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Intereye asymmetry of optic nerve head parameters and retinal nerve fibre layer thickness in patients with open angle glaucoma detected by spectral domain optical coherence tomography

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ABSTRACT

INTRODUCTION. The aim of the study is to evaluate intereye asymmetry of optic nerve head (ONH) parameters and the circumpapillary retinal nerve fibre layer (cpRNFL) thickness in patients with primary open angle glaucoma (POAG).

MATERIALS AND METHODS. The study included 44 patients with POAG in both eyes, 48 binocular glaucoma suspects, and 75 individuals with two healthy eyes. A mixed group of 20 patients had only one eye that met the criteria for POAG. We evaluated the differences between right and left eyes and absolute intereye asymmetry for the individual ONH parameters and cpRNFL thickness, measured by spectral domain optical coherence tomography (SdOCT).

RESULTS. The comparison of average values of the ONH parameters between the right and left eyes in the group of healthy subjects showed no significant differences apart from the significantly higher rim volume (RV) in the right eye. In addition, the cpRNFL was an average of 4.23 μm thicker in the right eye than in the left eye in healthy subjects. The absolute difference of ONH parameters between the eyes of patients with POAG was higher than in healthy patients for most parameters, but statistical significance was only reached for cup volume (CV). The asymmetry of the cpRNFL thickness increased in patients with glaucoma compared with healthy subjects. The absolute asymmetry of the average cpRNFL thickness in all quadrants was 12.07 μm in patients with glaucoma versus 6.56 μm in healthy subjects ($p < 0.05$). In the group of glaucoma suspects, cpRNFL intereye asymmetry decreased in almost all parameters in comparison to healthy patients with statistical significance for superior and inferior quadrant.

CONCLUSIONS. In patients with POAG, the intereye asymmetry increases for ONH and cpRNFL parameters compared with healthy eyes; however, statistically significant differences were only found for the cup volume and cpRNFL thickness average for all quadrants. The onset of glaucoma is associated with a reduction of the physiologically occurring asymmetry that results from greater cpRNFL thickness in the right eye.

KEY WORDS: intereye asymmetry, primary open angle glaucoma, optic nerve head parameters, RNFL thickness, spectral domain OCT

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INTRODUCTION

Intereye asymmetry in the appearance of the optic nerve head (ONH) during fundus examination is considered a symptom indicative of glaucoma [1]. In all major clinical trials, asymmetry of the vertical cup-to-disc ratio (VCDR) above 0.2 was one of the criteria for the diagnosis of this disease [2–4]. In the Blue Mountains Study, where the assessment was made on the basis of stereoscopic fundus images, VCDR asymmetry above 0.2 was observed in 24% of the eyes with primary open angle glaucoma (POAG) and in 6% of healthy eyes [5]. Quantitative analysis using confocal scanning ophthalmoscopy confirmed greater asymmetry ONH parameters in glaucoma patients, but practical implementation of this finding was limited by low sensitivity [6].

Scanning laser polarimetry studies have shown asymmetry of the retinal nerve fibre layer (RNFL) thickness, and differences in the nerve fibre indicator (NFI) between the eyes are very important for the diagnosis of glaucoma using this method of imaging [7]. The introduction of optical coherence tomography (OCT) into clinical practice has allowed direct measurement of the RNFL thickness. To date, studies that implemented both time domain OCT (TdOCT) and spectral domain OCT (SdOCT) have focused either on circumpapillary RNFL (cpRNFL) analysis or measurement of RNFL thickness in the macular area [8–11]. These studies have demonstrated a significant increase in the asymmetry of the cpRNFL and total retinal thicknesses at the macula in patients with POAG when compared with a normal population [12–13]. All previously published studies on the differences between the eyes, determined by SdOCT, were performed with devices that allow either the assessment of the RNFL thickness or the thickness of the whole retina. To the best of our knowledge, no study has analysed the asymmetry of parameters describing objectively the structure of the ONH using SdOCT. The aim of our study was to quantitatively analyse the intereye asymmetry for ONH and cpRNFL parameters in patients with POAG, glaucoma suspects, and normal subjects.

MATERIALS AND METHODS

This was a prospective study conducted in accordance with the recommendations of the Declaration of Helsinki. It was approved by the Bioethics Committee of Nicolaus Copernicus University. All participants gave written informed consent.

