Right and Left Correlation of Retinal Vessel Caliber Measurements in Anisometropic Children: Effect of Refractive Error

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PURPOSE. Previous studies have reported high right–left eye correlation in retinal vessel caliber. We test the hypothesis that right–left correlation in retinal vessel caliber would be reduced in anisometropic compared with emmetropic children.

METHODS. Retinal arteriolar and venular calibers were measured in 12-year-old children. Three groups were selected: group 1, both eyes emmetropic (n = 214); group 2, right–left spherical equivalent refraction (SER) difference $\geq$1.00 but <2.00 diopter (D) (n = 35); and group 3, right–left SER difference $\geq$2.00 D (n = 32). Pearson's correlations between the two eyes were compared between group 1 and group 2 or 3. Associations between right–left difference in refractive error and right–left difference in caliber measurements were assessed using linear regression models.

RESULTS. Right–left correlation in group 1 was 0.57 for central retinal arteriolar equivalent (CRAE) and 0.70 for central retinal venular equivalent (CRVE) compared with 0.60 and 0.82 for CRAE and CRVE, respectively, in group 2 (P = 0.42 and P = 0.08), and 0.36 and 0.52, respectively, in group 3 (P = 0.08 and P = 0.07, referenced to group 1). Each 1.00-D increase in right–left SER difference was associated with a 0.74-μm increase in mean CRAE difference (P = 0.02) and a 1.23-μm increase in mean CRVE difference between the two eyes (P = 0.002). Each 0.1-mm increase in right–left difference in axial length was associated with a 0.21-μm increase in the mean difference in CRAE (P = 0.01) and a 0.42-μm increase in the mean difference in CRVE (P < 0.0001) between the two eyes.

CONCLUSIONS. Refractive error $\geq$2.00 D may contribute to variation in measurements of retinal vessel caliber. (*Invest Ophthalmol Vis Sci.* 2012;53:5227–5230) DOI:10.1167/iovs.12-9422

Measurement of retinal vessel caliber has been widely used in many studies in the last few decades, with associations found between retinal arteriolar or venular caliber and some ocular and systemic conditions.[1–5] It has been reported that measurement from retinal images can be affected by ocular parameters such as refractive error.[6–8] In the Blue Mountains Eye Study, central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) were found to be smaller in adults with myopic compared with hyperopic refraction.[8] Similarly, in the Beaver Dam Eye Study, myopic refraction was found to be associated with smaller retinal arteriolar and venular calibers.[9]

This effect of refractive error on image magnification can be rectified using a refractive correction,[8] which in turn helps to eliminate spurious associations.[10] Given that a high correlation of retinal vessel caliber between right and left eyes has been documented previously,[9,11] we hypothesized that such correlation would be reduced in anisometropic persons, if refractive error affects measurements. In this report, we aimed to validate the effect of refractive error on retinal vessel caliber measurement by assessing the correlation of retinal vessel caliber between right and left eyes in 12-year-old children with emmetropia compared with those with anisometropia.

METHODS

Study Population

The Sydney Myopia Study (part of the Sydney Childhood Eye Study) examined a population-based sample of school children from grade 1 (aged 6 years) and grade 7 (aged 12 years). The study was approved by the Human Research Ethics Committee, University of Sydney, the Department of Education and Training, and the Catholic Education Office, New South Wales, Australia, and adhered to the tenets of the Declaration of Helsinki. Details of this study population were previously described.[12] Briefly, 34 primary and 21 secondary schools were selected using random cluster sampling with proportionate public and private or religious schools and different socio-economic levels included. Of the 3144 eligible Year 7 students, 2353 (75.3%) were examined during 2004–2005. Data from a subsample of the 12-year-old participants were used in this study.

Three groups of children were selected from the 2353 participants, based on differences in spherical equivalent refraction (SER) between right and left eyes. Group 1 included 214 randomly selected children with emmetropia, defined as SER between –0.50 diopters (D) and 0.50 D (inclusive) in both eyes, and right–left difference in SER <0.25 D; group 2 included 35 children with right–left difference $\geq$1.00 D but <2.00 D; and group 3 included 32 children with anisometropia, right–left difference $\geq$2.00 D.

Assessment of Axial Length

Axial length was measured before cycloplegia with an optical biometer (IOLMaster; Carl Zeiss Meditec, Jena, Germany) that used dual-beam

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Supported by the National Health and Medical Research Council, Canberra, Australia (Grant 253732).

Submitted for publication January 1, 2012; revised May 31 and July 2, 2012; accepted July 5, 2012.

