doi: 10.17116/engoftalma20151312-2

Ocular blood flow and carotid artery malfunction

V.R. MAMIKONYAN[1], A.V. GAVRILENKO[2], N.S. GALOYAN[1], A.V. KUKLIN[2], A.V. ABRAMYAN[2], N.L. SHEREMET[1], S.I. KHARLAP[1], E.E. KAZARYAN[1], O.A. SHMELEVA-DEMIR[1], D.V. ANDZHELOVA[1], A.A. RAFAELYAN[1]

[1]Research Institute of Eye Diseases, 11 A,B Rossolimo St., Moscow, Russian Federation, 119021; [2]Russian Research Center of Surgery named after academician B.V. Petrovskiy, 2 Abrikosovskiy pereulok, Moscow, Russian Federation, 119991

Aim - to evaluate ocular hemodynamics and informativity of estimated individual normal range of intraocular pressure (IOP). **Material and methods**. A total of 12 patients (22 eyes) with carotid artery malfunction were examined. Ocular blood flow (OBF) and IOP were measured with Ocular Blood Flow Analyzer. Actual OBF was then compared with what is considered normal for a given axial length (AL). Individual normal range of IOP was calculated according to an original formula (described in previous publications). Doppler imaging of ocular vessels enabled blood flow velocity measurement. Morphological parameters and functional status of the retina and optic nerve were judged on automated perimetry (Octopus 900) and optical coherence tomography (Cirrus HD-OCT) findings. Statistical analyses were performed using Statistica 10 software. **Results**. Generally, OBF showed no correlation with the grade of carotid artery stenosis ($p<0.05$), however, was significantly reduced as compared to its AL-dependent norm in patients with greater than 85% narrowing of the internal carotid artery, which can cause misestimating of their individual normal range of IOP. A negative relationship was established between the blood flow velocity in short posterior ciliary arteries and the grade of internal carotid artery stenosis ($p<0.005$). Ocular blood flow deficit relative to the AL-dependent norm correlated with ophthalmic artery resistance index. **Conclusion.** OBF-based estimation of individual normal range of IOP is inexpedient in patients with greater than 80% carotid artery stenosis due to its possible influence on ocular hemodynamics. In most cases of less than 80% carotid artery stenosis OBF is adequate or slightly reduced as compared to its AL-dependent norm and, thus, has no significant impact on estimated individual normal range of IOP.

***Keywords**: carotid artery malfunction, ocular blood flow volume and velocity, ocular ischemic syndrome, individual normal range of IOP*

Vestnik oftal'mologii 2015; 2: 19-25

Introduction

Carotid artery stenosis and/or obstruction is most often due to arteriosclerotic *vascular* disease, but other conditions, such as ruptured carotid aneurysm, temporal arteritis, fibromuscular dysplasia, and Behcet's disease, may well be the cause [1].

It is known that only about 5% of severe internal carotid artery (ICA) stenosis (of more than 90% of arterial lumen) are accompanied by ischemic changes in the eyeball [1]. Ocular signs and symptoms secondary to severe obstructive carotid pathology were first described in 1963 [2] and then gathered under the term ocular ischemic syndrome (OIS) [1, 3]. The latter usually develops unilaterally in males aged 50-80 years. Reported occurrence of OIS is 7.5 cases per million [4], however, these estimates might be understated, because the link between ocular manifestations and carotid malfunction often remains unnoticed.

More than 90% of OIS cases are associated with visual impairment [5]. About 10% of patients develop a transient monocular visual loss with rapid recovery — amaurosis fugax [1]. Ocular pain, usually ischemic, is present in 40% of patients [1]. Anterior segment involvement can be in the form of rubeosis iridis, moderate opalescence of the aqueous humor, isolated endothelial precipitates, or cataract [6]. Posterior segment manifestations of OIS include pale optic nerve head (ONH) (40%), enlarged cup (19%), papilledema (8%) [7], neovascularization of the ONH (13-37%) and retina (4-8%), narrowed retinal arteries and dilated retinal veins [8], central retinal artery occlusion (CRAO) (12%), ischemic optic neuropathies, CRA pulsations (4%), embolism of retinal arteries (2%), cotton wool spots (6%) [1, 9, 10], arteriovenous shunts [11], microaneurysms, telangiectasias, and hemorrhages (24%) [8, 12, 13].

