Corneal Biomechanics, Refractive Error, and Axial Length in Chinese Primary School Children

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PURPOSE. Low corneal hysteresis is associated with longer axial length in Chinese secondary school children. The authors sought to explore this association in primary school children.

METHODS. LogMAR presenting visual acuity, cycloplegic refractive error, ocular biometry, central corneal thickness (CCT), and corneal hysteresis (CH) was assessed for children in grades 1 to 3 at an academically competitive urban school in Shantou, China.

RESULTS. Among 872 eligible children (mean age, 8.6 ± 2.1 years), 651 (74.7%) completed the examination. Among 1299 examined eyes, 111 (8.5%) had uncorrected vision ≤6/12. Mean spherical equivalent refractive error for all eyes was +0.26 ± 1.41 D, and axial length (AL) was 22.7 ± 0.90 mm. CH for the lowest (mean AL, 21.7 ± 0.39 mm), two middle (mean AL, 22.4 ± 0.15 and 22.9 ± 0.15 mm), and highest quartiles (mean AL, 23.7 ± 0.74 mm) of AL were 10.6 ± 2.1 mm Hg, 10.4 ± 2.1 mm Hg, 10.3 ± 2.3 mm Hg, and 10.2 ± 2.3 mm Hg respectively (age- and gender-adjusted Pearson’s correlation coefficient r = −0.052; P = 0.001). In generalized estimating equation models adjusting for age, gender, and CCT, lower CH was significantly associated with longer AL (P < 0.001) and more myopic refractive error (P = 0.001).

CONCLUSIONS. CH measurement is practical in young children because this is when myopia undergoes its most rapid progression. Prospective follow-up of this cohort at high risk for myopia is under way to determine whether low CH is predictive, or a consequence, of long AL. (Invest Ophthalmol Vis Sci. 2011;52:4923–4928) DOI:10.1167/iovs.10-6211

Refractive error is the leading cause of vision disability among school-aged children in China1–4 and is associated with significant decreases in self-reported visual function.4 Although spectacles are a simple, safe, and effective intervention against refractive error, it has been shown that nearly two-thirds of Chinese children who would benefit from glasses are not wearing appropriate spectacles.3,5 As many as half of children who do wear glasses in rural China have inaccurate correction.6 Awareness of the benefit of spectacle wear in this setting is often limited or compromised by false beliefs that glasses will harm the eyes.7

For these reasons and because of the increased risk for retinal detachment,8 cataract,9 and glaucoma10,11 associated with increasing axial length, there is much interest in pharmacologic interventions such as atropine12,13 and pirenzepine14,15 to slow the progression of myopia and axial elongation. To make the most effective, targeted use of such therapies, and to limit the number of children experiencing side effects, it would be useful to be able to identify children at risk for myopia with early, noninvasive testing. Although indicators such as parental myopia and baseline refractive error16 have been shown to have moderate validity in predicting the onset of later myopia, the former may be impractical to measure in the context of school-based programs. We sought to explore whether newly available measures of scleral deformability might potentially add to the predictive power of the latter.

Several recent studies have examined the association between corneal biomechanical properties and refractive error in children. Corneal hysteresis is a measure of the viscoelastic properties of the corneoscleral shell, which may be assessed rapidly and noninvasively.17 At least two cross-sectional studies have reported low hysteresis to be associated with longer axial length in secondary school students of Chinese descent,18,19 whereas a third study of a racially mixed cohort in Singapore failed to identify a significant correlation.20 However, inferences of causality from such cross-sectional studies are limited: it is unknown whether low hysteresis predisposes to expansion of the scleral shell or whether a primary increase in axial length results in a secondary reduction in hysteresis.

We measured hysteresis, refractive error, and ocular biometry in a large cohort of primary school children in an urban Chinese setting. The goals of the current investigation were to determine whether accurate hysteresis measurements were possible among the younger children in whom progression of refractive error is most rapid and who would thus be the natural targets for any program of early intervention against myopia and to establish a cohort for prospective follow-up of hysteresis and refractive error to better elucidate the direction of any causal association between axial length and corneal biomechanics.

The current report provides data on the baseline association between axial length, refractive error, and corneal biomechanics in our cohort.
Methods

In October 2008, we examined all children in elementary grades 1, 2, and 3 at the Jinsha Elementary School in Shantou, China, a level 1 (most selective) school with 2000 students and 88 teachers. Shantou is a prefectural-level city of 4.97 million residents (2006 population count), located in coastal Eastern Guangdong Province, China. Shantou is one of the most densely populated regions in China, and the economy is based largely on manufacturing. The protocol for the current investigation was approved in full by the Institutional Review Board at the Joint Shantou International Eye Center. Written informed consent was obtained from the parents of all participants, and the tenets of the Declaration of Helsinki were followed throughout.