Disclosure: **N. Joachim**, None; **E. Rochtchina**, None; **A.G. Tan**, None; **T. Hong**, None; **P. Mitchell**, None; **J.J. Wang**, None

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Table 1. Characteristics of 12-Year-Old Study Participants in Groups 1, 2, and 3

	Group 1* (n = 214)	Group 2* (n = 35)	Group 3* (n = 32)
Age, y (SD)	12.6 (0.5)	12.7 (0.5)	12.6 (0.4)
Sex (male), %	56.5	51.4	40.6
Ethnicity			
Caucasian, %	51.4	29.4	56.3
East Asian, %	23.4	41.2	34.4
Other, %	25.2	29.4	9.4
BMI, kg/m^2 (SD)	20.6 (4.6)	20.1 (3.8)	19.0 (2.8)
Mean blood pressure			
Systolic, mm Hg (SD)	114.1 (11.2)	109.2 (10.0)	109.7 (8.3)
Diastolic, mm Hg (SD)	66.0 (8.2)	62.9 (8.7)	63.6 (7.6)
Mean refractive error			
Right eye, D (SD)	0.2 (0.3)	−0.7 (2.9)	1.2 (3.8)
Left eye, D (SD)	0.2 (0.3)	−0.04 (3.4)	0.9 (3.4)
Mean difference in refractive error between two eyes, D (SD)	0.1 (0.1)	1.4 (0.3)	3.1 (1.1)

* Group 1, both eyes emmetropic and right–left difference in SER <0.25 D; group 2, right–left SER difference ≥1.00 D but <2.00; group 3, anisometropic with right–left SER difference ≥2.00 D.

partial coherence interferometry of 780-nm wavelength. The average of five measurements was used in the analyses.

Assessment of Refractive Errors

Cycloplegic autorefraction was performed 30 minutes after instillation of a corneal anesthetic, amethocaine hydrochloride 0.5%, followed by two cycles of cyclopentolate 1% (1 drop) and tropicamide 1% (1 drop) 5 minutes apart to induce pupil dilation. Spherical equivalent refraction was calculated as the sum of spherical power plus ½ cylindrical power. In this report, we defined anisometropia as a right–left difference in SER ≥2.00 D. There were 13 children with a right–left difference in SER ≥3.00 D in the study sample, and of these 13, retinal images of both right and left eyes were gradable for retinal vessel caliber in only 10 children.

Retinal Vessel Caliber Measurements

Digital 60° color photographs, centered on the optic disc, were taken with a Canon 60° mydriatic fundus camera (model CF-60Uvi, CF-DA camera adapter, EOS-10D digital camera; Canon, Inc., Tokyo, Japan).[12] Details of computerized measurement of retinal arteriolar and venular calibers have been previously described in detail.[9,13,14] Briefly, a semiautomated imaging program (IVAN; University of Wisconsin, Madison, WI) was used to measure the diameter of all retinal vessels in a zone 0.5- to 1.0-disc diameter away from the optic disc margin. Graders, masked to participant identity and characteristics, performed the retinal vessel measurements on the right and left eyes of each subject. The average value for retinal arteriolar or venular caliber of each eye was estimated using the Knudtson-Hubbard formula[14] (CRAE and CRVE for the two vessel types, respectively). Inter-grader reliability was high, with correlation between graders ranging from 0.82 to 0.88 for CRAE and 0.93 to 0.95 for CRVE. Intra-grader reliability was within a similar range (CRAE, $r = 0.85$; CRVE, $r = 0.97$).[15]

Statistical Analysis

Analyses were performed using SAS (version 9.1, SAS Institute, Cary, NC). Correlations between right and left eyes (right–left correlation) for CRAE and CRVE were presented as Pearson's correlation coefficient (r). Almost perfect correlation is represented by r between 0.81 and 1.00, substantial correlation by r between 0.61 and 0.80, moderate correlation by r between 0.41 and 0.60, and poor to fair correlation by $r < 0.40$.[16] Significant differences in the correlations between group 1 and groups 2 or 3 were assessed using Fisher's z transformation.[17] Additional linear regression models were constructed using the majority of the 12-year-old cohort from the Sydney Myopia Study ($n = 2246$ for analysis of refractive errors and $n = 2196$ for axial length, of 2353 total subjects, after excluding participants with no retinal fundus photographs or those where retinal vessel caliber grading could not be carried out because of poor photo quality) to assess the association of right–left differences in retinal vessel caliber with the corresponding differences in refractive error, and also with the corresponding differences in axial length.

Results

Table 1 presents characteristics of the three groups of 12-year-old study participants from the Sydney Myopia Study. Age, body mass index (BMI), and blood pressure were similar across the three groups. Mean refractive errors in right eyes were 0.18 D, –0.67 D, and 1.18 D for groups 1, 2, and 3, respectively.

Mean CRAE and CRVE of right and left eyes, and the correlations between the two eyes for each of the three groups, with and without adjustment for axial length, are presented in Table 2. Moderate inter-eye correlations of 0.57 and 0.60 were found for CRAE in groups 1 and 2, respectively; while correlation for CRVE was substantial, 0.72 in group 1 and 0.82 in group 2. No significant difference was found for right–left correlations of CRAE or CRVE between groups 1 and 2 ($P = 0.42$ for CRAE, $P = 0.07$ for CRVE). In group 3, right–left correlation was 0.36 for CRAE and 0.52 for CRVE, much lower than group 1, but the differences were marginally nonsignificant ($P = 0.08$ and $P = 0.07$, respectively). These inter-eye correlation coefficients remained similar before and after adjusting for inter-eye differences in axial length (Table 2).