Hemodynamics assessment of carotid arteries is based primarily on cerebral angiography [14]. However, as long as the latter is associated with severe complications, ultrasonography is even more often used for carotid visualization and measurement of blood flow velocity and the degree of stenosis [15-17]. Ultrasound examination enables detection of ipsilateral severe ICA stenosis or occlusion in 74% of OIS cases [7]. As reported by T.Guo et al. [18], who performed color Doppler flow mapping (CDFM) of carotid arteries, an ipsilateral ICA occlusion was diagnosed in 26.4% of OIS patients, 80%-95% stenosis — in 36.8%, and 52%-80% stenosis — in another 36.8%. Contralateral ICA stenosis of 40%-80% was also present in all patients, despite the absence of OIS in the fellow eyes.

Ocular blood flow (OBF) has been also assessed by means of ophthalmoplethysmography [16], ophthalmodynamometry, rheoophthalmography, fluorescein angiography, and CDFM of ocular vessels. The findings of CDFM of ocular vessels in patients with carotid malfunction usually include a decrease in systolic and, especially, diastolic

blood flow velocity in the ophthalmic artery (OA) and CRA. Retrograde OA flow may be also observed in some cases [19].

Evaluation of volumetric ocular blood flow rate (pulsatile OBF, POBF) demonstrated low sensitivity in patients with carotid artery stenosis or obstruction, and therefore, cannot be used in screening for this pathology [20]. The authors reported a 3%-49% decrease in POBF on the side of carotid malfunction (as compared to the fellow eye) in 14 out of 17 patients, while in the controls with no signs of carotid malfunction the interocular difference was not more than 0.3%-13%. But, at the same time there was a patient with about equal POBF in both eyes and another two patients with greater POBF on the side of carotid malfunction. It should be noted that even though the authors demonstrated awareness of the well-known dependence of ocular blood flow on ocular axial length (AL) (the latter only varied within 1 mm between the eyes), they did not considered intraocular pressure (IOP), which is also known to be in a negative correlation with POBF [21].

Y.Barkana et al. [22] came to a conclusion that POBF does not directly reflect the state of ipsilateral ICA blood flow, however, if low or unrecordable, might indicate carotid artery malfunction.

An original screening method for determination of individual normal range of IOP (INIOP) has been recently suggested and introduced in the Research Institute of Eye Diseases, Moscow [23, 24]. The method involves comparison of actual POBF and IOP values with specially developed AL-dependent norms of POBF. Before, there was no normative base for scientists to refer to when trying to evaluate POBF changes in different ocular pathology. Since such a base is now available, we consider it relevant to obtain further insight into ocular blood flow with account to its AL-dependent norms and the informativity of INIOP in patients with ICA malfunction, and determine correlations between CDFM and flowmetry findings in the presence of carotid pathology.

Thus, the aim of the present study was to evaluate ocular hemodynamics and the informativity of estimated individual normal range of intraocular pressure in patients with carotid artery malfunction.

Material and methods

A total of 12 patients (22 eyes) with carotid artery malfunction were examined, including 10 patients (20 eyes) with ICA stenosis of different degrees confirmed by duplex scanning of brachiocephalic branches of the aortal arch and 2 patients (both women) with a history of ICA aneurysms diagnosed with computed tomography and magnetic resonance angiography. One of these 2 women had clipping surgery for saccular aneurysm of the supraclinoid segment of the left ICA with intraoperative Doppler imaging in March 2014; the other — balloon occlusion of the right ICA in June 2002.

Comprehensive ophthalmic examinations (standard and special) were performed. Pulsatile ocular blood flow and intraocular pressure values were obtained with Paradigm's Ocular Blood Flow Analyzer. Only those measurements were taken into account whose mean deviation was not more than 12%. The actual pulsatile OBF was then compared with what is considered normal for a particular axial length (OBFn) according to the OBF/AL nomogram [24]. Blood flow deficit was calculated in both absolute (OBF-OBFn) and percentage terms (OBF/OBFn×100%). Individual normal range of IOP was determined according to the following formula [23, 24]:

INIOP = IOP×OBF/OBFn.

Linear velocity of blood flow was measured during color Doppler flow mapping of ocular and orbital vessels with Voluson 730 ultrasound machine using a multifrequency volume transducer (5-12 MHz). Systolic and diastolic blood flow velocity, pulsation and resistance indices of major ocular and orbital vessels (i.e. ophthalmic artery, central retinal artery, lateral and medial short posterior ciliary arteries (SPCA)) were evaluated.

Morphological parameters and functional status of the retina and optic nerve were judged on automated perimetry (Octopus 900) and optical coherence tomography (Cirrus HD-OCT) findings. The latter were set against pre-installed normative databases.