Participants

The parents of all children in grades 1, 2, and 3 at Jinsha Elementary School were sent invitation letters explaining the purpose and methods of the study. Parents were asked to check a box indicating whether they were willing for their child to participate in the study and to return the form to school with the child. Among 872 eligible participants, consent was obtained and examinations were completed on 651 (74.7%).

Assessment of Vision

Measurement of distance visual acuity with and without existing corrective lenses (if worn) was carried out at 4 m with back-illuminated (85 cd/m²) Tumbling E LogMAR (logarithm of the minimum angle of resolution) charts (Shantou City Medical Equipment Ltd., Shantou, China) in an area of each school with luminance in the range of 500 to 750 lux. The charts had five letters per line and 0.1 logMAR unit size progression between lines. The nontested eye was covered by the subject using a handheld occluder, with proper occlusion and neutral head position monitored by the examiner. The right eye was tested first. A single optotype of each size was presented first, starting at 6/30. If a letter was failed, testing began two lines above, with the child being asked to read all optotypes on the line sequentially. A subject had to identify correctly more than half the letters on a given line to be considered to have achieved that level of acuity.

Examination

All subjects underwent a detailed examination consisting of the following elements. All examiners were masked to the subjects’ results for modalities other than the test they were administering themselves. All equipment was calibrated according to the manufacturers’ specifications immediately before initiation of the study.

Cycloplegia was carried out with cyclopentolate 1% (Cyclogel; Alcon Laboratories, Fort Worth, TX) and tropicamide 1% (Mydriacyl; Tianjin Maida Medical Technology Co., Ltd., Tianjin, China). Three drops of each medication, followed one half-hour later, after a five-minute interval, with Mydriacyl, were instilled into each eye.

Spherical equivalent refractive error, D (if worn) was carried out at 4 m with back-illuminated (85 cd/m²) Tumbling E LogMAR (logarithm of the minimum angle of resolution) charts (Shantou City Medical Equipment Ltd., Shantou, China) in an area of each school with luminance in the range of 500 to 750 lux. The charts had five letters per line and 0.1 logMAR unit size progression between lines. The nontested eye was covered by the subject using a handheld occluder, with proper occlusion and neutral head position monitored by the examiner. The right eye was tested first. A single optotype of each size was presented first, starting at 6/30. If a letter was failed, testing began two lines above, with the child being asked to read all optotypes on the line sequentially. A subject had to identify correctly more than half the letters on a given line to be considered to have achieved that level of acuity.

A single measurement of axial length, anterior chamber depth, and lens thickness was made in each eye by ultrasound A-scan (ODM 2200; Tianjin Maida Medical Technology Co., Ltd., Tianjin, China). Intraocular pressure, central corneal thickness (CCT), and corneal hysteresis were measured in each eye of each subject (Ocular Response Analyzer; Reichert Instruments, Depew, NY). Five measurements were made in each eye after placement of topical anesthetic.

The ORA determines IOP and corneal hysteresis during rapid motion of the cornea in response to a short-duration (20-ms) air impulse. These cause the cornea to move inward, through application, and into slight concavity. Subsequently, the air pump shuts off, and the cornea moves through a second application while returning from concavity to its normal convex curvature. The pressure values at the inward and outward application event times are averaged to give the ORA reading of IOP, whereas the value for hysteresis, in millimeters of mercury, is the difference between the two pressures P1 and P2. The corneal resistance factor (CRF) is derived from the formula $(P1 - kP2)$, where $k$ is an empiric constant. The applanation regions of the ORA signals (spikes) were analyzed for the degree of “roughness” or nonmonotonicity, with the ideal signal having smooth monotonically rising and falling edges. The analysis determined an index (waveform score) based on the aggregate undesirable derivative regions of the rising and falling edges of the applanation signals.

There were no equipment failures during the testing; thus, all instances of failure to complete testing were attributed to the inability of young children to comply with examination protocols.

Statistical Analysis

Statistical analyses were performed (Statistical Package for Social Science (SPSS) version 15.0 for Windows XP, SPSS, Cary, NC). Logarithmic transformation was carried out for refractive error data to normalize the distribution. Multiple linear regression and generalized estimating equations (GEEs) were used to analyze the relationships among AL and CH, gender, age, CCT, and CRF, adjusting for the correlation between eyes of a single child. $P < 0.05$ was considered statistically significant.

