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Colour Doppler imaging of retrobulbar circulation in different severity of glaucoma optic neuropathy

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Abstract

Aims: To compare retrobulbar hemodynamic measured by colour Doppler imaging (CDI) in patients with a different severity of glaucoma and to correlate variables CDI with the structural parameters of the retina and optic disc. **Material and methods:** Of 89 eyes studied, 31 had preperimetric, 29 early, 12 moderate and 17 advanced glaucoma. Peak systolic velocity (PSV), end-diastolic velocity (EDV), resistance index (RI) in ophthalmic artery (OA), central retinal artery (CRA) and short posterior ciliary arteries (SPCAs) were evaluated by CDI and compared between study groups. Retinal nerve fibre layer thickness (RNFL) and optic disc parameters measured with optical coherent tomography (OCT) were correlated with the Doppler variables. **Results.** In eyes with advanced, moderate and early glaucoma EDV SPCAs were significantly lower as well as RI SPCAs were significantly higher compared to the eyes with preperimetric glaucoma. In eyes with advanced and moderate glaucoma RI CRA (0.74 and 0.71) were significantly higher than in eyes with preperimetric glaucoma (0.68) ($p=0.014$ and 0.026). In eyes with advanced glaucoma PSV OA and PSV CRA were significantly lower than in eyes with preperimetric glaucoma (32.5 vs. 40.7 cm/s $p=0.034$ and 8.25 vs. 9.7 cm/s $p=0.022$, respectively). Positive, variable correlations were found between RNFL and EDV of all measured arteries ($0.21<R<0.50$, $p<0,05$). **Conclusions:** Statistically significant alterations in the Doppler parameters of retrobulbar arteries in association with thinning of the RNFL were observed in patients with glaucoma along with a greater severity of optic neuropathy.

Keywords: glaucoma; colour Doppler ultrasonography; blood flow velocity; optical coherent tomography

Introduction

Glaucoma is a progressive, irreversible neuropathy of the optic nerve (ON) characterized by the loss of the retinal ganglion cells (RGCs) and ON fibres. The morphological and functional results of glaucomatous damage are the characteristic appearance of the ON disc, thinning of the retinal nerve fibre (RNF) layer and defects in the visual field (VF). The pathogenesis of glaucoma can involve both mechanical and vascular factors, influencing one another. Ocular ischemia, induced primarily by autoregulatory dysfunction and abnormal translaminar pressure intensified by elevated intraocular pressure (IOP) may contribute to RGCs apoptosis [1]. Numerous studies have shown evidence of altered autonomic nervous system activity and systemic endothelial dysfunction in glaucoma patients [2,3].

Glaucoma is asymptomatic for a long time and the VF defects can be detected using standard perimetric techniques in the loss of approximately 40% of the RNF [4]. Therefore, in early glaucoma structural examinations of the retina and the ON are of particular importance, as they allow to detect gradual atrophy of the nervous tissue even several years before VF changes occur. Optical coherent tomography (OCT) is currently the gold standard in diagnosis and monitoring of glaucoma. OCT enables in vivo quantification of the retinal nerve fibre layer (RNFL), the optic nerve head (ONH) and the macula [5].

Lowering of IOP is the only effective method to preserve VF in patients with glaucoma. However, some glaucoma patients continue to progress despite significant IOP reduction. A number of studies report the re-

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lationship between disturbed perfusion within the ONH and glaucoma progression [6].

At the present time there is no single diagnostic tool to assess all the vascular beds relevant for glaucoma. Colour Doppler imaging (CDI) is a noninvasive and reproducible technique that measures blood flow velocity and calculates resistive index of the ophthalmic artery (OA), central retinal artery (CRA) and short posterior ciliary arteries (SPCAs) [7]. CDI measures blood velocity rather than blood flow (BF); however, good correlation between them has been demonstrated in previous studies [8,9]. The results of the meta-analysis by Xu et al [10] revealed that patients with glaucoma showed a decrease of velocities and increase of the resistive indices of the CRA and SPCA compared with normal eyes. Few studies have shown a relationship between a reduction in the velocity of CRA [11,12] or SPCA [13,14] with the risk of glaucoma progression. Previous studies, however, have not specified which retrobulbar vessel has been shown to be most related to the progression of glaucoma [6].

