doi: 10.17116/engoftalma20151315-2

Ocular blood flow and retinal electrogenesis in retinitis pigmentosa

T.N. KISELEVA, I.V. ZOL'NIKOVA, O.N. DEMENKOVA, K.A. RAMAZANOVA, I.V. EGOROVA, E.V. ROGATINA, S.YU. ROGOVA

Moscow Helmholtz Research Institute of Eye Diseases, Ministry of Health of the Russian Federation, 14/19 Sadovaya-Chernogryazskaya St., Moscow, Russian Federation, 105062

Aim - to investigate correlations between changes in ocular hemodynamics revealed by color Doppler flow mapping (CDFM) and pulsed-wave (PW) Doppler imaging, one the one hand, and electrical activity of the retina, on the other, in patients with early, moderate, and severe retinitis pigmentosa (RP). **Material and methods.** A total of 20 patients (40 eyes) aged from 16 to 40 years (28.4 ± 8.2 years on average) with retinitis pigmentosa were enrolled. The control group consisted of 20 healthy volunteers of the same age range. All participants underwent full-field electroretinography (ERG), flicker ERG, and macular ERG as well as blood flow assessment in the ophthalmic artery (OA), central retinal artery (CRA), and short posterior ciliary arteries (SPCA) by means of CDFM and PW-Doppler. **Results**. Ocular blood flow in CRA and SPCA appeared disturbed in patients with early RP. In cases of moderate and severe RP, the peak systolic velocity of CRA and SPCA blood flow was significantly decreased. Systolic and end diastolic blood flow velocities in CRA and SPCA has been shown to be directly related to full-field ERG a-wave and b-wave amplitudes, correspondingly, but negatively correlated with their implicit times. **Conclusion**. The revealed decrease in CRA and SPCA blood flow indices proves retinal and choroidal circulation deficit in patients with advanced RP. As shown, moderate blood flow changes are already present in early RP and progress as retinal photoreceptors and bipolar cells become suppressed, which may be useful for RP diagnosis and monitoring.

Keywords: *ocular hemodynamics, electroretinogram, retinitis pigmentosa.*

Vestnik_Oftalmology_2015-5_14EN

Retinitis pigmentosa (RP) is the most widespread congenital degenerative disease of retina with the impairment of twilight vision and abnormal electroretinograms in early stages. The progression of RP is characterized by the damage caused to the macula and that can lead to visual loss [1, 2].

Pathogenesis of RP is complex and still remains unclear. With laser Doppler flowmetry [3-6], calibrometry of the retinal vessels [7], measurement of amplitude of pulsatile ocular blood flow [8], laser Doppler velocimetry [9] and Color Doppler Imaging (CDI) [6, 10, 11] many authors showed the impairment of ocular blood flow (OBF) in patients with RP.

K. Schmidt et al. [8] assessed the ocular pulse amplitude, which was decreased in late stages of RP. Based on the analysis of current studies of ocular blood flow examinations K. Konieczka et al. [12] supported the hypothesis of primary vascular dysregulation syndrome with the impairment of ocular blood flow in early stages of RP.

The correlation between the changes of visual functions and the impairment of retinal blood flow was presented by Y. Zhang et al. [13]. Using the new method of the magnetic resonance angiography (MRA) they determined significant correlation between the reduced choroidal and retinal blood flow and the decrease of the amplitude of a-wave of full-field electroretinography (ERG) in 6 patients with RP. However there was no assessment of ocular blood flow in early stages of RP.

Other CDI studies have shown reduced peak systolic velocity (PSV) of the central retinal artery (CRA) and the short posterior ciliary artery (sPCA) in patients with RP [6, 10]. Considering strong correlation between the neuronal system and the vascular system of retina, parallel investigations of ocular blood flow and electrophysiological studies of retinal cells function appear to be interesting in patients with RP.

The aim of present study has been to investigate the correlation between changes in ocular hemodynamics revealed by CDI and pulsed-wave (PW) Doppler, on the one hand, and the bioelectrical activity of the retina, on the other, in patients with the early stage, the intermediate stage and the late stage of RP.

Material and methods

Twenty patients (40 eyes) aged from 16 to 40 years (28.4±8.2 years on average) with RP were enrolled. The control group consisted of 20 healthy volunteers of the same age range.

