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Original article

VENOUS OCULAR BLOOD FLOW IN NORMAL TENSION AND HIGH TENSION GLAUCOMA

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Summary

Purpose: to study the eye's venous blood flow and the correlation between clinical data and ocular blood flow in normal tension and high tension open angle glaucoma (POAG).

Methods: Color Doppler imaging of arterial and venous blood flow was performed on 78 patients with normal tension glaucoma (NTG), 80 patients with high-pressure glaucoma (HPG) and 60 control subjects. The statistical analysis included the calculation of the correlation between clinical data and ocular blood flow parameters, as well as Pearson's correlation coefficient. The threshold P value for statistical significance was 0.05.

Results: Ocular blood flow (both arterial and venous) was significantly reduced in NTG and HTG, compared to the control group. While the arterial blood flow reduction was more significant in HTG than in NTG, a decrease in venous blood flow had a higher incidence in NTG. In contrast to the control group, POAG patients showed a correlation between clinical data and venous blood flow. The correlation was higher in NTG patients.

Conclusions: The results obtained indicate the potential importance of venous blood flow in glaucoma pathogenesis, especially in NTG.

Introduction

Reduced and/or unstable ocular blood flow leading to chronic ischemia and reperfusion of deep retinal layers and optic nerve head, are considered significant risk factors in primary open angle glaucoma (POAG) development and progression [1]. More than 30 years ago, Quigley et al., performed a histological analysis in post mortem eyes comparing the optic disc capillary bed in patients with early and advanced glaucoma. The authors reported that the amount of capillaries remained at a normal level, while there was a significant thinning of the retinal nerve fiber layer (RNFL) in advanced glaucoma [2]. On this basis, the author concluded that the development of glaucomatous optic neuropathy was not associated with vascular disorders of the optic nerve. However, Hayreh criticized this conclusion, emphasizing that the state of the capillary bed did not necessarily reflect the level of ocular perfusion, since capillaries were more resistant to ischemia than nervous tissue [3]. In humans, longitudinal studies

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are required to investigate whether such perfusion changes in glaucoma are a cause or consequence of the disease, which makes measuring ocular blood flow difficult in the absence of a gold standard method. Color Doppler imaging (CDI) has been proposed for glaucoma diagnosis showing relatively good sensitivity and specificity [4-23]. Moreover, several longitudinal studies using CDI indicate that reduced blood velocities in retrobulbar vessels are indeed a risk factor for glaucoma progression [4-10].

However, few studies mention the role of venous blood flow in glaucoma and explore how it's linked to disk hemorrhages, retinal vein occlusion [18] and retinal venous pulsation [14,15].

The purpose of our study was to evaluate venous blood flow in normal tension and high tension glaucoma patients and determine the correlation between local blood flow and clinical data in POAG patients.

Materials and Methods

Subject groups

The study was approved by the ethical committee (Institutional Review Board) at the Institution of Federal Medical and Biological Agency of Russian Federation and was conducted in accordance with Good Clinical Practice within the tenets of the Helsinki agreement. Each patient/ subject was required to sign an informed consent form before being enrolled in the study and prior to any measurements being taken.

The study included 156 patients (73 male and 83 female) with POAG between the ages of 46 and 67. 78 patients had normal tension glaucoma (NTG), and 80 had high-pressure glaucoma (HPG). 60 healthy individuals (22 males and 38 females) of the same age were used as the control group. Glaucoma was diagnosed based on the typical changes in the optic disc detected by ophthalmoscopy, which was performed by a glaucoma specialist (NK; pathological deviation from the normal neuroretinal rim, glaucomatous optic disc cupping, peripapillary atrophy, wedge-shaped defects of RNFL adjacent to the edge of optic disc, and hemorrhages on the optic disc boundary). The Standard automated perimetry (SAP) was calculated using the Humphrey perimeter (Carl Zeiss Meditec, Dublin, CA) and a 30-2 threshold test program with the SITA-Standard algorithm (threshold was studied at 176 points within the central 30° using Goldmann III white stimulus and presentation duration of 100 ms, with background illumination of 31.5 abs). The Mean deviation (MD) and pattern standard deviation (PSD) were determined. The results of the SAP had to be normally defined as: the pattern deviation plot has less than 3 contiguous points significantly different from normal ($P<0.05$) with at least one at the $P<0.01$ level on the same side of the horizontal meridian. An untreated intraocular pressure (IOP) above 21 mm Hg was required in order to diagnose HTG. Patients using eye drops prior to being enrolled in the study were recommended to discontinue treatment for up to 3 weeks (the washout period). Other patients were newly diagnosed with glaucoma. Diagnostic criteria for NTG were the same as for the patients with HTG; however, an IOP was not above 21 mmHg.