It is reasonable to hypothesize that identifying retrobulbar perfusion deficits may allow to stratify the risk of progression at earlier stages of the disease. Detection and more aggressive treatment of patients at risk of progression could contribute to the effectiveness of preventing VF damage. This suggests that detection and treatment could be improved by applying a combination of structural and hemodynamic parameters in the management of glaucoma.

The aim of our study was to compare Doppler hemodynamics of OA, CRA and SPCAs, in patients with different severity of glaucomatous neuropathy and to determine the correlation between the measured hemodynamic parameters of retrobulbar vessels and the OCT parameters of the retina and ON.

Material and methods

Forty-nine patients (31 women and 18 men) aged 68.7±9.1 years, with bilateral primary open-angle glaucoma (POAG), treated at the Ophthalmology out-patient department of Military Institute of Medicine in Warsaw, were enrolled in this open-label observational study. The study protocol was approved by an institutional Bioethics Committee and subjects signed informed consent before entry into the study. All procedures conformed to the tenets of the Declaration of Helsinki.

The diagnosis of perimetric glaucoma was based on the presence of glaucomatous changes in the optic disc, correlating with changes in the VF found on the Humphrey perimeter according to the central threshold program 24-2. Glaucomatous VF damage was identified on the basis of the diagnostic criteria of the European Glaucoma Society [15] and its degree of damage (early, moderate and advanced) were based on the classification system of Hoddapp et al [16]. Eyes with glaucomatous optic discs and the RNFL changes without any VF detectable defects were assigned to the preperimetric glaucoma group. Inclusion criteria also required subjects to be over 18 years of age, to have best corrected visual acuity 0.5 or more in each eye, to have no myopia over 6 dioptres and no history of ocular trauma and/or surgery and/or inflammation within the last 6 months. The use of anti-glaucoma and systemic medications was continued.

The exclusion criteria from the study were: ocular hypertension, other types of glaucoma than POAG, cataract, diabetic retinopathy and other chronic retinal diseases, any significant cardiac or pulmonary conditions, stenosis of the carotid arteries equal to and greater than 50% [17], pregnancy and hormonal therapy.

The patients were divided into 4 groups according to the severity of glaucoma based on: mean defect (MD) and pattern standard deviation (PSD) of standard automatic perimetry (SAP) parameters: group IA (preperimetric glaucoma) (MD >-3 dB, 0 dB> PSD>- 2 dB); group IB (early glaucoma) (-3 dB > MD >-6 dB, PSD <-2 dB); group II (moderate glaucoma) (-6 dB > MD >-12 dB); group III (advanced glaucoma) (MD <- 12 dB).

Participants were instructed to avoid caffeine intake, smoking and exercise for 3 hours prior to examination.

CDI examinations of the OA, CRA, nasal and temporal SPCAs were performed using the Logiq7 CDI System (GE Healthcare, Milwaukee, WI) with a 7-12 MHz linear transducer. The examination was carried out in a thermally controlled room (22°C) by the same radiologist (AZ) between 9 and 11 a.m., in a patient's supine position after a 10-min rest. First, the common carotid arteries and their branches were assessed to exclude vascular stenosis. The eye examination was performed bilaterally, starting with the left eye, with the eyelids closed, using acoustic coupling gel. The OA was examined close to its crossing the ON, 10-15 mm behind the globe and the angle between the transducer and the orientation of the vessel was corrected. The CRA was localized within the ON and measurement was performed immediately behind the globe. SPCA images were taken nasally and temporally to the ON just behind the posterior pole to the eye globe. For all vessels, peak systolic velocity (PSV) and end-diastolic velocity (EDV) were measured as well as Pourcelot resistance coefficient (RI) (RI= [PSV-EDV]/PSV) and pulsatility index (PI) (PI=[PSV-EDV]/mean velocity) were calculated by the machine. Color Doppler parameters and blood flow velocity waveforms in the OA, CRA and SPCA are presented in fig 1.