Depending on the stage of disease and the degree of visual field changes, all patients were divided into three groups. The first group included 6 patients (12 eyes) with early stage of RP and mean visual acuity of 0.98±0.05. The second group consisted of 7 patients (14 eyes) with the intermediate stage of RP and mean visual acuity of 0.49±0.34. The third group included 7 patients (14 eyes) with the late stage of RP and mean visual acuity of 0.36±0.17.

Except for a standardized ophthalmological investigation, including measurement of visual acuity and visual field, slit lamp examination, dilated fundoscopy, all pa-

tients underwent full-field electroretinography (ERG), flicker ERG, and macular ERG to red stimulus using "Electroretinograph" (MBN-6, Russia). The full-field ERG and flicker ERG were registered according to ISCEV Standards for clinical ERG [14]. The active electrode suction cup and the standard silver chloride reference cup electrode were used.

The methods of investigation of the ocular blood flow included CDI and PW Doppler with Voluson 730 Pro Ultrasound system (Healthcare,GE). We measured the blood-flow spectrum of the ophthalmic artery (OA), short posterior ciliary arteries (sPCA), the central retinal artery (CRA) and the central retinal vein (CRV) and their main quantitative indices: the peak systolic velocity (PSV), end-diastolic velocity (EDV) and resistance index (RI).

Statistical analysis was performed using SPSS statistical software and statistical measure of the strength of a linear relationship between paired data (Pearson's correlation coefficient). The *p* values of <0.05 were considered significant.

Results and discussion

Clinical findings included solitary bone spicule-shaped pigment deposits in the middle of the periphery of retina, monotone optic nerve head and concentric constriction of visual field to 40 degrees in patients with early stage of RP. Severe bone-spicule retinal pigmentation in the middle of the periphery of ocular fundus, waxy-pale optic nerve head and concentric constriction of visual field from 40 to 20 degrees were detected in patients with the intermediate stage of RP. The severe bone-spicule retinal pigmentation in the middle of the periphery, atrophy of optic nerve and chorioretinal atrophy and concentric constriction of visual field to ⩽20 degrees were registered in patients with the late stage of RP.

The full-field ERG (combined rod-cone response) has shown a statistically significant reduced amplitude of a-and b-waves directly related to the stage of RP that indicated progressive decrease of function of photoreceptors and neurons in the middle layers of the retina (**Fig.1**). The absence of ERG was registered in 5 (10 eyes) of 8 patients with the late stage of RP (**Tabl.1**). Increased implicit time of a-and b-waves were associated with the severity of disease. The reduced amplitude of 30 Hz flicker ERG indicated an early damage of the cones photoreceptors in this disease (**Fig.2**). Impaired cones' functions were increased during the pathological process according to the stage of the disease and cones' functions were significantly decreased in patients of the third group. The flicker ERG of 30 Hz was nonrecordable in 5 of 7 patients with the late of RP (**Tabl.2**). The investigation of the macular ERG to red stimulus demonstrated a significant decrease (developing dependant on the stage of disease) of a-and b-waves amplitudes in patients with early stage of RP (**Fig.3**). The macular ERG amplitude was significantly reduced in patients with the late stage of RP. These