Parametric and nonparametric statistical analyses of the data obtained were performed using Statistica 10 software suite.

Results and discussion

Carotid malfunction patient demographics are presented in **Table 1**.

ICA stenosis in these patients ranged from 50% to 100% (68±16% on the average). There were two patients (4 eyes) with no evidence of ocular pathology, despite 50%, 63%, 75%, and 80% ICA stenoses. The remaining 10 patients (18 eyes) presented with these or other symptoms of ocular involvement from **Table 2** and were diagnosed with certain conditions regarded as either part of OIS, or concomitant pathology (**Table 3**).

Thus, central/paracentral absolute/relative scotomas were the most common findings in patients with carotid artery malfunction. OCT usually showed thinning of retinal ganglion cell and nerve fiber layers, especially in the

Table 1. **Patient demographics**

Demographic data	Carotid artery malfunction	
	ICA stenosis	ICA aneurism
Patients (eyes)	10 (20)	2 (2)
Sex, abs (%)		
males	8 (80)	0
females	2 (20)	2 (100)
Age	70 ± 10,5*	65 and 51 years

Note. * - simple mean ± standard deviation

Table 2. **Frequency of ocular manifestations in the presence of carotid artery malfunction**

Signs and symptoms	Eyes	
	abs.	%
Decreased best corrected visual acuity	4	18
vis 0.6	1	4.5
vis 0.2	1	4.5
vis 0		
Ophthalmalgia	2	9
Iris and angle neovascularization	1	4.5
CRA pulsations	1	4.5
Retinal microaneurysms, hemorrhages, arteriovenous shunts	2	9
Perimetry:		
defects within the central 30 degrees	15	68
changes of the visual field boundaries	11	50
OCT:		
optic cup enlargement	6	27
retinal nerve fiber layer thinning	10	45.5
retinal ganglion cell layer thinning	13	59
central retinal changes	9	41

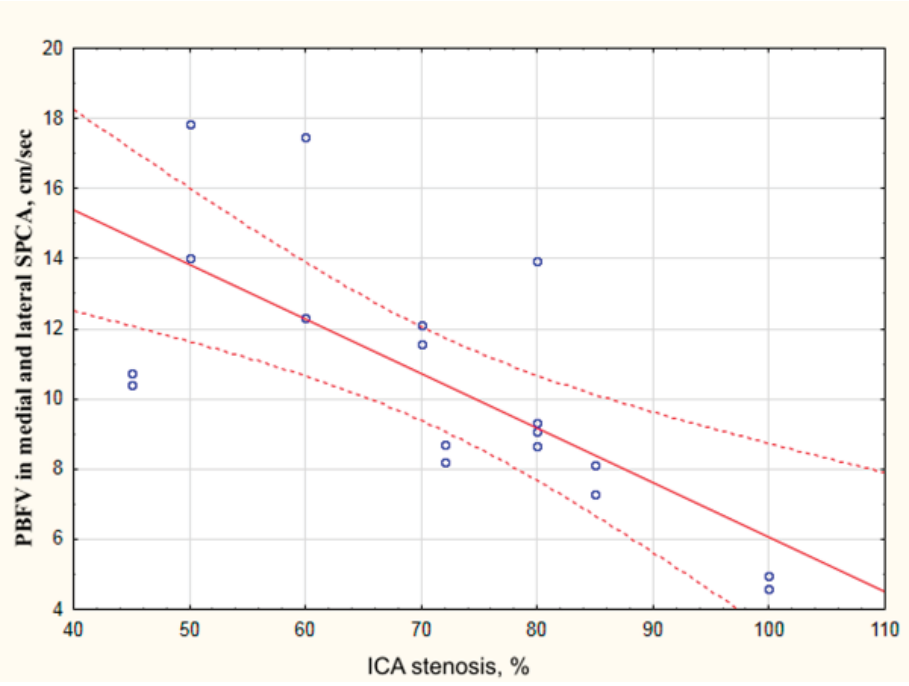
Table 3. **Frequency of ocular disease entities in patients with carotid artery malfunction**

Disease entity	Eyes	
	abs	%
CRA occlusion	1	4.5
Glaucoma:		
primary open-angle	5	23
neovascular	1	4.5
Chronic ischemic optic neuropathy	7	32
Chronic ischemic retinopathy	3	13.6
Epiretinal membrane	1	4.5

upper quadrant. Changes in cup and rim indices were less frequent. Three patients (5 eyes) were diagnosed with concomitant primary open-angle glaucoma (POAG), one other (1 eye) — with neovascular glaucoma, because of abnormal vessels in the anterior chamber angle (ACA) and on the surface of the iris developed in response to chronic ischemia of the eye ball.