Results

Among 872 eligible participants, consent was obtained and examinations completed on 651 (74.7%). Participants had a mean age of 8.6 ± 2.08 years (range, 7–12 years), and 311 (48.5%) were girls. Among 1299 examined eyes of 648 children, 111 (8.5%) had uncorrected vision ≤6/12, and the mean spherical equivalent refractive error was $-0.26 ± 1.41$ D. Axial length (1291 eyes of 643 children) was $22.7 ± 0.90$ mm, CCT (1296 eyes of 641 children) was $557 ± 29.5$ μm, and CH and CRF (1169 eyes of 575 children for each) were $10.4 ± 2.2$ and $11.2 ± 2.1$ mm Hg, respectively (Table 1). Myopia of $-0.5$ D or less was detected in 130 eyes (10.0%), and myopia of $-2.0$ D or less was detected in 60 eyes (4.6%).

Distances of axial length and refractive error are depicted in Figures 1 and 2, respectively, whereas Figure 3 depicts separate scattergrams of axial length and refractive error for boys and girls. The correlation between axial length and refractive error was $-0.653$ for girls and $-0.602$ for boys.

In view of the difficulty of achieving optimal ORA waveforms in young children, we examined the correlation between CH and axial length separately for three sets of eyes—those with data, which eliminated eyes with waveform scores in the bottom 25%, and eyes with waveform scores in the top 50%. When all eyes were included, the correlation between CH and AL was $-0.05$ ($P = 0.06$), whereas for the data set elimi-

<table>
<thead>
<tr>
<th>Character</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td>Axial length, mm (n = 1291)</td>
<td>$22.7 ± 0.90$</td>
</tr>
<tr>
<td>Spherical equivalent refractive error, D (n = 1299)</td>
<td>$0.26 ± 1.41$</td>
</tr>
<tr>
<td>CCT, μm (n = 1296)</td>
<td>$557 ± 29.5$</td>
</tr>
<tr>
<td>CH, mm Hg (n = 1169)</td>
<td>$10.4 ± 2.2$</td>
</tr>
<tr>
<td>CRF, mm Hg (n = 1169)</td>
<td>$11.2 ± 2.1$</td>
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</tbody>
</table>

Vision and refractive data could be obtained for only one eye in three children because of poor cooperation. Three children could not comply with axial length measurements in either eye, whereas five could do so in only one eye. Four children could not complete measurements of CCT in either eye, and six could do so in only one eye. Fifty-seven children were unable to perform CH/CRF testing in either eye, and 19 could perform it in only one eye.
nating the 25% and 50% poorest waveforms, respectively, the correlations were \(-0.09\) \((P < 0.0001)\) and \(-0.13\) \((P < 0.0001)\). When axial length was divided into quartiles for all eyes, the CH for the lowest (mean AL, 21.7 ± 0.39 mm), two middle (mean AL, 22.4 ± 0.15 and 22.9 ± 0.15 mm), and highest quartiles (mean AL, 23.7 ± 0.74 mm) were 10.6 ± 2.1 mm Hg, 10.4 ± 2.1 mm Hg, 10.3 ± 2.3 mm Hg, and 10.2 ± 2.3 mm Hg, respectively.

**FIGURE 1.** Distribution of axial length in 1291 eyes of 648 Chinese primary school children.

**FIGURE 2.** Distribution of spherical equivalent cycloplegic refractive error in 1299 eyes of 651 Chinese primary school children.
When adjusting for age and gender, lower CH ($P = 0.001$) but not CRF ($P = 0.37$) was significantly associated with longer axial length among all eyes. (Table 2) Adjusting for age and gender, lower CH was borderline associated ($P = 0.06$) with more myopic refractive error, whereas CRF ($P = 0.78$) was not associated with refractive outcome (Table 2). These associations remained constant in data sets that retained all eyes and those that eliminated eyes with waveforms in the bottom 25% and 50%, except that CH and refractive error were significantly associated ($P < 0.001$) among eyes with scores in the top 50% (Table 2).

In GEE models including all subjects, male gender ($P = 0.001$), older age ($P = 0.005$), lower CH ($P = 0.001$), and higher CRF ($P < 0.001$) were associated with longer axial length, and CCT ($P = 0.77$) was not associated with axial length. In GEE models of refractive error, older age ($P < 0.001$), lower CH ($P = 0.001$), and higher CRF ($P = 0.01$) were associated with more myopic refractive error, whereas CCT ($P = 0.24$) was not significantly associated (Table 3).

**DISCUSSION**

The results of this study were in accord with our own previous results and those of others in Chinese pediatric cohorts in finding a statistically significant, though modest, association between lower CH and longer axial length. The association between CH and refractive error was not consistent in the present study; it was present only in the multivariate model and in analyses adjusted for age and gender only when the 50% of subjects with the lowest waveform scores were removed. The lack of a strong and consistent relationship between CH and refractive error is again in accord with our previous results in older children.