Additional analyses using the entire 12-year-old study sample showed that each 1.00-D increase in right–left difference in SER was associated with a 0.74-μm increase in mean right–left difference in CRAE ($P = 0.02$; $R^2 = 0.002$), and a 1.23-μm increase in mean right–left difference in CRVE ($P = 0.002$; $R^2 = 0.004$). Similarly, a weak association was also observed between right–left axial length difference and right–left vessel caliber difference: every 0.1-mm increase in right–left difference in axial length was associated with a 0.21-μm increase in the mean difference in CRAE ($P = 0.01$; $R^2 = 0.003$) and a 0.42-μm increase in the mean difference in CRVE ($P < 0.0001$; $R^2 = 0.007$) between the two eyes.

Discussion

Given the high right–left eye correlation in retinal vessel caliber,[9,11,18] we hypothesized that children with anisometro-

Table 2. Mean Absolute Difference in Axial Length and Retinal Vessel Caliber Measurement between Right and Left Eyes and the Correlations of Retinal Vessel Caliber Measurements between the Two Eyes for Each Group of Children with Different Right–Left Refractive Error Status

	Mean Absolute Difference in AL between Right and Left Eyes, mm (95% CI)	Mean Absolute Difference in CRAE between Right and Left Eyes, µm (95% CI)	*r*	Adjusted *r**	Mean Absolute Difference in CRVE between Right and Left Eyes, µm (95% CI)	*r*	Adjusted *r**
Group 1† ($n = 214$)	0.08 (0.07, 0.09)	8.99 (8.02, 9.96)	0.57	0.58	10.52 (9.18, 11.87)	0.70	0.71
Group 2† ($n = 35$)	0.47 (0.39, 0.55)	11.73 (8.95, 14.51)	0.62	0.57	11.01 (7.78, 14.23)	0.82	0.82
Group 3† ($n = 32$)	1.08 (0.89, 1.27)	10.01 (6.61, 13.41)	0.36	0.35	13.60 (9.10, 18.09)	0.52	0.51

AL, axial length; CI, confidence interval.

* Adjusted for absolute difference in axial length between right and left eyes.

† Group 1, both eyes emmetropic and right–left difference in SER <0.25 D; group 2, right–left SER difference ≥1.00 D but <2.00; group 3, anisometropic with right–left SER difference ≥2.00 D.

pia (SER difference between the two eyes ≥2.00 D) would have lower right–left correlation in retinal vascular caliber estimates than those with emmetropia, owing to the effect of refractive error on image magnification of the retina and thus on measurements from retinal images. We tested this hypothesis in a sample of children with anisometropia compared with children emmetropic in both eyes. We found that right–left correlations of retinal vessel caliber measurements tended to be lower in anisometropic compared with emmetropic children. However, the observed differences were not statistically significant, which is likely attributable to the relatively small number of anisometropic children in the study sample. In addition, we were able to document a significant trend in the association between right–left differences in refractive error or axial length, and right–left differences in retinal vessel caliber estimates, confirming a weak effect of refractive error on the variation of retinal vessel measurement. Findings from our study indicate that refractive errors ≥2.00 D can lead to a detectable measurement error in retinal vessel caliber measurements, and therefore correction of refractive errors is needed for these subjects. This correction can be made using the formula described by Bengtsson.[19,20]

Previous studies have reported a substantial correlation in retinal arteriolar and venular caliber between right and left eyes in adult populations.[9,11,18] Reported correlation coefficients for CRAE (r values ranging from 0.70 to 0.76) between the two eyes were higher compared with the corresponding correlation observed in our sample ($r = 0.57$). For CRVE, the reported correlation coefficients (r values ranging from 0.74 to 0.79) were similar to our estimated r value from group 1 ($r = 0.70$).

Refractive errors, however, may not be the only factor contributing to potential measurement errors of retinal vessel caliber assessment. Poor image focus,[21,22] photographic distance,[6,23] and cardiac cycle variations[24] have been shown to affect measurement of fundus structures from retinal images. Although we documented similar weak associations of retinal vessel caliber with refractive errors and with axial length, the two associations appeared to be independent of each other, as suggested by findings presented in Table 2. We are not in a position to conclude whether the effect of refraction on vessel caliber estimates is due to magnification differences or to anatomic differences in retinal vessel caliber. Nevertheless, we previously documented in an older population-based sample that myopic retinopathy was associated with attenuation of retinal vessels.[24]

In summary, right and left eye correlation of retinal arteriolar and venular caliber estimates tended to be lower in anisometropic compared with emmetropic children, and increasing right–left differences in refractive error or in axial length were weakly associated with increasing right–left differences in retinal vessel caliber estimates. Correction for refractive error is needed in eyes with SER differences ≥2.00 D when examining associations with retinal vessel caliber in study samples with a wide range of refractive powers.

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