TARGET POPULATION

All study subjects were recruited in a consecutive manner from patients of Oftalmika Eye Hospital between January 2010 and July 2010. They underwent a complete eye examination, which consisted of: evaluation of refractive error, assessment of best corrected visual acuity, Goldmann applanation tonometry, slit lamp biomicroscopy, gonioscopy, dilated fundus evaluation, visual field (VF) test, and SdOCT. The inclusion criteria were: best corrected visual acuity of 0.5 or better, spherical correction within ± 3 DSph, cylindrical correction not exceeding 3 Dcyl, and open angle glaucoma by gonioscopy. Patients were excluded if they had undergone eye surgery, except for uncomplicated cataracts; in addition, the eyes with any underlying retinal disease, uveitis, and other than glaucomatous optic nerve atrophy were excluded. Monocular patients and those with anisometropia ≥ 3 D were also excluded.

The participants were divided into four groups: healthy subjects, patients with glaucoma, glaucoma suspects, and a mixed group. The healthy group included those with no history of eye disease, with intraocular pressure in both eyes < 21 mm Hg, without a history of increased intraocular pressure, normal appearance of the ONH, and a lack of changes in the VF test. The group of glaucoma patients was comprised of subjects who on the basis of fundus examination, VF test, and gonioscopy were diagnosed with POAG in both eyes. The diagnostic criterion for glaucoma in fundus examination was glaucomatous ONH damage, which manifested in the presence of one or more of the following changes: diffuse or focal thinning of the neuroretinal rim, haemorrhages on the edge of the ONH, abnormal CD > 0.6, and asymmetry of the CD between the eyes ≥ 0.2. The intraocular pressure in the patients with POAG was > 21 mm Hg at the moment of diagnosis. To confirm the presence of glaucoma the VF test was performed. The VF assessment was based on the Swedish Interactive Thresholding Algorithm using standard automated perimetry (SITA Standard 24-2, Humphrey Field Analyzer II; Carl Zeiss Meditec). Glaucomatous VF loss was defined as a pattern standard deviation (PSD) outside the 95% normal limits, glaucoma hemifield test results outside the normal limits, and/or a cluster of at least three points with a p-value < 0.05 on the pattern deviation plot, one with p < 0.01 affecting the same hemifield.

The third group was glaucoma suspects, which comprised patients with intraocular pressure > 21 mm Hg and ONHs in both eyes that appeared characteristic of glaucoma, but with no abnormalities in two consecutive VF tests. The fourth group was a mixed group, which included patients in whom the criteria for POAG were met only for one eye, while the other eye was healthy or suspected of glaucoma.

OCT EXAMINATION

All eyes were examined through a dilated pupil using the SOCT Copernicus device (Optopol Technology, Zawiercie, Poland), software version 4.10. Sd OCT "Copernicus" is accepted for use in the European Union but does not have FDA approval. The scanning of the ONH was composed of 50 linear, horizontal B scans, each consisting of 743 A-scans. The total number of A-scans amounted to 37,150, with a 7.00 mm × 7.00 mm scanning area and a scan speed of 25,000 A-scans per second. Only technically good measurements with an average quality index > 6 were selected for further analysis. Quality index was the signal-to-bias ratio calculated automatically for each B-scan by device software and displayed in a 10-degree scale. The average value for all the B-scans of the exam was evaluated in this study.

An automated image analysis mode was used, where a camera equipped with built-in software marked the boundaries of the ONH and then made the segmentation of the neuroretinal rim and the cup on each of the scans. Next, the surface and volume of these structures were calculated. Based on these data, the device automatically determined the centre of the head, and subsequently the position of the measurement ring in which the RNFL thickness was measured. The inner border of the measurement ring, which was 0.4 mm wide, was a circle with a 2.4 mm diameter, which was centred in the middle of the ONH. The cpRNFL thickness in four quadrants: the superior (RNFLS), inferior (RNFLI), nasal (RNFLN), and temporal (RNFLT), and the average thickness of the RNFL in the entire circumpapillary measurement area (RNFLM) were determined.

STATISTICAL ANALYSIS

The statistical significance of differences in the individual parameters of the ONH and cpRNFL thickness between the right and left eye was examined using the paired t-test in all groups. The asymmetry was defined as the absolute value of the difference between the eyes for individual parameters. Statistical significance of the asymmetry was tested in the group of POAG patients, as well as those with suspected disease and the mixed group, and compared with the healthy population by means of the Mann-Whitney U test. All correlations were analysed by Pearson correlation coefficient. $P < 0.05$ was considered statistically significant.