Since volumetric ocular blood flow rate and velocity are known to decrease when IOP rises [21], all glaucoma patients were excluded from analysis. One patient (2 eyes) with 80% and 55% ICA stenoses was also excluded because of our inability to obtain 5 valid POBF measurements required for further processing. Thus, in our experience, POBF was unrecordable in only 9% of cases (2 eyes), while Y.Barkana et al. [22] reported 25% of flowmetry failure in a larger group of carotid malfunction patients (14 out of 57 eyes). Despite lower failure rates, we agree that an incomplete series of pulses might indicate a disturbance in the carotid blood flow and that in such a case ultrasound examination of brachiocephalic branches of the aortal arch is needed.

After excluding the above-mentioned patients we looked into whether or not the degree of ICA stenosis correlates with ocular hemodynamic parameters, particularly blood flow velocity in SPCA obtained from CDFM and pulsatile OBF (both actual measurements and deficit relative to AL-norm expectations). The former (blood flow velocity in SPCA) was found to be negatively correlated with the degree of ICA stenosis ($p<0.0005$, *Spearman's* correlation coefficient) (**see the figure**).



Relationship between peak blood flow velocity (PBFV) in SPCA (medial and lateral) and the degree of ICA stenosis (*R*=0.76)

Table 4. **Flowmetry results and morphological and functional data of patients with carotid artery malfunction**

Patient, age	eye	ICA stenosis, %	Pulsatile OBF, μm/sec	Pulsatile OBFn, μm/sec	Morphological and functional changes
K., 65	right	100	11 (41)	18.6	++
P., 72	right	50	10.9 (44)	19.5	+
	left	95	3.6 (82)	19.5	++
D., 71	right	80	16.7 (13)	19.1	++
	left	85	9.6 (48)	18.6	++
K., 85	right	80	24.1 (0)	21.8	+
	left	60	27.1 (0)	21.8	+
M., 75	right	80	21.2 (4)	22	–
	left	50	20.4 (8)	22.1	–
D., 63	right	72	14.9 (0)	14.2	+
G., 52	right	63	18.3 (8)	19.9	–
	left	75	15 (24,6)	19.9	–
K., 78	right	50	23.2 (0)	22.3	++
	left	70	18.3 (18)	22.3	++

Note. Pulsatile OBF deficits (%) are given in parenthesis. – — absent, + — moderate, ++ — significant.

As for flowmetry findings, there was no correlation between either actual pulsatile OBF, or its relative deficit and the degree of ICA stenosis ($p>0.05$), which agrees with data of Y.Barkana et al. [22], who also reported no correlation between absolute OBF values and the degree of ICA stenosis. However, allowances should be made for small sample size (8 patients, 14 eyes). The possibility of a relationship between these parameters in a larger group cannot be excluded. Additionally, we compared degrees of ICA stenosis, pulsatile OBF deficits, and ONH and retinal changes of all patients with ICA malfunction and no POAG. This data is summarized in **Table 4**.

As shown, the biggest OBF deficit (more than 40%) relative to its AL-dependant normal values was registered in patients with 85%, 95%, or 100% ICA stenosis. Morphological and functional ocular changes (manifestations of OIS) were also common and generally more pronounced in patients with greater than 80%-85% ICA stenosis, however, could be absent in some of those or, on the contrary, present in a 50% stenosis patient. In cases of greater than 85% ICA stenosis, estimation of individual normal range of IOP (based on the inverse dependence of POBF on IOP) appeared inexpedient due to the impossibility of identifying the exact cause of blood flow decrease. In cases of less than 85% ICA stenosis, ipsilateral POBF was mostly adequate or slightly reduced as compared to its AL-norm expectations, which might be due to some local vascular regulation and collateral circulation that together ensured compensation of regional blood flow deficit. So, ICA stenosis of less than 75%-80% is associated with only insignificant reduction in POBF and no impact on estimated INIOP.

There is also considerable interest in studying relationship between volumetric rate and velocity of ocular blood flow provided by CDFM and flowmetry. Pulsatile OBF is known to correlate with resistance index of SPCA in the norm, however, not in glaucoma [25]. POBF dependence on resistance index of ophthalmic artery in patients with normal-tension glaucoma or ischemic optic neuropathy outcome was also reported [26]. The present study revealed a positive correlation between POBF deficit and resistance index of OA in patients with carotid artery malfunction, which suggests increased local vascular resistance in the presence of chronic ocular ischemia.