The more complex observed relationship between CH and refractive error may be due, in part, to the process of vision-driven emmetropization, whereby corneal power and axial length adjust to match one another to reduce refractive error. In fact, it has been reported that low hysteresis is significantly associated with flatter corneas in Chinese children; this would tend to compensate for the association between low hysteresis and long axial length, leading to a less significant association between low hysteresis and myopic refractive error. From a practical standpoint, it appears likely that the pathologic effect of myopia on ocular conditions such as retinal detachment and glaucoma is mediated largely through increased axial length. It must be noted, however, that CH explained only a modest amount of the variation in AL in this cohort; it is likely that if CH measurements are of practical use in predicting AL change, they would have to be combined with...

**Table 2.** Relationship between CH and CRF with Axial Length and Refractive Error, Indicated by Pearson’s Correlation Coefficient, and GEE Models Adjusting for Age and Gender, in 1299 Eyes of 651 Chinese Children Aged 7 to 12 Years

<table>
<thead>
<tr>
<th></th>
<th>Axial Length</th>
<th></th>
<th>Refractive Error</th>
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<tbody>
<tr>
<td></td>
<td>CH</td>
<td>CRF</td>
<td>CH</td>
<td>CRF</td>
</tr>
<tr>
<td>All subjects included</td>
<td>$r = -0.052$</td>
<td>$\beta = -0.001$ $P = 0.001$</td>
<td>$r = 0.013$ $\beta = -0.002$ $P = 0.37$</td>
<td>$r = 0.027$ $\beta = 0.005$ $P = 0.06$</td>
</tr>
<tr>
<td>Bottom 25% waveform scores removed</td>
<td>$r = -0.084$ $\beta = -0.001$ $P &lt; 0.001$</td>
<td>$r = -0.019$ $\beta = -0.001$ $P = 0.11$</td>
<td>$r = 0.036$ $\beta = 0.002$ $P = 0.37$</td>
<td>$r = 0.021$ $\beta = -0.002$ $P = 0.36$</td>
</tr>
<tr>
<td>Bottom 50% waveform scores removed</td>
<td>$r = -0.131$ $\beta = -0.001$ $P &lt; 0.001$</td>
<td>$r = -0.044$ $\beta = -0.001$ $P = 0.06$</td>
<td>$r = 0.060$ $\beta = 0.004$ $P &lt; 0.001$</td>
<td>$r = -0.007$ $\beta = -0.002$ $P = 0.58$</td>
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Bold type indicates that the value was significant at the $P < 0.05$ level.
other noninvasively measured indicators that are more strongly associated with refractive error.

A strength of the present study is that it documented for first time an association between low hysteresis and greater axial length in younger, primary school children. Previous studies have been carried out in subjects whose mean age was 3 to 4 years older than those we observed.\cite{18,19,20} The early primary school years are the time of most rapid myopia progression, and any effort at myopia prevention would naturally be aimed at such children. Though the observed correlation between AL and CH improved when eyes with poor waveforms were removed, our results generally suggest that accurate measurement of CH may be practical in this age range.

The mechanisms whereby low CH might theoretically be linked causally to longer axial length remain unclear. Scleral remodeling occurs in myopia with changes in the orientation and content of collagen fibrils.\cite{23,24} In animal models, induced ametropia is also associated with changes in the collagen makeup of the cornea.\cite{25,26} Finite-element models have suggested that the biomechanical properties of the anterior segment reflect those of the entire globe.\cite{27} Further work is needed to fully elucidate the complex relationship between the biomechanical characteristics of the different components of the eye wall and the biomechanical changes occurring during development of the normal eye and the myopic eye.

The results and implications of this study must be understood in view of the study’s limitations. Most important, the current data set is cross-sectional, with the resultant limitations on inference of causality that have affected other studies on the relationship between CH and axial length in children. We are carrying out a 2-year follow-up on this cohort to address this issue. In addition, given that the data are not population based and are drawn from a single large school, application of these results to other groups must be made with caution. Finally, there are inherent limitations in the quality of data that can be obtained from ORA measurements in children in this age range, though the resultant inaccuracies would be likely to obscure rather than artificially inflate any relationship between CH and axial length.

Despite its limitations, the current report provides further evidence of a modest relationship between CH and axial length in Chinese children and demonstrates the practicality of carrying out such testing in young children. Further follow-up of this cohort will help to elucidate the directionality of any causal association between these two parameters.

### References