RESULTS

The study included 187 Caucasian patients, with 127 women and 60 men. In 44 subjects, POAG was diagnosed in both eyes, while 48 patients met the criteria for suspected glaucoma in both eyes. Twenty people represented the mixed group, in which one eye met the criteria for POAG and the other was healthy or suspected of glaucoma. The control group consisted of 75 patients with two healthy eyes. Demographic data are presented in Table 1.

In the group of healthy subjects, the average values for the ONH parameters were not significantly different between the right and left eyes, except for the rim volume (RV), which was significantly higher in the right eye. There was a similar difference in the eyes of glaucoma suspects, but the difference only approached the limits of statistical significance. In the group of subjects with glaucoma, the only parameter outside the RV that constituted a significant difference was the horizontal cup-to-disc ratio (HCDR). This value was higher in the left eye. In all groups, the mean disc areas (DAs) in the right and left eyes were not significantly different. The average values of the individual ONH parameters in the right and left eye in all groups are presented in Table 2.

Table 1. Demographics of the examined population

	Normal	Glaucoma	Glaucoma suspects	One eye glaucoma
No. of patients	75	44	48	20
Male/female	24:51	14:30	17:31	6:14
Mean age (years)	57.7	60.4	56.1	58.2

Table 2. Average optic nerve head parameters for the right and left eyes in the examined groups

Parameter	Normal			Glaucoma			Glaucoma suspects			One eye glaucoma		
	R	L	p	R	L	p	R	L	p	R	L	p
DA [mm^2]	1.74	1.71	0.20	1.68	1.70	0.58	1.77	1.73	0.25	1.75	1.75	0.94
CA [mm^2]	0.50	0.52	0.65	0.97	1.03	0.10	0.71	0.69	0.55	0.74	0.78	0.63
RA [mm^2]	1.23	1.19	0.09	0.71	0.66	0.12	1.06	1.04	0.42	1.02	0.96	0.52
CD	0.28	0.29	0.27	0.56	0.60	0.08	0.39	0.39	0.85	0.39	0.43	0.40
CV [mm^3]	0.10	0.10	0.94	0.26	0.27	0.67	0.16	0.16	0.79	0.18	0.22	0.37
RV [mm^3]	0.16	0.14	**0.001**	0.13	0.11	**0.01**	0.16	0.15	0.08	0.16	0.16	0.59
HCDR	0.49	0.49	0.78	0.74	0.78	**0.03**	0.62	0.62	0.71	0.61	0.62	0.82
VCDR	0.5	0.5	0.39	0.75	0.77	0.35	0.62	0.61	0.39	0.60	0.64	0.28

R — right eye; L — left eye; DA — disc area; CA — cup area; CD — cup-to-disc-area ratio; CV — cup volume; RV — rim volume; HCDR — horizontal cup-to-disc ratio; VCDR — vertical cup-to-disc ratio

Table 3. Intereye asymmetry of the optic nerve head parameters in the examined groups

Parameter	Normal	Glaucoma	p*	Glaucoma suspects	p*	One eye glaucoma	p*
DA [mm^2]	0.14	0.12	0.26	0.13	0.71	0.14	0.89
CA [mm^2]	0.15	0.19	0.17	0.16	0.51	0.30	**0.03**
RA [mm^2]	0.15	0.16	0.78	0.13	0.42	0.28	**0.02**
CD	0.07	0.10	0.08	0.07	0.76	0.16	**0.02**
CV [mm^3]	0.04	0.09	**< 0.0001**	0.06	**0.03**	0.12	**0.01**
RV [mm^3]	0.04	0.03	0.57	0.03	0.60	0.03	0.75
HCDR	0.07	0.09	0.25	0.08	0.54	0.16	**0.02**
VCDR	0.08	0.09	0.39	0.06	0.33	0.12	0.21

*The statistical significance of differences was calculated vs. the normal group; DA — disc area; CA — cup area; CD — cup-to-disc-area ratio; CV — cup volume; RV — rim volume; HCDR — horizontal cup-to-disc ratio; VCDR — vertical cup-to-disc ratio

The absolute difference of ONH parameters between the eyes of patients with POAG was higher than in healthy patients for most parameters, but statistical significance was only reached for cup volume (CV). There were no differences in the asymmetry size between glaucoma suspect patients and healthy subjects, and there was only weak statistical significance for CV. The highest asymmetry increase, compared with healthy subjects, was observed in the mixed group (Tab. 3). These differences were statistically significant for the cup area (CA), rim area (RA), CD, CV, and HCDR.

