

Corneal Biomechanical Properties and Retinal Vascular Caliber in Children

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PURPOSE. To examine the relationship between corneal biomechanical properties and retinal vascular caliber in Singaporean children in a cross-sectional study of 257 healthy subjects from the Singapore Cohort Study of Risk Factors for Myopia.

METHODS. Corneal hysteresis (CH), corneal resistance factor (CRF), central corneal thickness (CCT), and corneal compensated intraocular pressure (IOP_{CC}) were measured with a patented dynamic bi-directional applanation device. Digital retinal photography was performed, and retinal vascular caliber was measured with custom software. The central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) were calculated, representing the average arteriolar and venular calibers. Spherical equivalent (SE) refraction, axial length, height, weight, and mean arterial blood pressure (MABP) were measured.

RESULTS. Mean values of this study were as follows: age of study subjects, 13.97 ± 0.90 years; CH, 11.80 ± 1.55 mm Hg; CRF, 11.83 ± 1.72 mm Hg; CCT, 578.76 ± 34.47 μ m; IOP_{CC}, 15.12 ± 2.84 mm Hg; CRAE, 151.70 ± 15.54 μ m; CRVE, 227.51 ± 22.82 μ m. After controlling for age, sex, ethnicity, body mass index, father's educational level, MABP, IOP, and SE, there was a significant increase in CRAE by 1.40 μ m (95% CI: 0.17–2.61; $P = 0.03$) for every 1.55 mm Hg increase in CH and by 1.68 μ m (95% CI: 0.21–3.15; $P = 0.03$) for every 1.72 mm Hg increase in CRF. There were no significant associations between CRVE and CH, CRF, CCT, or IOP.

CONCLUSIONS. Lower CH and CRF are associated with narrower retinal arterioles in Singaporean children. (*Invest Ophthalmol Vis Sci.* 2009;50:121–125) DOI:10.1167/iops.08-2352

Based on new understanding that central corneal thickness (CCT) is an independent risk factor for glaucoma, it has been proposed that the biomechanical properties of the cornea may be a surrogate marker for glaucoma susceptibility.^{1–3} Measurement of biomechanical properties of the cornea in vivo has been facilitated by the development of a dynamic

bi-directional applanation device (Ocular Response Analyzer [ORA]; Reichert Ophthalmic Instruments, Depew, NY).^{4–7} The principal biomechanical parameter measured by the ORA is corneal hysteresis (CH), which is best described as a measure of corneal viscoelasticity. Lower CH has been associated with visual field progression in eyes with open-angle glaucoma (OAG).⁸

Recent investigations into vascular theories of glaucoma have focused on the association of retinal vascular caliber with glaucoma risk.⁹ For example, the parapapillary retinal vessels have been shown to be narrower in eyes with OAG than in those without OAG.¹⁰ This has been further demonstrated in population-based studies, including the Blue Mountains Eye Study in white persons and the Beijing Eye Study in Chinese persons,¹¹ in which retinal arteriolar narrowing is associated with glaucomatous optic neuropathy.^{11,12}

To the best of our knowledge, the relationship between corneal biomechanical properties and retinal vascular caliber has not been described. Corneal biomechanical properties may be associated with structural and biomechanical properties of the tissues within and surrounding the optic nerve, including the lamina cribrosa.^{13,14} Like the cornea, vessel walls are known to exhibit viscoelastic properties because of their primarily collagenous composition.^{15–19} The mechanical properties of the lamina cribrosa may be linked to those of the cornea through their continuity in the corneoscleral shell,²⁰ and the lamina cribrosa may be related to retinal vascular caliber because it provides structural support to the proximal retinal vessels. Therefore, in this study, we examined the relationship of corneal biomechanical properties and retinal vascular caliber in young children without glaucoma. Specifically, we tested the hypothesis that lower CH is associated with narrower retinal vessels.

METHODS

Study Population

This study was part of the Singapore Cohort Study of Risk Factors for Myopia (SCORM), which examined 1979 children aged 7 to 9 years at baseline in three local schools in Singapore. The study methodology and details of the study population have been previously described.^{21,22} Exclusion criteria included significant systemic illnesses and ocular conditions including media opacity, uveitis, or a history of intraocular surgery, refractive surgery, glaucoma, or retinal disease. Two hundred seventy-one subjects from one participating school (Western) were systematically sampled for ORA measures during the 2007 visit, and retinal vessel caliber measurements were normal in 257 subjects. For the purposes of the study, all ocular measurements from the right eye were included in the analysis.

