· Original Article ·

Inter-ocular asymmetry of retinal parameters in Caucasian healthy children and young adults measured with optical coherence tomography

Zeyad Alzaben[1,2], *Genís Cardona*[1], *Ahmad Zaben*[3], *Miguel A. Zapata*[4]

[1]Department of Optics and Optometry, Universitat Politècnica de Catalunya, BarcelonaTech, Terrassa E08222, Spain
[2]Opticalia Olot, Olot E17800, Spain
[3]Optipunt Zaben, Figueres E17600, Spain
[4]Ophthalmology Department, Vall d'Hebron Hospital, Barcelona E08035, Spain
Correspondence to: Genís Cardona. Terrassa School of Optics and Optometry, Violinista Vellsolà, 37, Terrassa E08222, Catalonia, Spain. genis.cardona@upc.edu
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Abstract
● **AIM: To evaluate retinal parameters in a sample of healthy young Caucasian adults to define the normal or physiological range of inter-ocular asymmetry in this particular age and ethnic group.**

● **METHODS: Study sample consisted of 37 Caucasian children and young adults aged between 12 and 23y (spherical equivalent from -3.00 D to +4.00 D, anisometropia <0.5 D and axial length differences <0.3 mm). Normal inter-ocular asymmetry values were determined and 95% inter-ocular difference tolerance values were obtained.**

● **RESULTS: Statistically significant inter-ocular differences were found in mean (*P*=0.003) and superior (*P*=0.008) retinal nerve fiber layer (RNFL) thickness, as well as in central macular thickness (*P*=0.039), with larger values in the left eye in all instances, and with tolerance limits of inter-ocular asymmetry of -9.00 μm to 6.00 μm, -28.00 μm to 9 μm and -39.00 μm to 29.00 μm, respectively. In addition, statistically significant differences were found between males and females in mean thickness of the RNFL in the right eye (*P*=0.020).**

● **CONCLUSION: The exploration of the normal asymmetries of the retina may be an effective approach to further understand myopia onset and progression, which is particularly relevant in this age group. Differences in instrumentation and sample characteristics compromise direct comparison with published research and warrant the need for further studies.**

● **KEYWORDS:** asymmetry; macula; optical coherence tomography; optic nerve; retinal nerve fiber layer; retinal thickness

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INTRODUCTION

Optical coherence tomography (OCT) is a non-invasive technique that uses low coherence interferometry for real-time *in-vivo* acquisition of retinal images akin to ocular biopsy[1]. This technique provides highly reproducible real-time *in-vivo* images of the retina, with an axial resolution of 10 microns or less[2-3]. Nowadays, OCT is widely used for the quantitative assessment of optic nerve head parameters, as well as for the measurement of the thickness of the macula and the retinal nerve fiber layer (RNFL)[4]. Also, it is the instrument of choice of many eye care providers for the diagnosis and follow-up of patients suffering from retinal and optic nerve alterations such as cystoid macular edema, glaucoma and age-related macular degeneration, among others[5]. Various types of OCT models are commercially available with differences in image acquisition time, depth of focus, resolution and other device specifications[6].

Optical coherence tomography has been employed to explore both inter-quadrant[7] and inter-ocular differences in retinal parameters. Indeed, a detailed knowledge of physiological retinal asymmetry is very relevant to discard certain unilateral or asymmetrical conditions, such as glaucoma or tumors of the optic nerve[3,8]. In addition, myopia onset and progression has been associated with an increase in axial length and with thinning of retinal structures[9]. This supports the need for exploration of normal (average or physiological) asymmetry in the absence of inter-ocular differences in refractive error as a means to better understand the changes occurring in myopia, which commonly appears during adolescence and early adulthood, an age range in which inter-ocular asymmetry is not well described in the literature. In particular, subsequent research on patients with different degrees of anisometropia may assist in understanding the development of these retinal alterations. Therefore, although absolute values of retinal parameters have received more attention than inter-ocular asymmetry, some research efforts have been devoted to define normality[3,10-16] and to determine which retinal parameter or combination of parameters may yield the best diagnostic sensitivity and specificity for the detection of early stages of a particular condition[16].