Conclusions

Relationships between volumetric and velocity parameters of ocular hemodynamics (with account to the original nomogram of pulsatile OBF and ocular axial length), on the one hand, and the degree of internal carotid artery stenosis, on the other, have been assessed. The informativity of estimated individual normal range of intraocular pressure in patients with carotid artery malfunction has been evaluated.

No correlation between volumetric ocular blood flow rate (pulsatile OBF, flowmetry) and the degree of internal artery stenosis ($p<0.05$) has been found, however, in cases of greater than 85% stenosis, POBF is always significantly reduced (by 41%-82%) as compared to its normal values for corresponding axial lengths.

Blood flow velocity in short posterior ciliary arteries has been found to be negatively correlated with the degree of ICA stenosis ($p<0.0005$).

OBF-based estimation of individual normal range of IOP is inexpedient in patients with greater than 80% carotid artery stenosis due to its possible influence on ocular hemodynamics. In most cases of less than 80% carotid artery stenosis, OBF is adequate or slightly reduced as compared to its AL-norm expectations and, thus, has no significant impact on estimated individual normal range of IOP.

Positive correlation between POBF deficit relative to its AL-dependant normal values (flowmetry) and resistance index of ophthalmic artery (CDFM) in patients with carotid artery malfunction has been revealed.

An incomplete series of pulses during flowmetry might indicate a severe disturbance in the carotid blood flow, which need to be excluded by ultrasound examination of brachiocephalic branches of the aortal arch.

Author contributions:

Study conception and design — V.M., A.G., N.G., N.Sh.
Acquisition and handling of data — N.G., A.K., A.A., N.Sh., S.Kh., E.K., O.Sh.-D., D.A., A.R.
Statistical analysis of data — N.G.
Drafting of manuscript — N.G.
Critical revision — V.M., A.G., S.Kh., N.Sh.

The authors declare that there are no conflicts of interest.