Compared with children in the same school who did not undergo ORA and retinal vessel caliber measurements, the 257 children included in the study were significantly older (mean age, 13.96 ± 0.90 years vs. 13.81 ± 0.87 years; $P = 0.047$) and had a lower percentage of Chinese ethnicity (68.9% vs. 79.5%; $P = 0.002$). There were no significant differences in sex distribution (boys, 50.9%; girls, 51.52%; $P = 0.47$), mean spherical equivalent (SE) refraction (-2.38 ± 2.48 D

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vs. -2.64 ± 2.60 D; $P = 0.23$) or axial length (24.54 ± 1.16 mm vs. 24.61 ± 1.20 mm; $P = 0.46$).

All study procedures were performed in accordance with the tenets of the Declaration of Helsinki as revised in 1989. Written informed consent was obtained from the parents of subjects with assent from the children, and the study was approved by the Institutional Review Board of the Singapore Eye Research Institute.

The Ocular Response Analyzer

The ORA, developed by Reichert Ophthalmic Instruments, is a non-contact device that measures IOP and corneal biomechanical properties. Each subject was seated on a chair and instructed to place the forehead on the headrest of the ORA device, which was adjusted to match the height of the subject through an adjustable table. To avoid startling the subject, each was first briefed about a noncontact probe that could move toward the eye and emit a sudden but gentle gust of air. Subjects were told to focus on a blinking red light in the device. Thereafter, the ORA was activated, and the air puff was emitted onto the center of the cornea. A typical applanation/pressure plot generated by the ORA for each eye showed two well-defined applanation peaks of almost similar height corresponding to inward and outward applanation. The intersection of a vertical line drawn from each applanation peak with the pressure curve defined two applanation pressures, the difference in magnitude of which was attributed to energy absorption during corneal deformation and formed the basis for the CH measurement. ORA readings were obtained consecutively, and only good quality readings were analyzed, as defined by the force-in and force-out applanation signal peaks on the ORA waveform being symmetric in height. All readings were vetted by a study expert (AK). The average of three readings was taken. The ORA software uses applanation pressure peaks to generate two additional parameters, the corneal compensated IOP (IOP_{CC}) and the corneal resistance factor (CRF).⁴ A Goldmann-correlated IOP (IOP_C) is also provided by the machine. No cycloplegic eyedrop or topical anesthetic was administered before the ORA measures, but a topical anesthetic was instilled before CCT measurement, with the contact ultrasound pachymetry probe included with the ORA machine. The probe was placed perpendicularly to the midpupillary axis, and the mean of three measurements was taken. Measurements were repeated two to three times for each eye.

Retinal Vascular Caliber Measurements

Methods for obtaining digital fundus photographs and for measuring retinal vascular caliber from these photographs have been detailed in earlier publications from SCORM.²³⁻²⁶ After the ORA examinations, cycloplegia was attained with 3 drops of 1% cyclopentolate 5 minutes apart. After an interval of at least 30 minutes after the third drop, retinal photographs centered on the optic disc were obtained with a digital fundus camera (CR6-NM45, EOS-D60 6.3 mega-pixel; Canon, Lake Success, NY). A computer-based program was then used to measure the caliber of all retinal vessels located between 0.5 and 1 disc diameter from the optic disc margin. A pair of indices, the central retinal arteriolar and venular equivalents (CRAE and CRVE), representing the average arteriolar and venular calibers for each eye, was then calculated using formulas previously described.^{27,28}

All retinal measurements were performed by a single grader who was masked to the subjects' identities and other measured parameters. Re-measurement of 50 images 2 weeks later showed high reproducibility, with intraclass correlation coefficients of 0.85 for arteriolar caliber and 0.97 for venular caliber.^{23,24,29}

Other Study Procedures

After the ORA examinations, cycloplegic refraction was performed with an autokeratorefractometer (model RK5; Canon, Inc., Ltd., Tochigiken, Japan). Cycloplegia was achieved with 3 drops of 1% cyclopentolate 5 minutes apart. After an interval of at least 30 minutes after the third drop, five consecutive readings were obtained with 1 of 2 calibrated autokeratorefractometers. Axial length (AL) measurements

were performed with a contact ultrasound A-scan biometry machine (Echoscan model US-800, probe frequency of 10 MHz; Nidek Co., Ltd., Tokyo, Japan), with 1 drop of 0.5% proparacaine for topical anesthesia. Measurements were repeated until the SD was less than 0.12 mm and the average of six measurements was taken.