The control group consisted of patients with no first-degree relatives with glaucoma, IOP<22 mm Hg, normal optic disc appearance, normal RNFL and absence of visual field defects.

All subjects underwent an ophthalmologic examination that included determination of visual acuity, biomicroscopy, applanation tonometry, gonioscopy, pachymetry, measurement of axial length and anterior chamber depth, and imaging of the anterior segment of the eye using OCT. Inclusion criteria were the refractive error ≤0.5 diopters and an open anterior chamber angle grater than 30°.

The exclusion criterion was presence of any of the following indications: systemic administration of beta-blockers and calcium-channel blockers, concomitant ocular disease (except early stage cataract), chronic autoimmune diseases, diabetes mellitus, acute circulatory disorders in past medical history, and any concomitant disease involving administration of steroid drugs. Additional exclusion criteria were: history of ocular arterial venous

obstructions (branch or central occlusion), or systemic conditions associated with venous congestion (e.g. heart failure). Only patients who had not previously undergone ocular surgery were included.
In glaucoma patients, the eye with more advanced stage glaucoma was included in the study. The control group had the hemodynamics of their right eye examined.
The information regarding functional and structural damage was collected from glaucoma patients during examinations performed on the day of the study visit.
The patients with suspected intracranial abnormalities underwent brain magnetic resonance imaging (MRI). A Doppler imaging was used to exclude any neck blood vessel pathology. The blood pressure was measured from the subject's right arm using an electronic sphygmomanometer (Omron, Schaumburg, USA).

Measuring devices

The intraocular pressure was measured using the Ocular Response Analyzer (ORA) (Reichert Ophthalmic Instruments, Depew, NY). The device uses a direct burst of air directed towards the cornea and uses applanation pressure measurements, one during the depression of the cornea and another during the recovery. The corneal hysteresis (CH) measure allows for the calculation of a corneal compensated IOP (IOPcc), which appears to be less affected by properties of the cornea than conventional applanation tonometry.
The mean ocular perfusion pressure (MOPP) was calculated based on measurements of the IOP and systemic blood pressure (BP) immediately before the OCT scanning and investigation of the retrobulbar blood flow, after a 10-minute resting period in the sitting position. The systemic BP was measured using the Riva Rocci technique. MOPP was calculated using the formula: MOPP= ([2/3diastolicBP + 1/3systolicBP] x 2/3-IOP).
The OCT was performed using the RTVue -100 OCT (Optovue, Inc., Fremont, CA) in the optic disc area (ONH protocols and 3D Disc) and macular area (GCC protocol) in tracking mode. In the ONH (optic nerve head) study protocol, retinal nerve fiber layer thickness (RNFLT) was investigated.
The method used for investigating blood flow velocity in retrobulbar vessels included gray-scale ultrasound, Color Doppler Imaging (CDI) and pulsed-wave Doppler (PWD). The ultrasound examinations were performed with a VOLUSON 730 Pro ultrasound system (GE Medical Systems Kretztechnik GmbH & Co OHG, Austria) and a SP 10-16 transducer. With the patient in a supine position, sterile ophthalmic gel was applied additionally to the closed eyelid, and the probe was positioned gently with minimal pressure. Performing a gray-scale ultrasound enabled us to obtain the image of the globe and orbit. The CDI-method was used to display directly the fine orbital vessels, including the ophthalmic artery (OA) and its branches, the central retinal artery (CRA), and the lateral and medial posterior ciliary arteries (PCAs). It was done according to expected anatomical position of the vessels and color code. The blood flow in the OA was evaluated at a depth of 35 mm. The CRA blood flow velocity was examined in the canal of the optic nerve at the distance of 5-6 mm from the posterior wall of the globe. The PCAs were identified on either side of the optic nerve, about the same distance from the fundus as the central retinal artery and vein. By using PWD we measured the blood flow spectrum of the vessels and their main indices: peak systolic velocity (PSV), end-diastolic velocity (EDV), mean velocity (Vmean), resistive index (RI), and the pulsatility index (PI).
Patients were instructed to avoid caffeine intake, smoking and exercise for 5 hours prior to the visit for the study.

