Changes in the Retrobulbar Hemodynamic Parameters after Decreasing the Elevated Intraocular Pressure in Primary Open-angle Glaucoma Patients

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SUMMARY

Introduction Ocular blood flow (OBF) disturbances could be involved both in the pathogenesis and in progression of glaucomatous damage.

Objective The aim of the study was to compare the retrobulbar hemodynamic parameters in the ophthalmic artery (OA), central retinal artery (CRA) and short posterior cilliary arteries (SPCA) after decreasing the elevated intraocular pressure (IOP) in primary open-angle glaucoma (POAG) patients by using color Doppler imaging (CDI).

Methods We examined 60 patients (21 male and 39 female) with diagnosed and treated POAG. Thirty-nine patients had increased IOP (>25 mm Hg). Peak-systolic velocity (PSV), end-diastolic velocity (EDV), Pourcelot resistance index (RI), and pulsatility index (PI) were assessed in the OA, CRA, and SPCA. IOP was measured both with the Goldmann Applanation tonometer (GAT) and with the Dynamic Contour tonometer (DCT), three times respectively. Ocular pulse amplitude (OPA) was measured using DCT.

Results The retrobulbar parameters between the baseline and after IOP reduction showed no difference in measurements. After Bonferroni correction (p≤0.0056, alpha/9) statistical significance was recorded only in the following retrobulbar hemodynamic parameters; DCT (29.8±6.2 vs. 15.5±5.0), GAT (33.8±9.0 vs. 15.0±6.6) and OPA measurements (4.3±1.0 vs. 3.0±1.6), as compared to the baseline. There was no correlation between the changes in IOP measured with either DCT or GAT and changes in the hemodynamic parameters (p>0.05 for all). Pearson correlation coefficient (95% CI) showed very good correlation for IOP measurements between DCT and GAT: at baseline 0.83 (0.71 to 0.90) and at the end 0.71 (0.55 to 0.83); p<0.0001 for both measurements, but without any difference between them (p>0.05).

Conclusion There was a lack of correlation between the changes in IOP measured with either DCT or GAT and the changes in the hemodynamic parameters.

Keywords: retrobulbar vessels; color Doppler imaging; elevated intraocular pressure; glaucoma

INTRODUCTION

There is increasing evidence that ocular blood flow (OBF) disturbances are involved both in the pathogenesis of glaucoma [1-5] and in progression of glaucomatous damage [6-9]. However, the question of whether OBF disturbances are a secondary effect, caused either by increased intraocular pressure (IOP) or the presence of the glaucomatous optic neuropathy or whether changes in OBF are an independent primary factor remains.

Many different methods are used to visualize and measure directly or calculated indirectly in vivo OBF. Color Doppler imaging (CDI) uses ultrasound technology to measure blood flow parameters in the vessels supplying ocular tissues. CDI combines two dimensional structural ultrasound images with velocity measurements derived from the Doppler shift of sound waves reflected from erythrocytes as they travel through the retrobulbar vessels. In ophthalmology this method is used to measure blood flow velocities in the retrobulbar vessels [3, 10].

OBJECTIVE

Our study aimed to compare the value of CDI measurements, peak-systolic velocity (PSV), end-diastolic velocity (EDV), and Pourcelot resistivity index (RI) in the ophthalmic artery (OA), central retinal artery (CRA) and short posterior cilliary arteries (SPCA), after the decrease of elevated IOP in primary open-angle glaucoma (POAG) patients.

METHODS

We examined 60 patients (21 male and 39 female) with a clinical diagnosed of POAG from December 2009 to December 2010 referred to or recruited at the Eye Clinic and Neurology

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Clinic, Clinical Center of Serbia in Belgrade. Thirty-nine patients who met the inclusion/exclusion criteria and signed a written consent form were included in this prospective and interventional study. Institutional review board approval was obtained and the study adhered to the tenets of the Declaration of Helsinki.

Only one eye that fulfilled all the inclusion criteria and none of the exclusion criteria was designed as the study eye in each patient; in patients in whom both eyes fulfilled all inclusion criteria and none of the exclusion criteria one randomly chosen eye was included for the purpose of statistical analysis.

All participants were required to meet the following inclusion criteria: age equal or over 50 years; clinical diagnosis of POAG; IOP higher than 25 mmHg; willingness to comply with investigators and protocol indications.

Excluded patients were those with any form of glaucoma other than POAG, previous treatment with ocular filtering surgery, history of previous refractive surgery, diabetes, history of progressive retinal or optic nerve disease of any cause; asthma or any other obstructive pulmonary disease, and pregnancy or lactation.