Height was measured with the subjects standing without shoes. Weight in kilograms was measured using a standard portable weighing machine calibrated before the beginning of the study.^{21,22} Blood pressure was measured on the school premises according to a standard protocol.^{21,22} After 5 minutes of rest, blood pressure was measured with the use of an automated sphygmomanometer (Omron Healthcare, Bannockburn, IL) and the appropriate cuff size with the subjects in a seated position. The cuff size was selected to ensure that the bladder spanned the circumference of the arm and covered at least 75% of the upper arm without obscuring the antecubital fossa. Three separate measurements were taken and averaged for analysis. Mean arterial blood pressure (MABP) was defined as two-thirds of the diastolic blood pressure plus one-third of the systolic blood pressure.

The parents of the subjects completed several questionnaires that covered several topics, including indicators of socioeconomic status such as father's education. The father's education level was classified as no formal education, primary school education, secondary school education, preuniversity education or diploma, and tertiary/university education.

Statistical Analyses and Definitions

Spherical equivalent (SE) was calculated as sphere plus half-negative cylinder. Multivariable linear regression models were constructed with CRAE or CRVE as the dependent variable to assess the relationship with CH, CRF, CCT, and IOP_{CC}, with initial adjustments for age, sex, and ethnicity. BMI, father's education as an indicator of overall socioeconomic status, SE, IOP, and MABP were added as covariates in a second multivariable linear regression model because these factors had been identified as covariates associated with retinal vascular caliber in previous studies from the same cohort.^{25,26,29,30} The completed educational levels of both parents were ascertained, but father's education was the best indicator of socioeconomic status in the SCORM study and was thus used in the statistical analysis. All probabilities quoted are two sided, and all statistical analyses were undertaken using the a commercial system (Statistical Analysis System, version 8; SAS Institute, Cary, NC).

RESULTS

Two hundred fifty-seven eyes of 257 subjects were included in the analysis. The mean age of the study subjects was 13.97 ± 0.90 years, there was a slight male preponderance (130 boys; 50.6%), and most subjects (177; 68.9%) were Chinese. The mean CRAE was 151.70 ± 15.54 μ m, and the mean CRVE was 227.51 ± 22.82 μ m. The mean CH was 11.80 ± 1.55 mm Hg, the mean CRF was 11.83 ± 1.72 mm Hg, the mean CCT was 578.76 ± 34.47 μ m, and the mean IOP_{CC} was 15.12 ± 2.84 mm Hg.

Baseline characteristics of the study population, by sex, are described in Table 1. Boys had lower CRAE values than girls (149.02 ± 14.20 μ m vs. 154.44 ± 16.41 μ m; $P = 0.005$) and higher MABP than girls (76.86 ± 9.38 mm Hg vs. 73.61 ± 7.89 mm Hg; $P = 0.003$). All other parameters were not significantly different between sexes.

After controlling for age, sex, and ethnicity and then further controlling for BMI, father's educational level, IOP, MABP, and SE, there were significant increases in CRAE by 1.40 μ m (95% CI: 0.17-2.61; $P = 0.03$) for every 1.55 mm Hg increase in CH and by 1.68 μ m (95% CI: 0.21-3.15; $P = 0.03$) for every 1.72 mm Hg increase in CRF. In models that controlled for age, sex, and ethnicity only, there was a 1.12 μ m (0.02-2.23; $P = 0.047$) increase in CRAE for every 1.72 mm Hg increase in CRF and a

TABLE 1. Differences in Retinal Vascular Measurements and Corneal Biomechanical Parameters by Sex

	Total (<i>n</i> = 257)	Male (<i>n</i> = 130)	Female (<i>n</i> = 127)	<i>P</i>
Race				
Chinese	177 (68.9)	87 (66.9)	90 (70.9)	0.41
Malay	48 (18.7)	27 (20.8)	21 (16.5)	
Indian	30 (11.7)	14 (10.8)	16 (12.6)	
Other races	2 (0.8)	2 (1.5)	0 (0)	
Father's educational level				
No formal education	8 (3.1)	4 (3.1)	4 (3.1)	0.13
Primary school education	65 (25.3)	38 (29.2)	27 (21.3)	
Secondary school education	109 (42.4)	45 (34.6)	64 (50.4)	
Pre-university education or diploma	45 (17.5)	27 (20.8)	18 (14.2)	
Tertiary/university education	30 (11.7)	16 (12.3)	14 (11.0)	
CRAE (μm)	151.70 \pm 15.54	149.02 \pm 14.20	154.44 \pm 16.41	0.005
CRVE (μm)	227.51 \pm 22.82	225.55 \pm 22.37	229.51 \pm 23.20	0.17
CH (mm Hg)	11.80 \pm 1.55	11.68 \pm 1.58	11.93 \pm 1.52	0.19
CRF (mm Hg)	11.83 \pm 1.72	11.62 \pm 1.68	12.03 \pm 1.75	0.06
CCT (μm)	578.76 \pm 34.47	580.82 \pm 35.29	576.65 \pm 33.63	0.34
IOP _{CC} (mm Hg)	15.12 \pm 2.84	14.99 \pm 2.70	15.25 \pm 2.98	0.47
Age (y)	13.97 \pm 0.90	13.97 \pm 0.87	13.97 \pm 0.93	0.99
BMI (kg/m ²)	19.47 \pm 3.90	19.67 \pm 3.88	19.28 \pm 3.93	0.42
MABP (mm Hg)	75.26 \pm 8.81	76.86 \pm 9.38	73.61 \pm 7.89	0.003
IOP (mm Hg)	16.25 \pm 3.01	15.93 \pm 2.75	16.57 \pm 3.24	0.09
SE refraction (D)	-2.38 \pm 2.48	-2.63 \pm 2.59	-2.14 \pm 2.35	0.12