Statistical analysis

Analyses were performed with the "SPSS 11.0 for Windows" software. The statistical analysis included the calculation of mean, standard deviation, standard error as well as Pearson's correlation coefficient. The threshold P value for statistical significance was 0.05.
Since a number of parameters (GCC, CDI parameters of the vortex vein, the mean velocity and RI in the superior ophthalmic vein and corneal hysteresis) depended on

the axial length (AL) and age of the subjects, they were adjusted on a linear regression model basis with an allowance for AL and age.

	NTG	HTG	Healthy subjects	Pairwise NTG versus HTG (p-value)
n	78	80	60	
Age, years	64.2 (9)	69.3 (12)	63.5 (10)	0.68
Axial length, mm	23.1(0.7)	23.3 (0.8)	22.9 (1.0)	0,35
IOP, mm Hg	13.5 (2.5)	24.6 (4.8)*	14.8 (3.6)	<0.001
Visual acuity	0.8 (0.1)	0,75 (0,08)	0,9 (0,07)	0.73
Systolic BP mean, mm Hg	136.7 (10.1)	132,3 (16.1)	127 (13)	0.56
Diastolic BP mean, mm Hg	76.7 (9.3)	78.5 (11.3)	81.0 (9,3)	0.55
MOPP, mm Hg	51.2 (8.3)*	59.4 (9.1)	61.1 (8.5)	0.03
Corneal thickness, µm	533.5 (26.3)	538.3 (35.9)	532.9 (20.7)	0.35
MD, dB	-6.6 (3.3)*	-7.6 (5.9)*	-0.7 (2.1)	0.44
GCC avg, µm	73.9 (20.1)*	69.9 (18.2)*	92.3 (15.7)	0.62
Disk area, mm^2	2.3±0.5	2.1±0.5	2.1± 0.2	0.31
Cup volume, mm^3	0.30±0.19*	0.24±0.26*	0.06± 0.07	0.1
Rim volume, mm^3	0.29±0.13*	0.28±0.203*	0.6 ± 0.14	0.19
RNFL S avg, µm	91.8±25.5*	81.8±24.5*	119.1± 19.0	0.24
RNFL I avg, µm	99.5±23.9*	89.7±29.7*	125.1± 19.4	0.67
RNFL avg, µm	84.7±15.8*	79.6±18.6*	97.5± 12.6	0.53
** the difference between the studied group and healthy control subjects is statistically significant (p<0.05).*				

Table 1. Patient characteristics. The figures represent mean values and standard deviation (SD).

RNFL S avg, RNFL I avg, RFNL avg = retinal nerve fibre layer thickness (RNFL thickness) above the optic disc, below the optic disc and average RNFL thickness respectively. IOP=intraocular pressure; MD=mean deviation; BP=blood pressure; MOPP=median ocular perfusion pressure; GCC avg=ganglion cell complex.