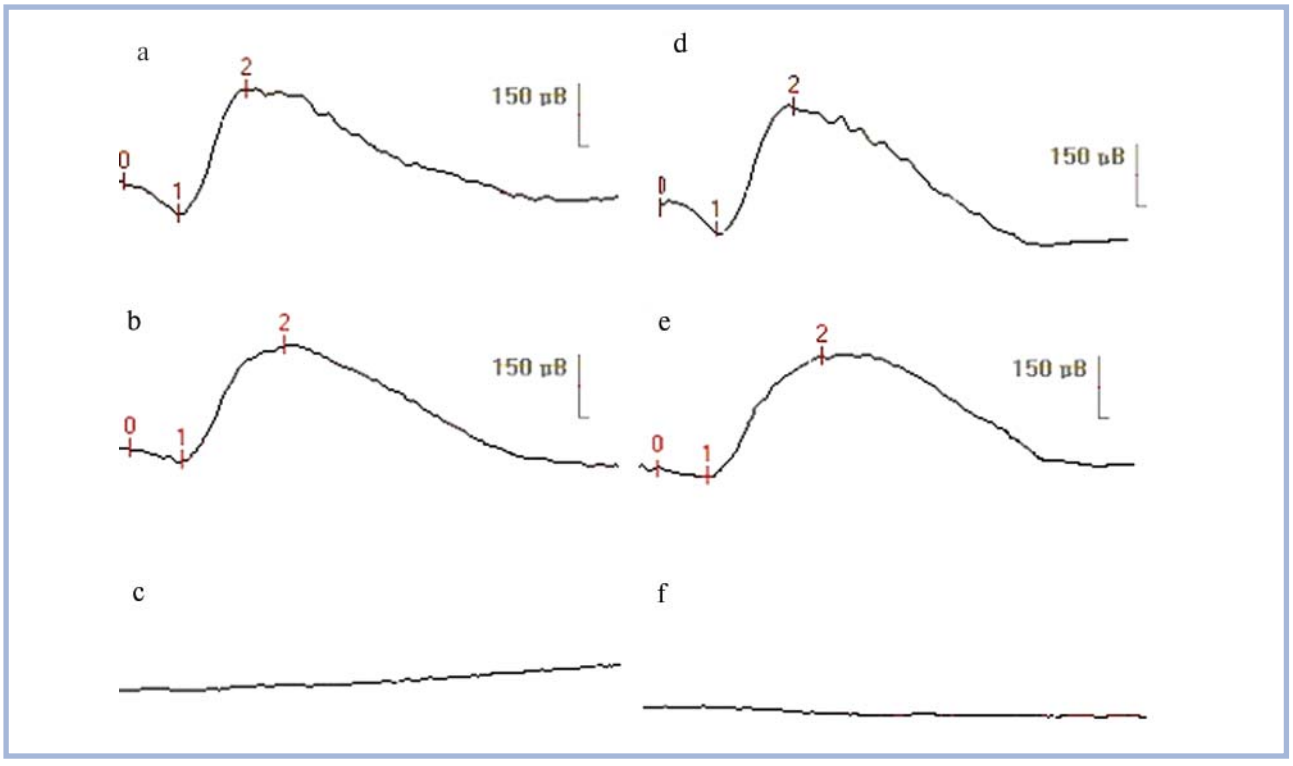

Fig. 1. **The full-field ERG**

a — right eye, b — left eye with the early stage of RP; c — right eye, d — left eye with the intermediate stage of RP; e — right eye, f — left eye with the late stage of RP.

***Table 1*. Mean parameters of the full-field ERG in patients with RP (mean±SD)**

Group	Parameters of the full-field ERG				
	a-wave		b-wave		b/a
	Amplitude	Implicit time	Amplitude	Implicit time	
Control group	94,6±17,0	30,4±2,5	406,0±81,0	61,5±1,4	5,0±1,9
I group (n=12)	57,4±23,8*	31,3±2,0	270,5±119,9*	63,4±4,8	3,7±1,6
II group (n=14)	39,1±28,1*	39,2±5,8*	36,07±27,7*	63,9±9,9	4,2±2,6
III group (n=14)	9,53±9,15*	39,5±4,3*	5,02±2,87*	66,2±3,7*	0,5±0,8

Note: n – number of eyes; * – $p<0,05$ – significance relative to the parameters recorded in the control group.

***Table 2*. Mean parameters of the macular ERG and the 30 Hz flicker ERG in patients with RP (mean±SD)**

Group	macular ERG				Function
	a-wave		b-wave		30 Гц flicker
	Amplitude	Implicit time	Amplitude	Implicit time	
Control group	3,6±1,1	24,8±2,1	16,7±4,0	54,8±4,1	29,3±9,1
I group (n=12)	2,3±0,7*	27,7±1,8*	5,8±2,0*	54,9±2,9	27,8±5,6
II group (n=14)	2,0±1,3*	29,1±4,5*	5,56±5,34*	61,23±7,0*	17,1±15,4*
III group (n=14)	1,8±1,9*	30,7±6,8*	1,39±1,05*	61,5±6,0*	3,3±3,4*

Note: n – number of eyes; * – $p<0,05$ – significance relative to the parameters recorded in the control group.