REFERENCES

1. Brown GC, Magargal LE. The ocular ischemic syndrome. Clinical, fluorescein angiographic and carotid angiographic features. Int Ophthalmol. 1988; 11: 239–251. http://dx.doi.org/10.1007/bf00131023
2. Kearns TP, Hollenhorst RW. Venous stasis retinopathy of occlusive disease of the carotid artery. Proc Mayo Clin. 1963; 38: 304–312.
3. Brown GC, Magargal LE, Simeone FA et al. Arterial obstruction and ocular neovascularization. Ophthalmology. 1982; 89: 139–146. http://dx.doi.org/10.1016/s0161-6420(82)34837-x
4. Sturrock GD, Mueller HR. Chronic ocular ischaemia. Br J Ophthalmol. 1984; 68: 716–723. http://dx.doi.org/10.1136/bjo.68.10.716
5. Sivalingam A, Brown GC, Magargal LE. The ocular ischemic syndrome. III. Visual prognosis and the effect of treatment. Int Ophthalmol. 1991; 15: 15–20. http://dx.doi.org/10.1007/bf00150974
6. Schlaegel T. Symptoms and signs of uveitis. In: Duane TD, ed. Clinical Ophthalmology, vol. 4. Hagerstown, Harper and Row; 1983: 1–7.
7. Mizener JB, Podhajsky P, Hayreh SS. Ocular ischemic syndrome. Ophthalmology. 1997; 104(5): 859—64. http://dx.doi.org/10.1016/s0161-6420(97)30221-8
8. Green WR, Chan CC, Hutchins GM, Terry JM. Central retinal vein occlusion. A prospective histopathologic study of 29 eyes in 28 cases. Retina 1981; 1: 27–55. http://dx.doi.org/10.1097/00006982-200507001-00008
9. Brown GC. Anterior ischemic optic neuropathy occurring in association with carotid artery obstruction. J Clin Neuro-Ophthalmol 1986; 6: 39–42.
10. Waybright EA, Selhorst JB, Combs J. Anterior ischemic optic neuropathy with internal carotid artery occlusion. Am J Ophthalmol. 1982; 93: 42–47. http://dx.doi.org/10.1016/0002-9394(82)90697-3
11. Bolling JP, Buettner H. Acquired retinal arteriovenous communications in occlusive disease of the carotid artery. Ophthalmology. 1990; 97: 1148–1152. http://dx.doi.org/10.1016/s0161-6420(90)32444-2
12. Foncea Beti N, Mateo I, Diaz La Calle V et al. The ocular ischemic syndrome. Clin Neurol Neurosurg 2003; 106: 60–62. http://dx.doi.org/10.1016/j.clineuro.2003.09.001
13. Campo RV, Reeser FH. Retinal telangiectasia secondary to bilateral carotid artery occlusion. Arch Ophthalmol 1983; 101: 1211–1213. http://dx.doi.org/10.1001/archopht.1983.01040020213009
14. Pokrovskiy A.V., Kazanchyan P.O., Buyanovskiy, Skrylev SI, Kuntsevich GI, Buklina SB, Zafar Rame MKh. Surgical treatment of vertebrobasilar insufficiency. Khirurgiia. Moscow, 1989; (9): 23-29. (In Russ).
15. Bosley TM. The role of carotid noninvasive tests in stroke prevention. Semin Neurol 1986; 6: 194–203. http://dx.doi.org/10.1055/s-2008-1041463
16. Castaldo JE, Nicholas GG, Gee W et al. Duplex ultrasound and ocular pneumoplethysmography concordance in detecting severe carotid stenosis. Arch Neurol 1989; 46: 518–522. http://dx.doi.org/10.1001/archneur.1989.00520410052023
17. Neale ML, Chambers JL, Kelly AT et al. Reappraisal of duplex criteria to assess significant carotid artery stenosis with special reference to reports of the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial. J Vasc Surg 1994; 20: 642—9. http://dx.doi.org/10.1016/0741-5214(94)90290-9
18. Guo T, Zhang HR. Clinical features and carotid artery color Doppler imaging in patients with ocular ischemic syndrome. Zhonghua Yan Ke Za Zhi. 2011 Mar; 47(3): 228—34.
19. Gavrilenko A.V., Kuklin A.V., Kiseleva T.N., Abramyan A.V., Omarzhanova I.I. Immediate and remote results of surgical treatment of patients presenting with pathological tortuosity of internal carotid arteries and accompanying ocular ischemic syndrome. Angiologiya I sosudistaya khirurgiya. 2013; 19(4): 114—119. (In Russ.)
20. Lam CH, Ng PW, Tsoi TH, Chan ST. Pulsatile ocular blood flow in patients with asymmetric internal carotid artery stenosis. Clin Exp Optom. 2005 Nov; 88(6): 382-6. http://dx.doi.org/10.1111/j.1444-0938.2005.tb05104.x
21. Agarwal H.C., Gupta V., Sihota R. et al. Pulsatile ocular blood flow among normal subjects and patients with high tension glaucoma. Indian. J. Ophthalmol.2003; 51(2): 133—138.
22. Barkana Y, Harris A, Hefez L, Zaritski M, Chen D, and Avni I. Unrecordable pulsatile ocular blood flow may signify severe stenosis of the ipsilateral internal carotid artery. Br J Ophthalmol. 2003 Dec; 87(12): 1478-1480. http://dx.doi.org/10.1136/bjo.87.12.1478
23. Avetisov S.E., Mamikonyan V.R., Kazaryan E.E., Shmeleva-Demir O.A., Mazurova Yu.V., Ryzhkova E.G., Galoyan N.S., Tatevosyan A.A. New screening method for determining the tolerant intraocular pressure. Vestnik oftal'mologii. 2009; 125(5): 3—7. (In Russ.).
24. Avetisov S.E., Mamikonyan V.R., Kazaryan E.E., Shmeleva-Demir O.A., Galoyan N.S., Mazurova Yu.V., Tatevosyan A.A., Ryzhkova E.G. Results of clinical evaluation of a new screening method for determining the individual normal level of intraocular pressure. Vestnik oftal'mologii. 2010; 126(2): 5-7. (In Russ.).
25. Deokule S, Weinreb RN. Relationships among systemic blood pressure, intraocular pressure, and open-angle glaucoma. Can J Ophthalmol. 2008; 43(3): 302–307. http://dx.doi.org/10.1139/i08-061
26. V.R. Mamikonyan, N.S. Galoyan, N.L. Sheremet, E.E. Kazaryan, S.I. Kharlap, O.A. Shmeleva-Demir, D.V. Andzhelova, A.A. Tatevosyan. Features of ocular blood flow in ischemic optic neuropathy and normotensive glaucoma. Vestnik oftal'mologii. 2013; 129(4): 3-8. (In Russ.).