Variables	NTG	HTG	Healthy subjects
CRA PSV, cm/s	**11.3±3.4***	**10.6±2.6***	14.1±1.8
CRA EDV, cm/s	2.7±1.7*	2.5±1.5*	3.7±0.9
CRA Vmean, cm/s	5.8±2.0*	5.5±1.6*	7.0±1.3
CRA RI	0.78±0.13	0.8±0.22*	0.74±0.04
CRV PSV, cm/s	6.5±1.9	5.8±1.3*	6.9±1.1
CRV EDV, cm/s	3.1±1.8*	3.2±1.5*	5.2±1.0
CRV Vmean, cm/s	3.8±1.3*	4.0±1.2*	5.6±0.9
CRV RI	0.49±0.27*	0.58±0.47*	0.28±0.11
CRV PI	0.8±0.61*	0.71±0.64*	0.39±0.18
lat. PSV, cm/s	**12.1±2.6***	**11.1±2.6***	14.4±1.8
lat. EDV , cm/s	3.6±1.6*	3.5±1.6*	5.2±1.2
lat. Vmean, cm/s	**6.8±1.6***	**6.3±1.8***	8.5±1.3
lat. RI	0.71±0.12*	0.69±0.11*	0.63±0.07
lat. PI	1.3±0.42*	1.26±0.37*	1.09±0.2
med. PSV , cm/s	**11.5±2.6***	**10.4±2.4***	13.8±2.2
med. EDV , cm/s	**3.6±1.8***	**3.3±1.5***	4.7±1.0
med. Vmean, cm/s	6.3±1.7*	6.0±1.6*	8.2±1.6
med. RI	0.69±0.14	0.69±0.12*	0.65±0.06
OA PSV, cm/s	34.4±6.2*	33.1±7.4*	39.3±6.2
OA EDV, cm/s	9.6±3.1	9.1±3.6	9.3±3.7
OA Vmean, cm/s	**18.5±4.1**	**17.5±5.0**	17.2±4.5
OA RI	**0.76±0.2**	**0.73±0.08***	0.77±0.06
OA PI	1.39±0.34*	1.43±0.36*	1.77±0.37
VV PSV, cm/s	4.9±1.0*	5.1±1.1*	7.1±1.1
VV EDV, cm/s	**1.6±1.3***	**2.7±1.8***	4.3±1.4
VV Vmean, cm/s	**2.9±0.8***	**3.6±1.1***	5.2±1.3
VV RI	**0.67±0.23***	**0.51±0.29***	0.39±0.16
VV PI	**1.32±0.85**	**0.82±0.7***	1.07±1.44
SOV PSV, cm/s	**5.0±5.6***	**7.7±2.2***	10.4±1.8
SOV EDV, cm/s	**3.2±2.3***	**4.2±2.4***	6.4±2.8
SOV Vmean, cm/s	**4.7±1.4***	**5.2±2.3***	8.0±2.3
SOV RI	**0.54±0.32**	**0.46±0.23***	0.41±0.23
SOV PI	**0.98±0.78**	**0.82±0.72**	0.72±0.49

* the difference between the studied group and the healthy control subject group is statistically significant ($p<0.05$).

Table 2. CDI variables of the retrobulbar vessels in the studied groups

Abbreviations**: CRA – central retinal artery, CRV – central retinal vein, PCA - lateral and medial short posterior ciliary arteries, OA - ophthalmic artery, VV - vortex veins, SOV - superior ophthalmic vein; PSV – peak systolic velocity, EDV – end diastolic velocity, Vmean – mean velocity, RI – resistive index, PI – pulsatility index. **Blood flow velocities showing a statistically significant difference in NTG and HTG are given in bold.

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Results

Table 1 summarizes patient characteristics in the observed groups. A significant difference was detected between POAG patients and healthy control subjects in all studied parameters except age, visual acuity, axial length, disk area and blood pressure. However, there was no difference between glaucoma patients, except in IOP and mean ocular perfusion pressure, which was significantly lower in NTG patients than the HTG group and healthy subjects.

CDI variables of the retrobulbar vessels for each group studied are shown in Table 2. Blood flow was significantly reduced in all vessels supplying blood to the retina and optic disc in patients with NTG and HTG, compared to the healthy subjects. Arterial blood flow velocity parameters were higher in NTG than in HTG; some parameters showed a statistically significant difference ($p<0.05$). However, venous blood flow deficiency was more pronounced ($p<0.05$) in NTG than in HTG patients.