For glaucoma diagnosis visual field (VF) examinations were performed using the 24-2 Swedish Interactive Thresholding Algorithm Standard strategy (SITA standard) using the Humphrey visual field analyzer (Carl Zeiss Meditec, Dublin, CA, USA). Glaucomatous VF defects were defined as follows: a minimum of one location in the paracentral or nasal step regions corresponding to sectors 1 or 2 or to the inferior 3 location in the sector 3 of the Glaucoma Hemifield Test [11] exhibiting repeatable abnormality at the p<0.5% level by pattern deviation probability analysis, or by two or more locations in a cluster exhibiting repeatable abnormality at p < 2% by pattern deviation probability analysis, excluding any location in the cluster located in the opposite horizontal hemifield.

At baseline, all subjects underwent a standard ophthalmic examination including visual acuity (Snellen chart), slit-lamp biomicroscopy, gonioscopy, intraocular pressure measurement with Goldmann applanation tonometry (GAT) and Dynamic Contour tonometer (DCT), central corneal thickness measurement with ultrasound pachymeter, lens examination of the fundus, and central corneal thickness (CCT) three times consecutively with ultrasound pachymetry (Palm Scan AP 2000, ophthalmic ultrasound, Micro Medical Devices, Inc. Clabasas, CA, USA). Diagnostic observation also included automated perimetry on the Humphrey visual field analyzer (Carl Zeiss Meditec, Dublin, CA, USA) and scanning laser ophthalmoscopy (HRT II, Heidelberg Engineering, GmbH, Dossenheim, Germany) exam at least once a year.

IOP was determined three times, each consecutively, using DCT (Swiss Microtechnology AG, Port, Switzerland) and GAT (Goldmann tonometer; Haag Streit AG, Koeniz, Switzerland). Ocular pulse amplitude (OPA) appeared during DCT measurement.

All CDI examinations (model Antares; Siemens, Munich, Germany) were performed at all study visits by the same experienced observer who was masked to the treatment.

A 7.5-10 MHz vector-array transducer was applied to the closed eyelid using a coupling gel; any pressure on the eye itself was avoided. Measurements were taken using the conventional technique [12], which is identical to the technique we have used in many previous studies [8, 13-18]. In brief, OA flow measurements were performed approximately 10-15 mm posterior to the globe where ultrasound signals were stronger. SPCA images were taken temporally and nasally to the optic nerve just behind the posterior pole of the eye. The angle between transducer and vessel orientation was corrected. CRA measurements were taken at the optic nerve head level.

PSV and EDV were measured in the OA, CRA and medial and lateral SPCAs. Although the medial and lateral posterior cilliary arteries (PCAs) were individually assessed, the mean value of both was used for the statistical analysis. PSV and EDV were used to calculate the RI using the following equation: RI=PSV-EDV/PSV [19]. Evaluations of blood pressure (BP) and radial pulse were obtained in a supine position after 10 min of rest. Systolic (SBP) and diastolic blood pressure (DBP) were measured in the upper right arm using a mercury sphygmomanometer and heart rate (HR) was measured by palpation of the radial pulse. These parameters were obtained every 10 min during CDI examination.

After baseline examinations, the patients received treatment, either medical or surgical, for decreasing IOP. Treatment assignment was based on the clinical situation of each patient. The patients were asked to return one month after treatment, and at the end of this time the same measurements were repeated.

Statistical analysis

Before the study, it was determined that a sample of at least 36 patients was required to detect a difference of 0.05 units in the mean RI in the OA, SPCA, and CRA at a significance level of 0.01, with a power of 0.95, and assuming a standard deviation of 0.05 units. The adjusted power of the study was 0.86 (0.95 ´ 0.95 ´ 0.95).

Descriptive statistics (mean ± standard deviation) and 95% confidence intervals (95% CIs) were used to report demographic and ocular baseline characteristics. Data were tested for normal distribution using the Kolmogorov–Smirnov test. As data were normally distributed, the two-tailed, paired Student's t-test was used to evaluate IOP and hemodynamic parameters by intragroup comparisons made between the values obtained under baseline conditions and treatment conditions.

Because of the large number of tests, simultaneous inference using the Bonferroni correction was used to correct the p-value (α/9 Statistical significance was accepted for p<0.0056).

To analyze the correlation between changes in the retrobulbar hemodynamics and changes in IOP assessed with both GAT and DCT, Pearson correlation coefficients were calculated for every parameter.

Statistical analysis was performed using Med-Calc 11.5.1.0 (MedCalc software, Mariakerke, Belgium).