Some researchers have documented thicker average values of RNFL in the right than in the left eye[10-12], although other authors have failed to disclose statistically significant inter-ocular differences in average RNFL thickness[3,13-15]. Similarly, a quadrant per quadrant analysis has revealed thicker RNFL in the right than in the left eye in the nasal and temporal quadrants, without a consensus in the literature regarding superior and inferior quadrants[3,10,12,14]. In turn, macular thickness has been described as a more symmetrical parameter than RNFL thickness[3,16]. Finally, good symmetry in disc and rim area, and cup-to-disc ratio (CDR) has also been documented, with reported values of inter-ocular asymmetry of less than 0.02 mm for disc diameter and less than 0.04 mm^2 for rim area[14], and with only between 1% and 6% of healthy adults with CDR asymmetry larger than 0.2[14].

Given the relevance of defining the normal range of inter-ocular asymmetry in the age group at risk of myopia onset and progression (school age, that is, from early puberty to emerging adulthood)[17], a study was designed in which a spectral-domain optical coherence tomographer (3D OCT-2000) was employed to explore several retinal parameters in a sample of healthy Caucasian children and young adults. Inter-ocular differences were determined to define the corresponding thresholds for physiological asymmetry (*i.e.*, the range of normal inter-ocular asymmetry which may be encountered in the absence of significant anisometropia and in the absence of unilateral or asymmetrical pathological conditions) for each parameter under evaluation for this particular age, ethnic group and measurement device. In addition, the possible associations between the various parameters under evaluation were investigated.

SUBJECTS AND METHODS

Study Sample Thirty-seven Caucasian patients were recruited from those attending an eye clinic (Optipunt Zaben, Figueres, Spain) between April 2014 and July 2014 for routine visual examination. Inclusion criteria were age from 12 to 23y, spherical equivalent between +4.00 D and -3.00 D, best corrected monocular distance visual acuity ≥0.0 logMAR and intraocular pressure <21 mm Hg. Participants with a history of ocular trauma or pathology, ocular or refractive surgery, diabetes mellitus and those without central fixation were excluded from the study, as were those with anisometropia ≥0.5 D or axial length differences larger than 0.3mm. Participants with first-degree relatives diagnosed with glaucoma or retinal disease were also excluded from the sample.

Full explanation of the research was provided, including OCT measurement procedures, and written informed consent was obtained from each patient or from a parent or legal guardian when patients were underage. The study was conducted in accord with the Declaration of Helsinki tenets of 1975 (as revised in Tokyo in 2004) and received the approval of an institutional review board (Department of Optics and Optometry, Universitat Politècnica de Catalunya).

Instrumentation: The 3D OCT-2000 The spectral-domain 3D OCT-2000, Optical coherence tomography (Topcon Spain, S.A., Barcelona, Spain), was employed for the exploration of the retina. According to the manufacturer, this device incorporates noise reducing algorithms and infrared/3D tracking technology to obtain high resolution scans of the retina. An integrated 16.2 megapixel digital non-mydriatic fundus camera with less than 1ms of flash was used for image capture.

A 6×6-mm^2 exploration of the macular area was conducted with the macular cube 512×128 protocol, which performs 128 horizontal scan lines containing 512 A-scans. A thickness map with concentric sectors defining the nine regions of the macular area is generated, whereby the average of all points within the inner 1 mm circle is defined as the central macular thickness. Mean macular thickness and macular volume may also be determined. Similarly, disc parameters including rim area, disc area and CDR were obtained with a 6×6 mm^2, 512×128 protocol with the scan adjusted to the size of the optic disc, as close as possible to the disc margin and without crossing the border of the optic nerve. Finally, average and quadrant per quadrant measurements of RNFL thickness were obtained using the automated software measurement analysis protocol provided by the 3D OCT-2000.