The correlation between morphology, function and blood flow parameters in POAG patients and healthy control subjects is summarized and shown in Table 3. The control group showed a correlation between clinical parameters and blood flow in the short posterior ciliary arteries. In glaucoma patients there was a significant correlation between clinical data and venous blood flow (especially in NTG) rather than with arterial blood flow. This result is given by the correlation between the ganglion cell complex thickness and blood flow in the central retinal vein and vortex veins.

Discussion

Our results indicate that ocular blood flow deficiency might be present in glaucoma in general, which has already been reported in numerous studies [14, 16, 17, 20]. Impaired blood flow in NTG is not greater than in HTG. This wasn't an unexpected result, because it had been previously described in the literature [22].

The most significant results were found regarding venous blood flow in glaucoma, which wasn't analyzed enough by previous studies. This is mainly due to the lack of precise and reliable ocular blood flow evaluation methods [1, 24]. The CDI of ocular blood vessels is regarded as a standard method, which has been a well-validated tool in ocular blood flow research. However, R. Ehrlich and A. Harris, in a recent study, stated that it is not accurate if used to examine small vessels and venous blood flow. Nevertheless, they also noted that high skilled professionals were nevertheless able to visualize small blood vessels [25]. In a recent meta-analysis by Rusia et al., the CDI data collected from 3061 glaucoma patients was compared with 1072 healthy subjects. The authors concluded that CDI parameters could be used as a diagnostic criterion for distinguishing glaucomatous patients from healthy individuals [26].

Our results show decreased blood flow in CRV, as well as in vortex veins and superior ophthalmic vein in both POAG groups. Moreover, blood flow in NTG turned out to be lower than in HTG in several veins. We assume that this result is linked to the development of glaucomatous optic neuropathy. The findings show a high correlation between clinical data and venous blood flow parameters in glaucoma – especially in NTG – and no

	MD	PSD	Cup volume	Rim volume	Lin c/d ratio	RNFL S avg µm	RNFL I avg µm	RNFL Avg µm	GCC Avg µm
CRV PSV		-0.422 (0.039)		**0.372 (0.001)**					
CRV EDV			0.731 (0.007)		-0.617 (0.043)	**0.409 (0.001)**	**0.318 (0.009)**	**0.415 (0.001)**	
CRV Vmean		-0.675 (0.01)	-0.71 (0.01)	**0.368 (0.001)**		**0.461 (0.001)**		**0.403 (0.001)**	0.32 (0.003)
CRV RI		0.788 (0.002)	0.702 (0.01)		0.629 (0.038)			**-0.375 (0.002)**	
CRV PI	**-0.432 (0.001)**	0.878 (0.001)	0.674 (0.016)				**-0.384 (0.001)**	**-0.427 (0.001)**	
lat. PSV			*-0.738 (0.036)*						
lat. EDV,						0.615 (0.004)			
lat. Vmean						0.604 (0.005)			
med. PSV,			*-0.7 (0.05)*						
med. PI							*-0.98 (0.02)*		
OA EDV				0.408 (0.048)				0.467 (0.02)	
OA RI			0.48 (0.017)	-0.509 (0.01)	0.41 (0.05)	-0.5 (0.025)		-0.512 (0.01)	
OA PI			0.47 (0.02)	-0.57 (0.004)	0.476 (0.02)			-0.577 (0.003)	
VV Vmean									0.32 (0.016)
VV EDV									**0.38 (0.004)**
VV RI									-0.37 (0.045)
SOV PSV							0.53 (0.04)		

Table 3. Correlation between morphology, function and blood flow parameters in POAG patients and healthy control subjects