***Table 3*. Mean hemodynamic parameters in the orbital arteries in patients with RP**

Group	OA			CRA			sPCA			CRV
	V syst, cm/s	Vdiast, cm/s	RI	V syst, cm/s	Vdiast, cm/s	RI	V syst ,cm/s	Vdiast, cm/s	RI	V syst , cm/s
Control group	32,7±3,7	9,2±2.1	0,72±0,1	10,6±0,8	2,9±0,3	0,73±0,1	14,7±1,7	4,2±1,1	0,67±0,1	4,36±0,7
I group (n=12)	40,2±4,0	8,0±4,4	0,8±0,09	10,0±3,1	2,8±1,1	0,7±0,12	12,0±1,7	4,6±1,3	0,6±0,07	5,1±0,9
II group (n=14)	42,4±3,9	10,3±2,9	0,7±0,07	6,4±1,7*	2,3±0,5	0,8±0,15	10,9±2,6*	4,1±1,8	0,6±0,13	4,4±0,4
III group (n=14)	32,3±7,7	8,6±4,8	0,7±0,11	5,6±0,9*	2,0±1,2	0,6±0,19	9,7±2,9*	3,7±1,4	0,6±0,08	3,4±0,4*

Abbreviations: CRA — central retinal artery; OA — ophthalmic artery; s PCA — short posterior ciliary arteries (medial and lateral);
Vsyst — peak systolic velocity; Vdiast — end-diastolic velocity; RI — resistance index
Note: n – number of eyes; * – $p<0,05$ – significance relative to the parameters recorded in the control group.

findings indicated severe impairment of macula function (**Tabl.2**). The a-and b-waves implicit times were longer in correlation with the degree of the disease severity.

Analysis of ultrasound investigations data of ocular blood flow showed no significant changes of the hemodynamic parameters in the OA of patients with RP compared to control group. There were no significant changes of blood flow in the CRA of patients with the early RP (*Vsyst* = 12,5 cm/s, *Vdiast*=4,24 cm/s, *RI*=0,66) (**Fig.4,a**). In cases of the intermediate stage and the late stage of RP, the peak systolic velocity of CRA blood flow was significantly decreased (*Vsyst* = 6,5 cm/s, *Vdiast*=2,6 cm/s, *RI*=0,6) (**Fig.4,b**). However, mean *Vdiast* and *RI* in CRA in patients with RP did not differ significantly from those in healthy subjects (Tabl.3). We registered similar changes of blood flow in sPCA. There were no significant changes of blood flow in the sPCA in early stage of RP (*Vsyst* = 12,17 cm/s, *Vdiast*=4,35 cm/s, *RI*=0,64). There were significant decreases of *Vsyst* and normal resistance indices in the sPCA in patients with intermediate stage of RP (*Vsyst* = 8,93 cm/s, *Vdiast*=2,32 cm/s, *RI*=0,74) and in patients with the late stage of RP (*Vsyst* = 6,03 cm/s, *Vdiast*=2,66 cm/s, *RI*=0,56) (**Tabl.3**).

Significantly decreased *Vsyst* in the CRA, CRV and sPCA indicated the substantial deficiency of blood flow in the retinal and choroidal vessels in patient with the intermediate stage and the late stage of RP.

The correlation of hemodynamic indices and parameters of retinal function revealed the statistically significant direct association between the peak systolic and end diastolic blood flow velocities (*Vsyst* and *Vdiast)* in sPCA and the a-wave amplitude of full-field ERG (r=0,81 and r=0,82, respectively), but they correlated negatively with the implicit time of full-field ERG a-wave (r=- 0,47 and