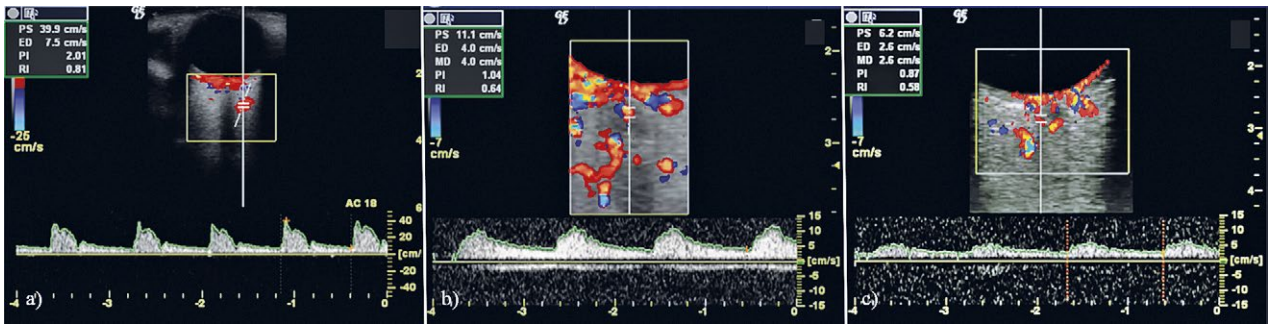

Fig 1. Blood flow velocity waveforms in the ophthalmic artery (a), central retinal artery (b) and short posterior ciliary artery (c). PS, peak systolic velocity; ED, end-diastolic velocity; MD, mean diastolic velocity; PI, Pourcelot index; RI, resistance index; PI, Pourcelot index.

Each subject underwent an ophthalmologic examination including measurement of IOP using a Goldmann applanation tonometer, VF testing with Humphrey perimeter (Carl Zeiss Meditec) (using a central 24-2 SITA program), OCT of the ONH and the RNFL with Stratus OCT 3 (Carl Zeiss Meditec) according to Fast ONH and Fast RNFL protocols. OCT assessment of rim area, cup area, cup/disc area ratio, mean RNFL thickness (RNFL m) and average RNFL thickness in four quadrants: inferior (RNFL I), superior (RNFL S), nasal (RNFL N) and temporal (RNFL T) was evaluated.

Statistical analysis

Statistical analyses were performed using the STATISTICA 10 and 12 programs. The Kruskal-Wallis test was applied for the analysis of the population variables between study groups. To compare structural and hemodynamic parameters ANOVA analysis was used. The correlations between the OCT RNFL and ONH and the hemodynamic parameters were tested with the Spearman r-correlation. The correlations between the OCT and SAP parameters were tested using Pearson's r-correlation. A p-value of 0.05 or less was regarded as significant.

Results

After excluding 14 patients with carotid artery stenosis, 89 eyes of 49 patients (56 eyes of 31 female patients and 33 eyes of 18 male) were included in the study. The demographic data are summarized in Table I.

There was no significant difference in the mean age, gender and IOP between groups. The groups differed significantly in terms of the SAP and all OCT parameters.

The Doppler parameters of the OA in the study groups are shown in Table II.

The examination of the OA hemodynamic showed a tendency to decrease the velocity parameters and increase the flow resistance indices with the severity of glaucomatous neuropathy. There were statistically significant differences for the PSV OA between groups IA and III (p=0.034), for the EDV OA between IA and II (p=0.047) between IA and III (p=0.018) and for the RI and PI between groups IA and II (p=0.004 and p=0.014, respectively).

The comparison of Doppler variables of CRA and SPCAs between study groups are presented in figure 2.