A significantly greater cpRNFL thickness was found in the right eyes of healthy control subjects. The RNFL in all quadrants together (RNFLM) was 4.23 μm (mean) thicker in the right eye than the left eye. This difference (mean = 6.7 μm) was greatest in the inferior quadrant (RNFLI), but also reached statistical significance in the superior and nasal quadrants (Tab. 4). The greater thickness of the right eye decreased and lost statistical significance for the eyes of subjects with suspected disease, POAG, and in the mixed group.

The analysis showed that the asymmetry of the cpRNFL thickness increased in patients with glaucoma compared with healthy subjects and reached statistical significance for the average thickness in all quadrants (RNFLM). The absolute differences between eyes in the mixed group were statistically significantly larger, compared with the control group, for the following parameters: RNFLM, RNFLS, and RNFLI (Tab. 5). In contrast, in the group of glaucoma suspects, intereye asymmetry decreased in almost all parameters, and the difference compared with healthy subjects was statistically significant for the RNFLI and RNFLS quadrants.

To determine the effects of age of the subjects on the results obtained, the correlation between age and the intereye asymmetry was analysed for individual parameters. A small, statistically significant correlation was found only for the rim area (RA), with a Pearson correlation coefficient of 0.242 ($p = 0.038$). The ONH, cpRNFL thickness, and the size of the intereye asymmetry did not change with age (Tab. 6).

Table 4. Average retinal nerve fibre layer (RNFL) thickness for the right and left eyes in the examined groups

Parameter	Normal			Glaucoma			Glaucoma suspects			One eye glaucoma		
	R	L	p	R	L	p	R	L	p	R	L	p
RNFLM [μm]	119.42	115.19	**< 0.001**	90.34	86.69	0.50	108.31	106.85	0.09	103.12	98.67	0.39
RNFLT [μm]	77.75	75.47	0.071	64.47	63.40	0.58	71.31	70.00	0.27	73.53	68.55	0.26
RNFLS [μm]	126.64	123.18	**0.03**	95.21	91.12	0.39	113.72	114.41	0.10	112.15	108.44	0.56
RNFLN [μm]	104.08	100.29	**0.001**	76.34	71.79	0.08	88.32	84.88	0.05	83.77	86.07	0.45
RNFLI [μm]	134.92	128.22	**< 0.001**	96.01	91.15	0.51	113.50	112.34	0.46	115.83	105.94	0.19

R — right eye; L — left eye; RNFLM — mean for all quadrants; RNFLI — inferior quadrant; RNFLS — superior quadrant; RNFLN — nasal quadrant; RNFLT — temporal quadrant

Table 5. Interocular asymmetry of the retinal nerve fibre layer (RNFL) thickness in the examined groups

Parameter	Normal	Glaucoma	p*	Glaucoma suspects	p*	One eye glaucoma	p*
RNFLM [μm]	6.56	12.07	**0.003**	4.05	0.08	18.72	**< 0.0001**
RNFLT [μm]	7.68	9.61	0.10	6.30	0.73	13.38	0.12
RNFLS [μm]	9.58	13.47	0.18	6.54	**0.03**	23.49	**< 0.0001**
RNFLN [μm]	8.03	10.86	0.81	8.79	0.67	12.36	0.22
RNFLI [μm]	9.65	15.50	0.08	4.33	**< 0.0001**	28.54	**< 0.0001**

*The statistical significance of differences was calculated compared with the normal group; RNFLM — mean for all quadrants; RNFLI — inferior quadrant; RNFLS — superior quadrant; RNFLN — nasal quadrant; RNFLT — temporal quadrant

Table 6. Correlation between age and the interocular asymmetry of optic nerve head parameters and the retinal nerve fibre layer thickness (RNFL) in normal eyes

Parameter	Pearson cc	p
DA	0.09	0.44
CA	0.04	0.70
RA	**0.24**	**0.04**
CD	0.18	0.13
CV	0.01	0.99
RV	0.17	0.15
HCDR	0.19	0.13
VCDR	0.23	0.06
RNFLM	0.12	0.31
RNFLT	–0.03	0.78
RNFLS	–0.03	0.76
RNFLN	–0.01	0.97
RNFLI	0.03	0.82

DA — disc area; CA — cup area; CD — cup-to-disc-area ratio; CV — cup volume; RV — rim volume; HCDR — horizontal cup-to-disc ratio; VCDR — vertical cup-to-disc ratio; RNFLM — mean for all quadrants; RNFLI — inferior quadrant; RNFLS — superior quadrant; RNFLN — nasal quadrant; RNFLT — temporal quadrant

DISCUSSION

Studies have shown that in patients with bilateral glaucoma the intereye asymmetry increases for the ONH and cpRNFL parameters compared with healthy subjects. However, this increase is slight and only reaches statistical significance for CV and RNFLM. The increased asymmetry achieves statistical significance for most ONH and cpRNFL parameters in patients where the typical criteria for the diagnosis of POAG appear in only one eye.