Procedure Following a comprehensive case history, all patients underwent a complete optometric examination, including non-contact tonometry, to determine their suitability for the study in accordance to the predefined inclusion/exclusion criteria. Non-dilated pupil refraction in normal illumination conditions was conducted to determine refractive error. Best corrected monocular visual acuity (CDVA) was measured in logMAR with the retro-illuminated ETDRS chart (Lighthouse International, New York, USA), presented at a distance of 4 m. The health of the ocular structures was explored with a slit-lamp and non-mydriatic fundus camera confirmed by an independent experienced ophthalmologist.

All OCT measurements were performed by the same examiner and approximately at the same time of day (mornings). During

Table 1 Study sample corrected distance visual acuity and spherical equivalent for right and left eye

Parameters	Mean	Median	Range	*Z*	*P*
CDVA OD (logMAR)	-0.025	0.000	0.000, -0.160	-1.342	0.180
CDVA OS (logMAR)	-0.021	0.000	0.000, -0.160		
SE OD (D)	-1.33	-1.00	-3.75, +0.50	-1.297	0.195
SE OS (D)	-1.23	-1.00	-3.75, +1.00		

Data are presented as mean, median and range (minimum, maximum values). The Wilcoxon test was used to assess interocular differences (Z and *P* values are shown). CDVA: Corrected distance visual acuity; SE: Spherical equivalent; OD: Right eye; OS: Left eye.

image acquisition, three consecutive scans were obtained, whereupon the image with the highest signal strength was selected. Scans were considered unacceptable if signal strength was <7 or if there was any eye movement or blink artifact during image capture. Right and left eyes were examined in random order.

Data Analysis Statistical analysis was performed with the IBM SPSS software 19.0 for Windows (IBM Corporation, Armonk, NY). All data were analyzed for normality using the Kolmogorov-Smirnov test, revealing several instances of non-normal distributions, which, given the present sample size, recommended a non-parametric approach. Therefore, descriptive data summarizing results for each eye are presented as median and range (maximum and minimum values), although mean values are also shown to facilitate comparison with previous studies. Inter-ocular differences are shown as mean, median, and 2.5th and 97.5th percentiles. The Mann-Whitney *U* test was used to explore the statistical significance of the differences between non-paired data (such as between males and females), whereas the Wilcoxon signed ranks test was used when data was paired (comparing right with left eye). Finally, the Spearman coefficient of correlation test (ρ) was used to explore possible associations between the parameters under study. A *P* value of <0.05 was considered to denote statistical significance throughout the study.

RESULTS

Study Sample Thirty-seven Caucasian subjects (23 females, 14 males) participated in this study, with an age of 17.4±3.5y (mean±SD), ranging from 12 to 23y. Table 1 shows a summary of spherical equivalent (SE) and distance corrected visual acuity (CDVA) of right (OD) and left (OS) eyes. No statistically significant interocular differences were found in these parameters.

Retinal Parameters Table 2 presents a summary of RNFL, macular and disc parameters for both eyes. Statistically significant differences were found between right and left eye in mean RNFL thickness (median values of 102 μm in OD and 104 μm in OS, *P*=0.003), superior quadrant RNFL thickness (125 μm in OD and 130 μm in OS, *P*=0.008) and central macular thickness (183 μm in OD and 200 μm in OS, *P*=0.039). No statistically significant differences were found between both eyes in the rest of retinal parameters under study. In both eyes, RNFL was thicker in the inferior quadrant, followed by the superior, nasal and temporal quadrants (ISNT). Inter-ocular differences in retinal parameters are shown in Table 3, which also displays the 95% limits of difference in terms of the 2.5th and 97.5th percentiles. It may be noted that disc parameters were very symmetrical, with a median difference of 0.025 mm^2 in disc area, 0.04 mm^2 in rim area and 0.02 in CDR.