***Abbreviations**: CRV – central retinal vein, PCA – lateral and medial short posterior ciliary arteries, OA – ophthalmic artery, VV – vortex veins, SOV – superior ophthalmic vein; PSV – peak systolic velocity, EDV – end diastolic velocity, Vmean – mean velocity, RI – resistivity index, PI – pulsatility index. MD - mean deviation, PSD – pattern standard deviation, Lin. c/d ratio - linear cup/disc ratio, RNFL thickn. – retinal nerve fiber layer thickness, RNFL S avg, RNFL I avg, RFNL avg = retinal nerve fiber layer thickness (RNFL thickness) above the optic disc, below the optic disc and average RNFL thickness respectively, GCC – ganglion cell complex (average thickness).*

The healthy subject control group data is given in italics and underlined, the parameters in HTG are given in bold, and in NTG – in regular font.

such correlation with arterial blood flow support this assumption.

The ocular venous outflow pathway includes the CRV, the vortex veins and the superior ophthalmic vein, as well as several small orbital veins. It is important to keep in mind that the venous system anatomy may vary. The central retinal vein exits the eye through the lamina cribrosa along with the optic nerve. Narrowing of CRV past the lamina cribrosa is a typical anatomical trait, and 4 out of 5 patients have an intraorbital portion of the CRV 43-116% wider than normal, which runs through the lamina cribrosa [17]. Thus, a narrow lamina cribrosa opening combined with its unique anatomical features may severely limit the venous outflow. Apparently, there are 3 options: 1) the narrowing is significant, 2) insignificant or 3) moderate. If the segment of the CRV that goes through the lamina cribrosa is significantly narrowed, the pressure in the intraocular portion of the CRV is significantly higher than IOP. Therefore, the actual ocular perfusion pressure (OPP) in such cases is much lower than the pressure calculated by using the standard formula (see above), where IOP is thought to be equal to BP in the CRV.

However, it should be kept in mind that even a minor increase in IOP, which lowers OPP only by 4 – 5 %, may double the pressure difference between the prelaminar and postlaminar portions of CRV. As adequately noted by A. Bill, if we suppose that the pressure in the intraocular segment of the CRV would equal IOP, it is always slightly higher than that in the postlaminar portion of the CRV [27]. This results in turbulent blood flow. If IOP becomes higher than the pressure in CRV, the turbulence increases putting the vein wall at risk of mechanical damage. Notably, it can also happen in cases of minor IOP increase, for instance in NTG. The situation is worsened by enlargement of CRA, which might compress the vein situated below it. Thus, CRA enlargement does not lead to an increase in OPP; instead, it decreases it due to higher pressure in the CRV. Severe pressure increase may lead to CRV thrombosis, which is basically typical in glaucoma.

A new theory has recently been suggested to explain the origin of retinal vein thrombosis. It is based on certain similarities between the pathogenesis of vein thrombosis and glaucoma [28]. The hypothesis is that the inner vein wall – such as the endothelium of arteries and capillaries – responds to various vasoconstrictive and vasodilatory factors. What do CRV thrombosis and glaucoma have in common? On the molecular level, there is an overproduction of the following substances: hypoxia-inducible factor (HIF-1α), endothelin-1 (ET-1), vascular endothelial growth factor (VEGF) and erythropoietin. The aforementioned chemical stimuli may lead to vasospasm and increase vascular permeability. These factors are thought to be able to diffuse through the permeable wall of choroidal blood vessels into the optic nerve head. This is the first location to become affected by vasospasm and increased permeability, which in severe cases manifest with optic disc hemorrhage [23]. It is notable that in both phenomena venous blood pressure is increased [29].

Short-term IOP increase results in capillary stasis due to microstructural damage of arterioles (which can occur in vessels adjacent to the lamina cribrosa or be caused by spasm of arterioles) [21]. Capillary stasis immediately leads to stasis in the adjacent venule, which spreads to the CRV. The reason is the aforementioned blood flow turbulence in the retrolaminar part of the CRV due to an IOP increase and pressure drop in the vein below the IOP. The period of IOP increase might be too short to activate blood flow autoregulation. As a result it leads to a decrease in OPP [16], followed by the release of inflammatory mediators, arrival of leukocytes and other thrombosis-inducing factors.