Data for race and father's educational level are *n* (%); all other data are mean \pm SD.

0.69 μm (-1.36 – -0.01 ; $P = 0.046$) decrease in CRAE for every 2.84 mm Hg increase in IOP_{CC} (Table 2)

There were no significant associations between CRVE and CH, CRF, CCT, or IOP (Table 2). Relationships and correlation coefficients among CH, CRAE, and CRVE are shown in the scatterplots in Figure 1. CRAE showed a weak but significant correlation with CH.

DISCUSSION

Our study on a population of healthy children has demonstrated a significant association between CH and CRF measured with the ORA and retinal vascular caliber. Specifically, we showed that lower CH and CRF, measures of corneal viscoelasticity previously linked with glaucoma in adults,⁸ is associated with narrower retinal arteriolar, but not venular, calibers. To our knowledge, there are no comparable studies.

Current understanding of the corneal biomechanics indicates that the viscoelastic properties of the cornea are conferred primarily by stromal collagen fibrils and their interactions with the extracellular proteoglycan matrix.³¹ The association between lower CH and CRF with narrower retinal arteriolar caliber suggests that the biomechanical properties of the cornea may be linked to those of other collagen-based structures in the eye, specifically the retinal vasculature. Alternatively, we speculate that CH and CRF may be more directly associated with the viscoelastic properties of the lamina cribrosa because of their direct continuity in the eye wall. Corneal thickness is known to be linked to scleral thickness (Albekioni Z, et al. *IOVS* 2003;44:ARVO E-Abstract 103). In a study correlating the CCT with changes in optic nerve head blood flow after IOP reduction, Lesk³² found that thin CCT was associated with smaller improvements in optic nerve head blood flow after therapeutic IOP reduction. The authors hypothesized that

TABLE 2. Relationships among CH, CRF, CCT, IOP, and Retinal Vascular Caliber

	Retinal Arteriolar Caliber (μm)		Retinal Venular Caliber (μm)	
	Mean Difference (95% CI)	<i>P</i>	Mean Difference (95% CI)	<i>P</i>
CC per SD (1.55 mmHg) increase				
Age and sex adjusted, Model 1*	1.75 (0.54–2.97)	0.005	1.32 (–0.50–3.14)	0.16
Multivariate adjusted, Model 2†	1.43 (0.18–2.68)	0.03	1.31 (–0.57–3.21)	0.17
CRF per SD (1.72 mmHg) increase				
Age and sex adjusted, Model 1*	1.12 (0.02–2.23)	0.047	0.54 (–1.11–2.19)	0.52
Multivariate adjusted, Model 2†	1.68 (0.21–3.15)	0.03	1.55 (–0.67–3.77)	0.17
CCT per SD (34.47 μm) increase				
Age and sex adjusted, Model 1*	0.05 (–0.003–0.11)	0.07	0.02 (–0.06–0.11)	0.60
Multivariate adjusted, Model 2†	0.05 (–0.02–0.11)	0.15	0.02 (–0.07–0.11)	0.63
IOP per SD (2.84 mmHg) increase				
Age and sex adjusted, Model 1*	–0.69 (–1.36–0.01)	0.046	–0.84 (–1.84–0.16)	0.10
Multivariate adjusted, Model 2†	–0.41 (–1.09–0.28)	0.25	–1.24 (–2.99–0.51)	0.16

* Model 1: Adjusted for age, sex, and ethnicity.

† Model 2: Adjusted for age, sex, ethnicity, father's education, body mass index, mean arterial blood pressure, intraocular pressure and spherical equivalent.