In healthy subjects, there is a slight intereye asymmetry for the cpRNFL thickness. It is related primarily to the increased thickness of this layer in the right eyes compared with the left eyes. In our study, the mean difference in all quadrants was 4.23 μm. This observation is consistent with the results of other authors, but the difference was smaller and ranged from 0.52 μm to 3.27 μm [8–10]. The only difference in ONH parameters was the larger RV in the right eyes. The beginning of the disease process, which probably occurred at least in some patients with suspected glaucoma group, eliminated the physiological dominance of the right eye for the

RNFL thickness, which resulted in a decrease in the asymmetry in all cpRNFL quadrants, except the nasal quadrant. Further development of the disease and the emergence of changes in the VF probably lead to a renewal of asymmetry for the RNFL and ONH parameters, but without a significant advantage for the right eye.

To date, two papers have been published that analysed the asymmetry of cpRNFL thickness using SdOCT [12, 13]. Both studies were carried out using a Spectralis device and compared only two groups of patients: healthy subjects and those diagnosed with glaucoma. Sullivan-Mee et al. found a significantly higher asymmetry, reaching 14.6 μm in all quadrants of patients diagnosed with glaucoma and 2.7 μm in a group of healthy subjects. Similar results were achieved by Field et al; however, the asymmetry difference between healthy subjects and patients also exceeded 10 μm. In the present study, these values were 12.1 μm in patients with glaucoma and 6.5 μm in patients with healthy eyes. Although these values differed significantly, unlike the studies above, we did not identify the presence of highly significant differences within particular quadrants. The greater asymmetry for the cpRNFL in previously published papers can be explained by the greater range of severity in the patients diagnosed with glaucoma, who more resembled a mixed group; the measuring device used; and the RNFL segmentation algorithm diversity.

None of the studies that used SdOCT for the diagnosis of glaucoma analysed intereye asymmetry for the ONH parameters. We found no difference between the left and right eye for most parameters in all groups. Only a significantly higher RV in the right eyes of healthy subjects was observed, which may be connected with a slightly thicker RNFL in this particular group. No significant differences in the ONH parameters between the right and left eyes of healthy individuals were found in studies using stereoscopic fundus images and a scanning laser ophthalmoscope [5, 14]. Studies using a Heidelberg Retina Tomograph 3 showed a significantly greater RV in the right eyes of healthy subjects, which is consistent with the results of our work [14].

The emergence of glaucoma increases intereye asymmetry. On the basis of stereoscopic ONH images, a significantly greater asymmetry was observed in the cup diameter, the rim diameter, and the CD in patients with POAG, compared with healthy subjects. However, no differences were observed in these parameters between healthy eyes and eyes with ocular hypertension [5]. A similarly significant increase in intereye asymmetry in glaucoma was observed using a confocal scanning laser ophthalmoscope with the RADAAR parameter [6, 15]. In the present work, we analysed the asymmetry of ONH parameters by means of SdOCT. We determined that with the onset of the disease, the asymmetry increased for most parameters (except for DA and RV), but it was only statistically significant for CV. Statistically significant differences emerged for most parameters of the disc if the disease developed asymmetrically and POAG was recognised in only one eye.

The present study has several limitations. First, we enrolled to the glaucoma group all the patients with VF abnormalities regardless of their severity. Subgroup analysis according to disease severity with a large number of cases will be mandatory. Second, to evaluate the meaning of physiological asymmetry reduction found in glaucoma suspects the identification of eyes that progressed to fully developed glaucoma should be done. A further study with a larger cohort of patients will be required to investigate this issue.

The current study differs from previous works analysing asymmetry changes. The SdOCT Copernicus device was able to measure not only the cpRNFL thickness but also ONH parameters. Most previous studies focused on distinguishing glaucoma patients from healthy individuals [16]. When considering only these two groups of patients, the appearance of POAG is associated with increased intereye asymmetry for the majority of parameters. The introduction of a glaucoma-suspected patient group allowed us to claim that the onset of glaucoma is probably associated with a reduction of physiologically occurring asymmetry that results from a greater cpRNFL thickness in the right eye.

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