According to published data, a blood flow decrease itself is not as important in POAG pathogenesis as vascular dysregulation [1]. It is suggested that it is typical of both glaucoma and retinal vein occlusion because it affects the venous system as well [28].

We have recently discovered that ocular blood flow is dependent on heart rate variability, especially in NTG [19]. Other

authors note that OPP is not as relevant as its fluctuation, which may be caused by blood flow instability in the setting of vascular dysregulation. The latter is believed to be one of the mechanisms of glaucomatous optic neuropathy progression (due to ocular blood flow autoregulation failure) in patients with normal IOP [20].

The factors previously mentioned might be the cause of venous blood flow impairment found in both groups of POAG patients, and especially pronounced in NTG. It is known that short-term IOP and OPP fluctuation does not immediately lead to an axonal injury: the retina can even withstand increased IOP for an hour, and the axons for weeks and months after the development of local ischemia. In contrast to that, ocular microcirculation becomes impaired several minutes after moderate IOP fluctuation [18]. This is an exact mechanism that triggers other pathologic processes leading to neuron apoptosis. It is fair to assume that microvasculature (arterioles, venules, and capillaries) involvement is just as important in GON development as venous outflow impairment in larger ocular blood vessels. Another assumption is that CRV architectonics – mainly in the part that goes through the lamina cribrosa – may also be an underlying cause of venous stasis in patients with IOP fluctuation. Moreover, these factors could be hereditary.

As mentioned above, there are three possible anatomical features of CRV. The first one is a significant narrowing of CRV past the lamina cribrosa. In this case IOP increase in systole leads to higher blood inflow, which in turn results in dramatic pressure increase in the part of CRV passing through the lamina cribrosa. The blood is pushed through the narrow space creating turbulence in the intraorbital segment of the vein and ultimately resulting in venous stasis and a drop in OPP.

The second option is completely different; there is an insufficient CRV narrowing in the lamina cribrosa. In such instance, CRV starts to pulsate intensely with each systole leading to pressure drop below IOP, followed by collapse in the prelaminar part of CRV and venous stasis. In both scenarios, the vein wall is at risk of mechanical damage. Only in the third scenario – moderate (adequate) CRV narrowing – the systolic pressure in this blood vessel equals IOP, and the diastolic pressure is slightly higher than that. In this case no turbulence is observed. Apparently, the abovementioned clinical phenomenon is not common in glaucoma. Whether it is true or not, due to the lack of modern visualization systems, it is yet to be determined through the available morphological studies of the eye.

Only in a few studies have focused on the blood flow in glaucoma. In this case the authors studied venous blood flow velocities using CDI. Plange et al. (2006) observed that end diastolic blood flow velocity in CRV was strongly correlated to the optic disc retinal rim volume ($r = 0.56$) and RNFLT ($r = 0.49$). It is noteworthy that the authors have not observed any correlation with the arterial blood flow parameters. Interestingly, the velocity of the blood flow in CRV was not correlated to the age of patients, or to the level of IOP [30].

The reduced blood flow velocity in the CRV in POAG (including NTG) was also noted in other studies [31-32]. Furthermore, an increase in pressure in the CRV was observed in glaucoma associated with the reduced blood flow velocities in this vessel [33]. The spontaneous CRV pulsation, a sign of an increased venous blood flow, is correlated to visual field defects [34]. Some studies have noted that the increased venous pressure has an influence on the POAG progression [35].

In a recent study conducted using a Doppler OCT, reported a significant decrease in the retinal blood flow and retinal venous blood flow velocity in patients with glaucoma compared to healthy subjects [36]. A regression analysis carried out by these authors showed that the lower values of retinal blood flow and morphometric (structural) parameters were independent predictors of the occurrence of visual field defects.

Conclusion

The effects of venous blood flow found in this study (decreased venous blood flow and its correlation with clinical data), as well as previously discovered signs of vascular dysregulation in POAG, and more pronounced in NTG, might serve as significant proof of the role of vascular disorders – mainly the venous system – in GON pathogenesis. These findings warrant further research and development of new treatment options.

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