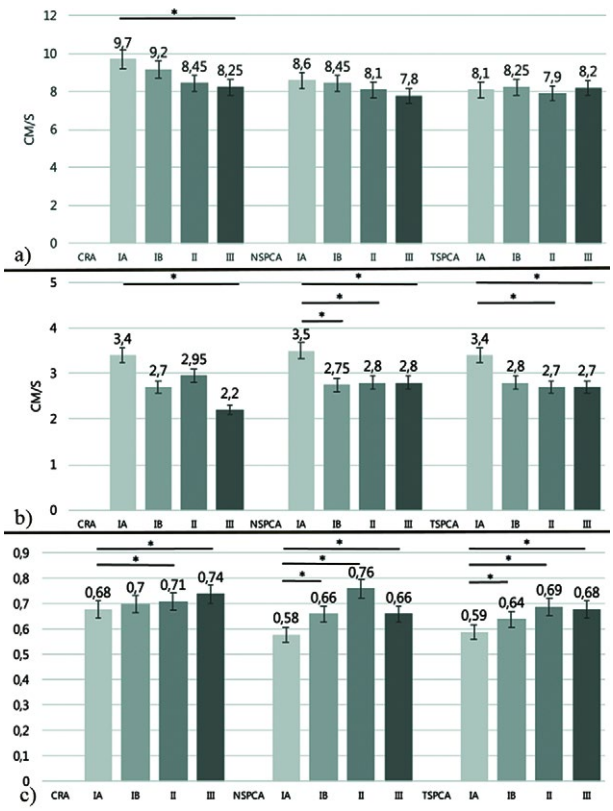

Fig 2. Peak systolic velocity (a), end diastolic velocity (b) and resistive index (c) in the central retinal artery (CRA), nasal short posterior ciliary artery (NSPCA) and temporal short posterior ciliary artery (TSPCA) determined in the study groups. IA, preperimetric glaucoma; IB, early glaucoma; II, moderate glaucoma; III, advanced glaucoma; * statistical significance of differences between the groups.

Table I. Characteristics of the study groups

	IA	IB	II	III	p-value
N of patients	16	15	8	10	0.107
Age (years)	61.2 ± 9.2	66.3 ± 10.7	77.3 ± 5.3	69.2 ± 13.9	0.076
Gender (F/M)	12/4	12/3	5/3	2/8	0.058
N of eyes	31	29	12	17	0.033
IOP (mmHg)	15.9 ± 2.4	16.1 ± 2.4	15.8 ± 1.5	14.9 ± 2.5	0.524
MD (dB)	-1.21 ± 0.87	-3.23 ± 1.34	-8.66 ± 1.96	-20.58 ± 5.01	0.000
PSD (dB)	-1.64 ± 0.24	-2.63 ± 0.80	-9.18 ± 3.42	-8.59 ± 2.12	0.000
RNFL (nm)	94.1 ± 9.8	89.3 ± 13.3	77.1 ± 18.2	53.0 ± 23.5	0.000

The results are expressed as number or mean ± standard deviation. N, number; SD, standard deviation; F, female; M, men; R, right; L, left; IOP, intraocular pressure; MD, mean defect; dB, decibels; PSD, pattern standard deviation; RNFL, retinal nerve fibre layer; nm, nanometres.

Table II. Colour Doppler parameters of the ophthalmic artery in the study groups

	IA	IB	II	III	p-value
PSV (cm/s)	40.7 (33.3-46.8)	36.8 (31.9-48.0)	35.5 (28.2-43.7)	32.5 (27.5-36.8)	0.045
EDV (cm/s)	10.5 (9.2-13.5)	9.8 (5.8-13.0)	6.8 (5.1-11.5)	7.2 (6.1-10.6)	0.046
RI	0.63 (0.69-0.76)	0.60 (0.71-0.82)	0.70 (0.73-0.80)	0.57 (0.64-0.79)	0.082
PI	1.32 (1.21-1.50)	1.45 (1.25-1.80)	1.53 (1.34-1.77)	1.51 (1.13-1.81)	0.012

The results are expressed as median (interquartile range). PSV, peak systolic velocity; EDV, end-diastolic velocity; RI, resistive index; PI, pulsatility index.