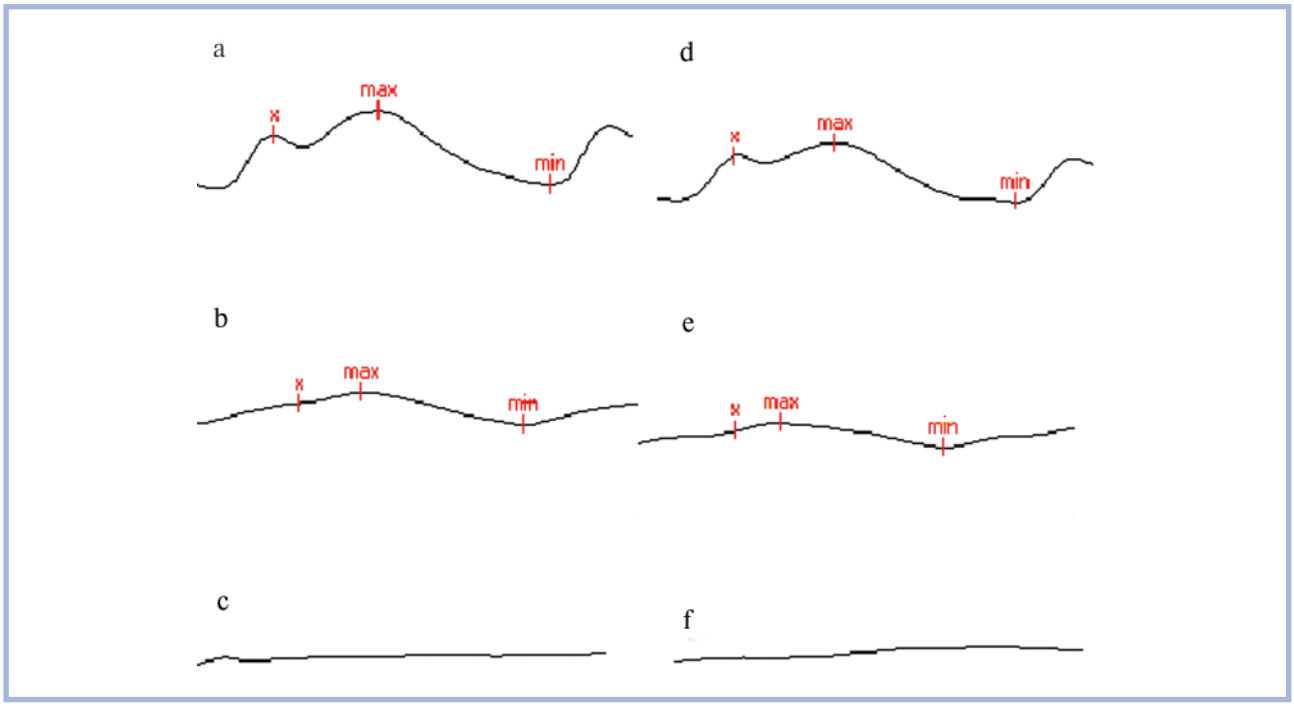

Fig. 2. **The flicker ERG of 30 Hz.**

a –right eye, b – left eye with the early stage of RP; c – right eye , d – left eye with the intermediate stage of RP; e – right eye, f – left eye with the late stage of RP.

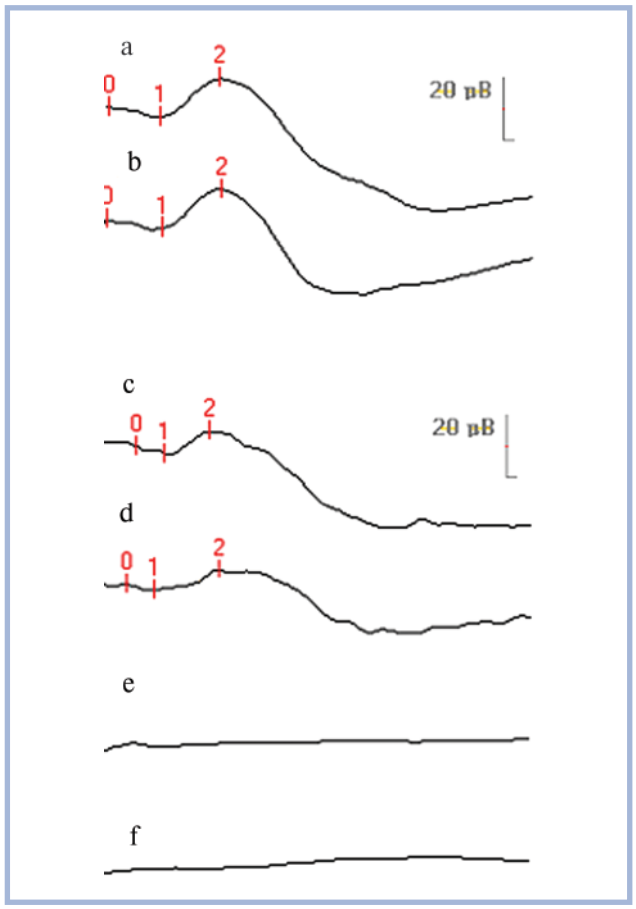

Fig .3. **The macular ERG to red stimulus.**

a — right eye, b — left eye with the early stage of RP; c — right eye, d — left eye with the intermediate stage of RP; e — right eye, f — left eye with the late stage of RP.

r=- 0,38, respectively). The *Vsyst* and *Vdiast* in CRA were directly related to b-wave amplitude of full-field ERG (*r*=0,55 and *r*=0,44, respectively), but correlated negatively with the latency of full-field ERG b-wave.