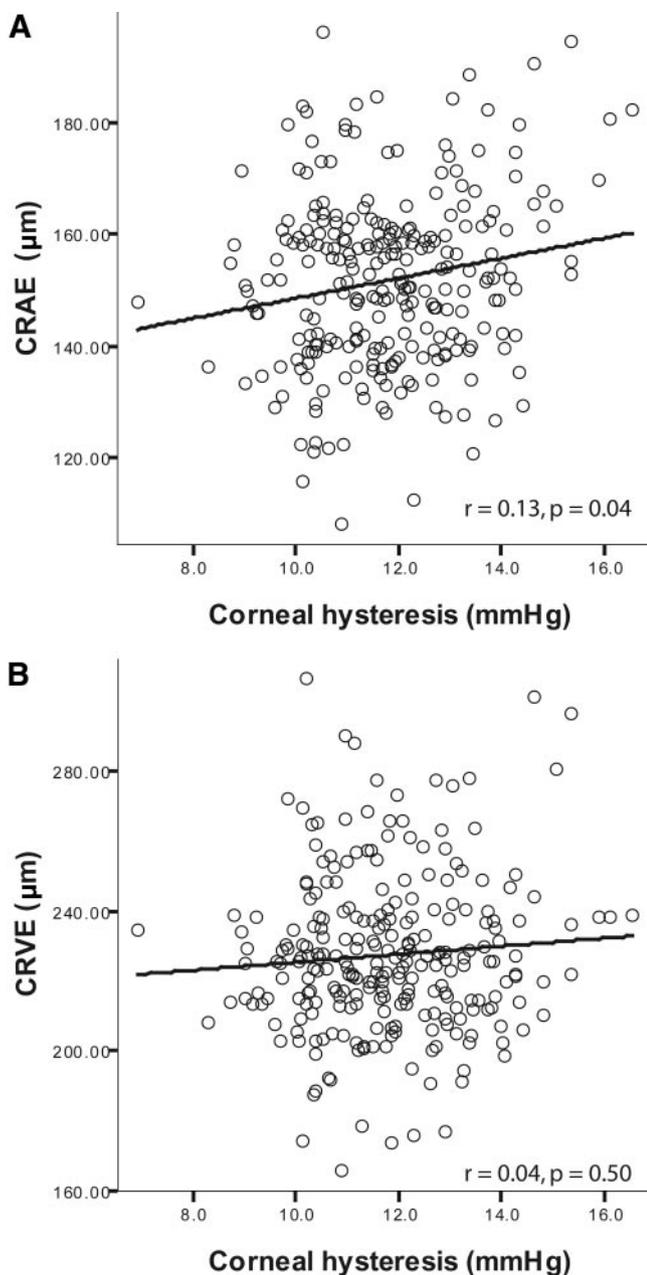


FIGURE 1. Scatterplots of (A) CRAE and (B) CRVE versus corneal hysteresis.

thin CCT may be associated with a thin lamina cribrosa, and the reduced mechanical support for blood vessels passing through the lamina cribrosa may in turn lead to compression of the vessel walls. Such a mechanism may provide a plausible explanation for our findings because a “viscoelastic” lamina cribrosa is likely to be more resistant to physiologic or pathologic variations in IOP.

In contrast to arteriolar caliber, venular caliber did not show significant associations with any of the corneal biomechanical parameters in our study. This may be because, unlike arterioles, small postcapillary venules have an almost nonexistent tunica media,³³ and their caliber may thus be correspondingly determined less by the biomechanical properties of the vessel wall. Alternatively, it supports the vascular theory of glaucoma in that retinal arteriolar narrowing may be a preceding factor involved in glaucoma development

The strengths of our study design include in vivo assessments of corneal biomechanical properties and retinal vascular caliber in Asian children by independent and masked observers, standardized assessment of cycloplegic refraction, biometry and anthropometric measures, and blood pressure. The availability of a healthy young population may also minimize the confounding effects of various systemic (e.g., diabetes, hypertension) and ocular (retinopathy) diseases associated with retinal vascular caliber in older populations.²⁵ General limitations of our study regarding errors inherent in retinal photography and measurement²⁸ and random errors associated with the timing of photography in relation to the cardiac cycle have been described.²⁵ These random errors, however, would likely bias our results to null. Finally, the possibility of selection bias cannot be totally excluded given that a significant proportion of participants was excluded because of lack of ORA data. Our findings, therefore, require validation from future studies.

In conclusion, we document an association between corneal biomechanical properties and retinal arteriolar caliber, supporting the concept that corneal structure may be linked to the structure of vascular tissues in or around the optic nerve head. We show that lower CH and CRF are associated with narrower retinal arterioles in children with no evidence of glaucoma. Our findings indicate that corneal biomechanical properties may have to be accounted for in studies on retinal vascular caliber.

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