CRA hemodynamic evaluation showed a statistically significant reduction in all Doppler parameters in eyes with advanced glaucoma (group III) compared to the eyes with preperimetric glaucoma (group IA) ($p=0.022$ for PSV, $p<0.001$ for EDV, $p=0.014$ for RI and $p=0.018$ for PI). Moreover, EDV was significantly lower in eyes with early glaucoma compared to the eyes with preperimetric glaucoma ($p=0.043$) and RI was significantly higher in the eyes with moderate glaucoma (group II) than in eyes with preperimetric glaucoma ($p=0.026$).

Doppler analysis of nasal and temporal SPCAs showed no significant differences in PSV between study groups. There were statistically significant reductions in EDV SPCAs in eyes with moderate and advanced glaucoma compared to the eyes with preperimetric glaucoma. The RI and PI of SPCAs were significantly higher in eyes with early, moderate and advanced glaucoma as compared to the eyes with preperimetric glaucoma.

Correlation analysis between CDI and OCT variables is presented in Table III.

Positive correlations were found between the RNFL thickness parameters: RNFL m, RNFL I, RNFL S, RNFL N and PSV OA and EDV OA as well as negative correlations between the above structural parameters and the RI OA and PI OA. Similar relationships were demonstrated for the CRA Doppler variables and RNFL parameters of all retinal quadrants. Positive correlations were found between RNFL m, RNFL S, RNFL N and EDV of both SPCAs. Negative correlations were found between these OCT variables and RI of temporal SPCA. No correlations were found neither between the SPCA variables and RNFL T nor between the RNFL thickness in the nasal and temporal quadrants and the Doppler variables of the homonymous branches of SPCAs.

There were no correlations between hemodynamic parameters and OCT ONH variables. In turn, strong correlations were demonstrated between all OCT parameters and SAP VF indices. Positive correlations were found between cap area, cup/ disc ratio and SAP MD as well as negative ones between rim area, RNFL and SAP MD.

Discussion

To our knowledge this study represents the first trial of evaluating and correlating retrobulbar vascular and structural optic nerve and retinal parameters in POAG patients with various severity of glaucomatous neuropathy. We found different Doppler characteristics of retrobulbar arteries depending on the degree of glaucomatous damage.

There were significant differences in velocity parameters and resistance indices of the OA between the eyes with preperimetric glaucoma and moderate glaucoma (EDV, RI, PI) and between the eyes with preperimetric glaucoma and advanced glaucoma (PSV, EDV). Single centre trials also reported a decrease in PSV OA and EDV OA and an increase in PI OA in glaucoma eyes [12,18,19]. In our study PSV OA and EDV OA in the

Table III. Correlation coefficients for colour Doppler imaging and optical coherent tomography retinal nerve fibre layer parameters in the study groups

	RNFL m	RNFL S	RNFL I	RNFL N	RNFL T
OA					
PSV	0.29	0,32	-	0.34	-
EDV	0.31	0.36	0.50	0.44	-
RI	-0.26	-0.26	-	-0.40	-
PI	-0.33	-0.32	-0.29	-043	-
CRA					
PSV	0.32	0.35	0.26	0.38	-
EDV	0.33	0.35	0.31	0.34	0,22
RI	-	-0.22	-	-0.23	-0,24
PI	-0.31	-0.29	-0.30	-	0.23
TSPCA					
PSV	-	0.25	-	-	-
EDV	0.26	0.35	-	0.26	-
RI	-	-	-	-	-
PI	-	0.40	-	-0.23	-
NSPCA					
PSV	-	-	-	-	-
EDV	0.25	0.27	0.21	0.34	-
RI	-0.27	-0.23	-0.23	-0.38	-
PI	-0.32	-0.29	-0.27	-0.42	-