Data are presented as mean, median and range (minimum, maximum values). The Wilcoxon test was used to assess inter-ocular differences (Z and *P* values are shown). RNFL: Retinal nerve fiber layer; t: Thickness; SQ: Superior quadrant; IQ: Inferior quadrant; NQ: Nasal quadrant; TQ: Temporal quadrant; CDR: cup-to-disc ratio; Vol: Volume; OD: Right eye; OS: Left eye.

Data are presented as mean, median and range (minimum, maximum values). Limits of difference are shown as the 2.5th and 97.5th percentiles. RNFL: Retinal nerve fiber layer; t: Thickness; SQ: Superior quadrant; IQ: Inferior quadrant; NQ: Nasal quadrant; TQ: Temporal quadrant; CDR: Cup-to-disc ratio; Vol: Volume; OD: Right eye; OS: Left eye.

Age, Gender and Refractive Error Statistically significant differences were found between males and females in mean RNFL thickness in the right eye (median of 106 μm in males versus 99 μm in females, *P*=0.020), but not in the left eye. Statistically significant, albeit weak correlations, were found between spherical equivalent and mean RFNL thickness (*ρ*=0.401; *P*=0.014 in OD and *ρ*=0.379; *P*=0.021 in OS), as well as between spherical equivalent and nasal (*ρ*=0.453; *P*=0.005 in OD and *ρ*=0.514; *P*=0.001 in OS) and inferior (*ρ*=0.352; *P*=0.033 in OD and *ρ*=0.421; *P*=0.019 in OS) RNFL thickness. Overall, however, age was not found to be correlated with neither mean RNFL thickness nor with spherical equivalent.

DISCUSSION

The main objective of the present study was to determine the limits of normal retinal asymmetry (defined by the 2.5th and 97.5th percentiles from Table 3) in a sample of Caucasian children and young adults with a spectral-domain OCT.

Table 2 Retinal parameters for right and left eye

Parameters	Mean	Median	Range	*Z*	*P*
Mean RNFL t OD (μm)	102.81	102.00	92.00, 122.00	-2.959	0.003
Mean RNFL t OS (μm)	104.51	104.00	91.00, 123.00		
SQ RNFL t OD (μm)	124.05	125.00	102.00, 146.00	-2.658	0.008
SQ RNFL t OS (μm)	128.40	130.00	105.00, 149.00		
IQ RNFL t OD (μm)	130.18	134.00	110.00, 163.00	-1.528	0.126
IQ RNFL t OS (μm)	132.75	135.00	108.00, 158.00		
NQ RNFL t OD (μm)	82.081	84.00	60.00, 108.00	-0.340	0.734
NQ RNFL t OS (μm)	82.72	80.00	60.00, 121.00		
TQ RNFL t OD (μm)	74.75	75.00	58.00, 87.00	-0.961	0.337
TQ RNFL t OS (μm)	74.21	73.00	60.00, 96.00		
Rim area OD (mm^2)	1.88	1.89	1.18, 2.64	-0.664	0.507
Rim area OS (mm^2)	1.92	1.93	1.25, 1.72		
Disc area OD (mm^2)	2.45	2.49	1.68, 3.52	-1.430	0.153
Disc area OS (mm^2)	2.48	2.47	0.12, 3.72		
CDR OD	0.22	0.21	0.05, 0.46	-1.318	0.187
CDR OS	0.24	0.24	0.02, 0.54		
Central macular t OD (μm)	194.73	183.00	169.00, 310.00	-2.067	0.039
Central macular t OS (μm)	200.03	200.00	171.00, 314.00		
Macular Vol OD (mm^3)	7.75	7.72	7.17, 8.52	-0.574	0.566
Macular Vol OS (mm^3)	7.75	7.75	7.17, 8.60		
Mean macular t OD (μm)	274.21	273.50	253.60, 301.40	-0.558	0.577
Mean macular t OS (μm)	274.35	274.20	253.50, 304.20		