Table 1. Comparison of clinical and hemodynamic variables at baseline and after IOP reduction in open-angle glaucoma patients

Variable		Baseline		Final		p
		Mean (SD)	95% CI	Mean (SD)	95% CI	
DCT		29.8 (6.2)	28.3–31.3	15.5 (5.0)	14.3–16.7	<0.0001
GAT		33.8 (9.0)	31.6–36.0	15.0 (6.6)	13.4–16.6	<0.0001
OPA		4.3 (1.0)	4.1–4.6	3.0 (1.6)	2.6–2.8	<0.0001
OA	PSV	58.0 (28.9)	51.0–65.0	51.5 (22.2)	46.1–56.9	0.059
	EDV	20.3 (15.3)	16.6–24.0	16.9 (10.9)	14.3–19.5	0.066
	RI	0.70 (0.12)	0.68–0.73	0.71 (0.18)	0.67–0.75	0.824
CRA	PSV	40.1 (20.9)	35.0–45.1	37.4 (12.9)	34.3–40.5	0.292
	EDV	13.1 (7.4)	11.3–14.9	12.1 (6.3)	10.6–13.7	0.266
	RI	0.68 (0.12)	0.65–0.71	0.71 (0.16)	0.67–0.74	0.301
PCA	PSV	28.8 (13.9)	25.5–32.2	27.0 (10.9)	24.4–29.7	0.339
	EDV	9.4 (4.0)	8.4–10.4	9.7 (3.8)	8.8–10.7	0.576
	RI	0.67 (0.18)	0.62–0.71	0.68 (0.27)	0.62–0.74	0.689

SD – standard deviation; 95% CI – 95% confidence interval; CT – central corneal thickness; DCT – dynamic contour tonometry; GAT – Goldmann applanation tonometry; OPA – ocular pulse amplitude; OA – ophthalmic artery; PSV – peak systolic velocity; EDV – end-diastolic velocity; RI – resistivity index; CRA – central retinal artery; PCA – posterior cilliary artery

Table 2. Pearson correlation coefficient between IOP reductions, assessed with both DCT and GAT, changes in OPA and some hemodynamic parameters

Changes	DCT			GAT			OPA		
	R	95% CI	p	r	95% CI	p	r	95% CI	p
RI OA	-0.115	-0.342–0.124	0.345	-0.077	-0.308–0.162	0.528	0.091	-0.148–0.321	0.456
RI CRA	-0.159	-0.381–0.080	-0.159	-0.057	-0.290–0.181	0.639	0.130	-0.109–0.356	0.283
RI PCA	-0.254	-0.463–-0.018	0.035	-0.127	-0.353–0.113	0.297	-0.0948	-0.324–0.145	0.438

RESULTS

Of 60 patients who were screened, 39 fulfilled the respective demands of inclusion and exclusion criteria. Mean±SD (95% confidence interval – 95% CI) age was 64.7±13.9 years (60.3 to 69.2 years).

CCT was 555.1±44.5 μm (545.0 to 565.2 μm), visual field mean deviation was 12.9±13.6 dB (-19.5 to -6.4 dB), and visual field pattern standard deviation was 5.7±4.1 (3.4 to 7.9).

IOP, OPA, and retrobulbar hemodynamic parameters, at the baseline and after treatment, are summarized in Table 1.

Retrobulbar hemodynamic parameters did not change after therapy when Bonferroni correction was applied.

Pearson correlation coefficient (95% CI) showed very good correlation for IOP measurements between DCT and GAT: at baseline 0,825 (0,730 to 0,888) and at the end 0,878 (0,808 to 0.923); p<0.0001 for both measurements, with no differences between them (p=0.1451).

Pearson correlation coefficient between IOP reductions, assessed with both DCT and GAT, changes in OPA and some hemodynamic parameters is presented in Table 2. There was no correlation between the changes in IOP measured with either DCT or GAT, OPA and the changes

Table 3. Pearson correlation coefficient between changes in OPA and IOP reductions, assessed with both DCT and GAT

Changes	OPA		
	r	95% CI	p
DCT	0.264	0.029–0.471	0.028
GAT	0.279	0.046–0.484	0.020

in the hemodynamic parameters (RI in the retrobulbar vessels). The lack of correlation between the changes in IOP and changes in blood flow meant a lack of influence of IOP, even at high levels, on the ocular hemodynamics.

We found a lack of correlation between OPA and IOP reductions. Pearson correlation coefficient between changes in OPA and IOP reductions, assessed with both DCT and GAT is presented in Table 3.

DISCUSSION

In the present study it was not found that decreasing IOP in POAG patients with elevated IOP caused any significant change in retrobulbar hemodynamics.

The results of the present study suggest that although ocular hemodynamics may be influenced by elevated IOP, dramatic chronic decreases in IOP do not lead to changes in ocular blood flow as measured by the technique utilized in this cohort of POAG patients.

These results agree with those previously published by our group [17] that reported no significant changes in the retrobulbar circulation in open-angle glaucoma (OAG) patients after the reduction of IOP with either medical or surgical treatment. This study evaluated 46 open-angle glaucoma patients (primary + secondary OAG patients) who were assessed to have IOP too high for their degree of optic nerve cupping and visual field loss.