RNFL m, retinal nerve fibre layer thickness, m, mean; S, superior quadrant; I, inferior quadrant; N, nasal quadrant; T, temporal quadrant; OA ophthalmic artery; PSV, peak systolic velocity; EDV, end-diastolic velocity; RI, resistance index; PI, Pourcelot index; CRA, central retinal artery; TSPCA, temporal short posterior ciliary artery, NSPCA, nasal short posterior ciliary artery

eyes with preperimetric glaucoma were lower than in healthy eyes (40.70 cm/s vs. 41.90 cm/s and 10.50 cm/s vs. 12.75 cm/s, respectively), similar with our previous study [20]. Few studies confirmed no differences in OA Doppler variables between healthy and glaucoma patients [21].

We found differences in all hemodynamic parameters of the CRA between eyes with preperimetric glaucoma and eyes with advanced glaucoma. Also, significant differences were found for some Doppler variables between the groups with preperimetric glaucoma and the groups with early (PSV CRA) and moderate (RI CRA) glaucoma, as well as between the group with early and advanced glaucoma (EDV CRA). Doppler analysis of SPCAs showed a significant reduction of the EDV in the eyes with moderate and advanced glaucoma compared to the eyes with preperimetric glaucoma. Also, significantly higher values of flow resistance indices in the eyes with early, moderate and advanced glaucoma compared to the eyes with preperimetric glaucoma were observed. The PSV and EDV in CRA and SPCAs in the eyes with preperimetric glaucoma were lower than in healthy eyes [20].

The results are comparable with the results of the meta-analysis by Meng et al [21], which reviewed 23 studies, including 1.286 glaucoma eyes. A significant reduction in PSV in OA and CRA was confirmed earlier in 20 studies and in SPCA in 18 studies. Also, the results of the meta-analysis by Xu et al [10] showed a significant reduction in PSV and EDV in each retrobulbar artery and an increase in RI in CRA and temporal SPCA in eyes with glaucoma.

Interpretation of Doppler parameters in retrobulbar vessels is complex. The PSV indirectly reflects the strength of perfusion within the vessel, whereas the EDV reflects blood perfusion in distal organs. The reduction in EDV in retrobulbar arteries is a marker of increased vascular resistance, as a result of increased IOP and/or vasospasm and or/atherosclerosis [19,21]. As there were no differences in the mean IOP level and age between the study groups, the reduced EDV values in CRA and TSPCA might be rather related with the increased vascular tone along with glaucoma severity. The simultaneous reduction in PSV and EDV variables indicates a reduction in total volumetric BF [22]. Thus, the association of reduced EDV and increased RI in the retrobulbar arteries may be related with ONH ischemia [9].

Finding the differences in hemodynamic parameters only in some vessels between study groups is not sur-

prising. Previous studies revealed varied results. Some studies demonstrated altered Doppler hemodynamics in OA and CRA [23], others reported abnormalities only in one of the retrobulbar vessels [24] and still others - in all arteries [18,25].

Retrobulbar vessels differ as far as their sensitivity to IOP fluctuations and their reactivity to vasoactive compounds are concerned. The OA, as a large- calibre vessel, is rather resistant to changes in ocular perfusion pressure (OPP) induced by the IOP fluctuations, while it responds to hypoxia. In contrast, CRA and SPCA, as small calibre vessels, are sensitive to OPP fluctuations due to elevated IOP. The hemodynamic changes, caused by hypercapnia are rather local and subliminal to produce a measurable effect on OA, but sufficient to induce a change in flow velocity within CRA and SPCA [26].

According to Harris et al [27], BF within the retina and ON, which is supplied mainly by CRA and SPCA, depends on the level of IOP and the autoregulation capacity to compensate possible blood supply deficit. Different Doppler characteristics of retrobulbar arteries depending on the severity of glaucomatous neuropathy, may indicate the exhaustion of the compensatory mechanisms regulating BF and the subsequent chronic ocular ischemia in the group of eyes with moderate and especially advanced glaucoma.