Table 3 Inter-ocular difference in retinal parameters (right eye-left eye)

Parameter differences (OD-OS)	Mean	Median	Range	2.5^{th} perc.	97.5^{th} perc.
Mean RNFL t (μm)	-1.70	-1.00	-9.00, 6.00	-9.00	6.00
SQ RNFL t (μm)	-4.35	-4.00	-28.00, 9.00	-28.00	9.00
IQ RNFL t (μm)	-2.56	-2.00	-25.00, 14.00	-25.00	14.00
NQ RNFL t (μm)	-0.64	-2.00	-20.00, 18.00	-20.00	18.00
TQ RNFL t (μm)	0.54	2.00	-13.00, 12.00	-13.00	12.00
Rim area (mm^2)	-0.04	-0.04	-1.01, 0.35	-1.01	0.35
Disc area (mm^2)	-0.03	-0.09	-1.20, 2.07	-1.20	2.07
CDR	-0.02	-0.02	-0.28, 0.12	-0.28	0.12
Central macular t (μm)	-5.30	-9.00	-81.00, 31.00	-39.00	29.00
Macular Vol (mm^3)	-0.00	0.00	-0.33, 0.46	-0.33	0.46
Mean macular t (μm)	-0.13	0.00	-11.80, 16.10	-11.80	16.10

Retinal asymmetry is of relevance for the early detection of retinal conditions and for the study of myopia progression, which commonly manifests during adolescence and early adulthood[9,17]. Besides, by exploring asymmetry rather than absolute values, the influence of individual-specific factors such as age, gender or ethnicity on retinal parameters may be minimized. By the same reasoning, however, strict criteria need to be implemented to exclude from the study sample those patients with significant inter-ocular differences in refractive error and/or axial length. Indeed, Budenz *et al*[18] described a reduction in RNFL thickness of approximately 2.2 μm (95%CI 1.1-3.4 μm) for each 1 mm increase in axial length or 0.9 μm (95%CI 0.2-1.6 μm) for each 1D refractive error change towards greater myopia. Similarly, Park *et al*[12] disclosed weak, although statistically significant correlations between refractive error and mean, inferior and nasal quadrant RNFL thickness in both eyes, with increased thickness in hyperopic eyes. In addition, differences in axial length and/or refractive power may also influence actual measurements as a result of ocular magnification[15]. In the present study we opted to exclude patients with anisometropia ≥0.5 D or axial length differences larger than 0.3 mm and to examine eyes in a random order.

Overall, our measured absolute retinal parameter values are in agreement with those reported in previous studies, with small discrepancies accounting for the characteristics of each specific study population (age, ethnicity, *etc*.) and device employed for retinal exploration (time-domain OCT, spectral-domain OCT), as well as to the actual scan protocol (standard, fast, *etc*.) that was applied. In particular, in both eyes RNFL thickness follows the documented ISNT rule, with the thickest and thinner values corresponding to the inferior and temporal quadrants, respectively[19].

Statistically significant differences were found between the right and left eyes in mean and superior quadrant RNFL thickness, with larger thickness values in the left eye in both instances. Regarding mean RNFL thickness, these findings are in disagreement with previous reports in which either no significant inter-ocular difference was found[3,13-15] or the right eye was found to present thicker mean RNFL thickness values than the left[10-12]. It must be noted that our 2.5th and 97.5th percentiles of inter-ocular difference limits of -9.00 μm and 6.00 μm are lower than those reported in Caucasian children by Altemir *et al*[3] (-12.00 μm and 13.00 μm) and Huynh *et al*[14] (-16.00 μm and 17.00 μm), and in Korean adults by Park *et al*[12] (-19.11 μm and 25.61 μm), although the latter two studies were conducted with an earlier OCT version. In contrast, our findings are comparable with those of Hong *et al*[15] (-8.14 μm and 8.00 μm), in a sample of adults, also of Korean ethnicity. The narrow range in mean RNFL thickness which was found in the present sample of patients may be explained by our strict inclusion/exclusion criteria with reference to inter-ocular differences in refractive error and/or axial length. In effect, the importance of taking into consideration refractive error differences when assessing physiological asymmetry was evidenced by the statistically significant, albeit weak, correlation which was encountered between refractive error and mean RNFL thickness in both eyes.

