer wavelength light scatters less in the ocular media, resulting in a greater penetration depth. Second, the super luminescence diode has a shorter coherence length (30 µm) than the multimode laser diode (120 µm), a difference that permits our instrument to discriminate and, hence, measure reflecting layers within the retina at a higher resolution. Third, the super luminescence diode does not produce the artificial intensity peaks that are caused by the symmetric coherence function of the multimode laser diode. In high-amplitude signals, such intensity peaks are sometimes observed at equal distances of about 800 µm on both sides of an actual signal peak and may be confused, by the IOLMaster, with signal peaks corresponding to reflections from retinal layers. Another difference between the commercially available instrument and our PCI instrument is the power of the incident light at the cornea. The measurement beam of the IOLMaster has a power of about 450 µW at the cornea, which limits the recommended number of scans to 20 within any 24-hour period for safety considerations. Given the nonlinear relationships between wavelength, power, and permissible exposure times, the lower power level of 240 µW in our instrument permits more consecutive scans and makes it more suitable for serial measurements of eye length, especially in patients who may fixate somewhat erratically or whose attention may wander.

Besides the instrument differences listed earlier, the apparent greater precision of our PCI, compared with the IOLMaster, may result from factors related to the analysis of the waveforms. Because of its greater safety margin resulting in increased capacity for multiple measures (16 × 5 readings per measurement session), the PCI allows improved precision statistically based on better estimation of the ocular parameter measured. In addition, while we are uncertain of the proprietary analytical approach of the IOLMaster, we developed a semiautomated, signal averaging peak detection algorithm designed specifically to reduce potential sources of ambiguity within the complex interference waveforms from the fundus layers.

Clearly, the PCI measurement method has great potential applicability to investigations requiring precise eye measurements, such as congenital glaucoma, and monitoring eye growth in relation to refractive error. Applications to refractive development will be particularly informative. Based on available data, a myopia progression rate of 0.5 D per year is a reasonable and conservative assumption for the US pediatric population; the PCI should be able to detect AL changes corresponding to this refractive shift over a 5- to 6-week period. Such a capacity can greatly compress the time needed to undertake longitudinal studies of eye growth and refractive development in children and would enable novel studies of acute changes in human refractive development. As not only chicks but also mammals exhibit small intraday fluctuations of ocular dimensions, PCI also will permit extension of this work to adult humans and children.

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REFERENCES


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