Previous studies have shown a relationship between disturbed BF parameters and the progression of VF changes in patients with glaucoma [28,29]. Yamazaki et al [28] have found decreased velocities of retrobulbar arteries only in patients with progressive glaucoma, while no hemodynamic abnormalities have been noted in patients with stable glaucoma. These observations were also confirmed by other authors who have shown a relationship of decreased velocities of CRA [11,12,30], SPCA [13] and OA [31] with the risk of glaucomatous progression.

Our study reveals that in eyes with moderate glaucoma (group II), the median OA RI was 0.78, and the median EDV of nasal and temporal branches of SPCAs were 2.80 cm/s and 2.70 cm/s, respectively. Galassi et al [31], in a 7-year study, showed a correlation of OA RI exceeding the value of 0.78 with a six-fold higher risk of VF deterioration. Similarly, Januleviciene et al [32] revealed that patients with progressive glaucoma had increased both RI OA (mean 0.90) and RI CRA (mean 0.85) as well as decreased EDV SPCA (mean 3.34 cm/s). Thus, the detection of abnormal Doppler parameters in the retrobulbar arteries may help to identify patients at a higher risk of glaucoma progression.

Glaucoma is a progressive optic neuropathy that leads to thinning of the RNFL. In this study the mean RNFL thickness decreased significantly along with a greater severity of glaucoma and we found correlations between Doppler hemodynamic of retrobulbar arteries and RNFL thickness. Our results indicate positive correlations between the RNFL thickness and velocities of OA, CRA and SPCAs as well as negative correlations between RNFL thickness and RI of these vessels. No hemodynamic and structural relationships were observed between the SPCAs variables and the RNFL thickness in the temporal sectors of the retina around the optic nerve disc, and between the RNFL thickness in the nasal and temporal quadrants and the hemodynamic parameters of the homonymous SPCA branches. Lack of these correlation maybe be related with the complexity of the vascularization of the optic disc area and/or the insufficient size of the study groups. Janulevičiene et al [32] observed statistically significant thinning of the RNFL in association with reduced velocities of retrobulbar arteries in patients with OAG.

In contrast, our results did not show any correlation between Doppler variables and OCT ONH parameters. According to Nicolela et al [29], hemodynamic disturbances in CRA and SPCA may precede morphological changes in the ONH. Other authors have confirmed an association of BF reduction with the progression of structural and functional changes in glaucoma [33]. Tobe et al [14] has demonstrated that higher RI and lower PSV of TPCA were associated with a thinning of the rim area and an increase in the cup area within the ONH.

Our study has some limitations. First, we did not perform OCT measurements in healthy subjects due to the replacement of the OCT technologies during the course of the study. Therefore, in the discussion the study parameters were referred to the Doppler parameters of the group of healthy volunteers, previously measured by the same physician with the same ultrasound machine in order to create a laboratory standard. Second, topical and systemic therapy were continued and the potential impact of some drugs on the hemodynamic outcomes cannot be excluded. However, performing vascular measurements in the real-life conditions may assess the usefulness of Doppler technology in daily practice. Thirdly, due to the very small calibre and anatomical variability of retrobulbar vessels, their evaluation could be biased. However, the correction of the insonation angle used in this study was not higher than 20 degrees, which could generate a measurement error of less than 10% of the actual value [34]. Finally, because of relatively small size of study groups some differences between them and correlations could be undetectable.

In **conclusion**, our study has shown greater alterations in the Doppler parameters of the retrobulbar arter-

ies in patients with OAG along with a greater severity of glaucoma. As disturbed retrobulbar characteristics might be a predictor for glaucoma progression, CDI would represent a valuable additional diagnostic tool, whose outcomes would allow for more intense monitoring and/or treatment of glaucoma in patients that are at risk of a more aggressive course of neuropathy.

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Conflict of interest: none

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