Hemodynamics in the OA, CRA and SPCA were evaluated by using CDI. The results of this study suggested that despite the significant decrease in IOP following treatment (52.1%; p<0.001), there were no significant changes in the

PSV, EDV, or RI in OA. The PSV, EDV, and RI in the CRA also remained unchanged from baseline measures at all study visits.

Additionally, the results of this study agree partially with those previously published by Martinez and Sánchez [16], who reported no significant correlation between EDV and IOP either in OA or SPCA. Although it is difficult to compare the results of both studies because Martinez and Sanchez [16] evaluated pseudoexfoliative glaucoma patients.

However, the results of our study contrast sharply with those of several studies that reported a direct relationship between changes in IOP and altered ocular hemodynamics. Trible et al. [20] reported a statistically significant increase in the mean and EDV and a significant decrease in the vascular resistance of CRA and both SPCA after trabeculectomy.

Additionally, by using a suction cup, Findl et al. [21] increased IOP by 10 and 20 mmHg in normal subjects. In that study, a 20 mmHg increase in IOP caused a significant reduction in the mean flow velocity in the CRA. Moreover, the RI in the CRA increased significantly, with IOP elevation of just 10 mmHg.

A possible explanation for the findings in the present study, compared with previously published works, might be that many of previously cited studies used scleral suction cups to induce artificially acute IOP elevations in normal subjects, with normal baseline IOPs.

Our study has some limitations. The first one results from our use of a singular ocular imaging technology to study OBF without providing data on the retina or other vascular beds. The second limitation of our study is that it is a single center study, with a limited number of patients. Nevertheless, the sample size was calculated prior to study.

An important limitation of the present study is that the patients received glaucoma drug treatment for decreasing IOP and this may influence the OBF. On the other hand the results obtained were independent of the antiglaucoma therapy.

CONCLUSION

Despite these limitations, the results of our study suggested a lack of correlation between the changes in IOP measured with either DCT or GAT and the changes in hemodynamic parameters. These findings might point out that OBF disturbances, found in this cohort of POAG patients, seem to be independent of IOP.

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Промене у параметрима ретробулбарне циркулације након снижавања повишеног интраокуларног притиска код особа с примарним глаукомом отвореног угла

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КРАТАК САДРЖАЈ

Увод Поремећај протока крви у оку може бити укључен како у патогенезу, тако и у прогресију глаукомног оштећења.
Циљ рада Циљ рада је био да се упореде параметри ретробулбарне хемодинамике у офталмичкој артерији (*OA*), централној ретиналној артерији (*CRA*) и кратким задњим цилијарним артеријама (*SPCA*) након снижавања повишеног интраокуларног притиска (ИОП) код особа с примарним глаукомом отвореног угла (*POAG*) применом колор доплера.
Методе рада Испитано је 60 болесника (21 мушкарац и 39 жена) са дијагностикованим и леченим *POAG*. Код 39 испитаника установљен је повишен ИОП (>25 *mm Hg*). Параметри вршног систолног протока, крајњег дијастолног протока, Пурселов (*Pourcelot*) индекс резистенције и индекс пулзатилности мерени су у *OA*, *CRA* и *SPCA*. ИОП је мерен Голдмановим (*Goldmann*) апланационим тонометром (*GAT*) и динамичким контурним тонометром (*DCT*), по три пута узастопно. Окуларна пулсна амплитуда (*OPA*) је мерена помоћу *DCT*.
Резултати Параметри ретробулбарне циркулације се нису променили после снижавања ИОП. Након Бонферонијеве (*Bonferroni*) корекције (*p*≤0,0056, α/9) статистички значајна разлика у ретробулбарним параметрима је утврђена код оних мерених помоћу *DCT* (29,8±6,2 према 15,5±5,0), *GAT* (33,8±9,0 према 15,0±6,6) и код *OPA* (4,3±1,0 према 3,0±1,6), у поређењу с почетним вредностима. Није уочена корелација између промена ИОП који је мерен помоћу *DCT* или *GAT* и промена у хемодинамским параметрима (*p*>0,05 за све). Пирсонов коефицијент корелације (95-процентни интервал поверења) показао је веома добру корелацију за вредности ИОП између оних добијених мерењем помоћу *DCT* и оних измерених применом *GAT*: почетна вредност у просеку је била 0,83 (распон 0,71–0,90), а завршна 0,71 (распон 0,55–0,83); *p*<0,0001 за оба мерења и без разлике међу њима (*p*>0,05).
Закључак Није утврђена корелација између разлика у ИОП мерених помоћу *DCT* или *GAT* и промена у посматраним хемодинамским параметрима.

Кључне речи: ретробулбарни крвни судови; колор доплер; повишен интраокуларни притисак; глауком