Interestingly, statistically significant differences were encountered between males and females in mean RNFL thickness in the right eye. No clear consensus exists in the literature about the actual influence of age and gender on both absolute parameters and inter-ocular asymmetry. Thus, while some authors failed to observe any association between age and retinal parameters[13,20], other authors reported a decrease of 2 μm per decade in mean RNFL thickness[18], resulting in increased inter-ocular asymmetry[11]. Similarly, Turk *et al*[21] described a statistically significant difference between boys and girls in RNFL in the inferior quadrant, although other authors failed to encounter any influence of gender on retinal parameters[13,18]. Therefore, given the aforementioned differences in study sample characteristics and measurement device, inconsistencies with the present investigation must be interpreted with caution.

Discrepancies were more manifest in the quadrant per quadrant RNFL thickness analysis of inter-ocular asymmetry, in which a statistically significant difference between right and left eyes was found in the superior quadrant, with 95% limits of tolerance of -28.00 μm and 9 μm. In effect, whereas previous authors also noted thicker RFNL values in the left eye in the superior quadrant[3,10,14-15], the same authors described other quadrant asymmetries, with nasal and temporal quadrants in the right eye commonly presenting thicker RNFL values than in the left eye. On the contrary, our findings did not reveal significant inter-ocular differences in nasal, temporal and inferior quadrants.

In agreement with previous studies reporting good symmetry for mean macular thickness[16], no statistically significant inter-ocular difference was found in this parameter. In contrast, central macular thickness was found to present with statistically significant inter-ocular differences, with larger values in the left eye and 95% tolerance limits at -39.00 μm and 29.00 μm. Both Altemir *et al*[3] and Huynh *et al*[14] failed to report significant differences in central macular thickness, although their 95% tolerance limits were not dissimilar to those found in the present research, with values of -17.60 μm and 23.20 μm and of -22.00 μm and 22.00 μm, respectively. It is worth mentioning, to approximate an explanation for this discrepancy, that macular thickness and volume are also highly sensitive to ethnicity, both in adults and in children[22].

Finally, as expected in the light of published reports[14], a high level of symmetry was observed for disc parameters, particularly for CDR, with a median non-statistically significant inter-ocular difference of 0.02 and 95% limits of tolerance of -0.28 and 0.12.

Previous research has noted an association between inter-ocular asymmetry of retinal parameters and changes in retinal and choroidal vasculature morphometry. However, authors also advice that “setting reliable criteria by which to judge the symmetry of the retinal vasculature is challenging” and that there is a lack of detailed knowledge of properties of the retinal vasculature such as specific path and shape of individual vessels, location of bifurcations and junctions, vessel tortuosity and width, branching angles and geometry, *etc*. (see, for instance, Cameron *et al*[23]).

It must be acknowledged that one of the main limitations of the present study is the size of the sample and the slightly larger percentage of females than males in our group of participants. In consequence, caution is advised in the interpretation of the results, with further research being required to verify our findings. In particular, it may not be ruled out that the encountered differences between males and females originate in the uneven distribution of our sample in terms of gender. Besides, even though no correlation was evidenced between age and retinal parameters, it must be noted that the large age range under study may partially account for the considerable variance encountered in some of the variables under evaluation.

In conclusion, the present findings had a twofold relevance. On the one hand, they agree with published literature in stressing the need to acquire physiological asymmetry data from different populations and with different measurement devices to build a complete description of normality. On the other hand, they give support to the importance of further exploring such retinal parameters as CDR in which age, gender, ethnicity and other study sample characteristics are not so critical in order to consider them as anchor features to better reflect and understand changes occurring in other areas of the retina.

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