Our results revealed the reduced *Vsyst* in CRA and in sPCA in patients with RP similar to the results obtained by M.Cellini et al. [6] and N.Akyol et al.[10].

Unlike the study by Y.Zhang et al. [13] that reported correlation between the state of chorioretinal complex and electrogenesis of photoreceptors, our study suggests data about statistically significant correlation between the reduced parameters of choroidal blood flow velocities (sPCA) and the function of photoreceptors (the amplitude and the latency of full-field ERG a-wave) and also between the reduced parameters of retinal blood flow velocities (CRA) and abnormal bipolar cell function (the amplitude and latency of full-field ERG b-wave). These correlations show parallel changes of ocular blood flow and electrogenesis of external and middle layers of retina, which expands our understanding of the pathogenesis of RP.

Conclusion

The revealed decrease in CRA and SPCA blood flow indices proves retinal and choroidal circulation deficit in patients with advanced RP. As shown, moderate blood flow changes are already present in early RP and progress as retinal photoreceptors and bipolar cells become degenerated, which may be useful for RP diagnosis and monitoring.

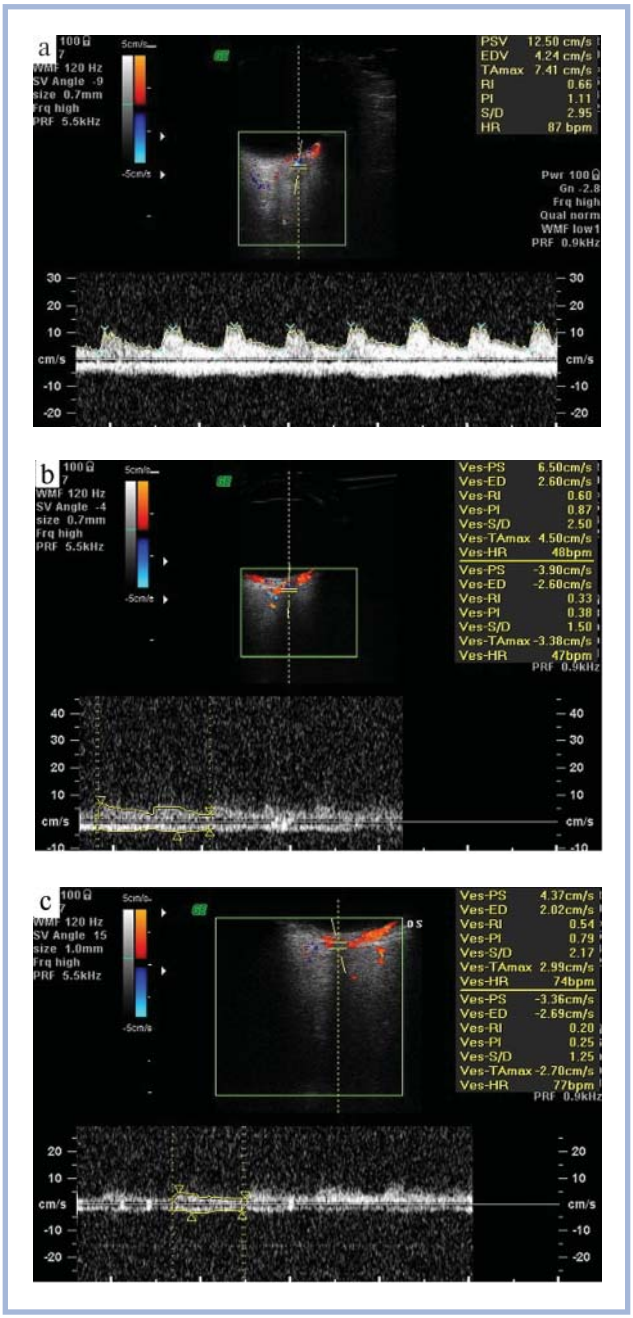

Fig. 4. **Doppler spectrum of blood flow in the CRA and CRV.**

a — in patient with the early stage of RP (Vsyst= 12,5cm/s,Vdyast= 4,24cm/s, RI = 0,66); b — in patient with the intermediate stage of RP (Vsyst=6,5cm/s, Vdyast = 2,6cm/s, RI = 0,6); c — in patient with the late of RP (Vsyst=4,37cm/s,Vdyast = 2,02cm/sc, RI =0,54).

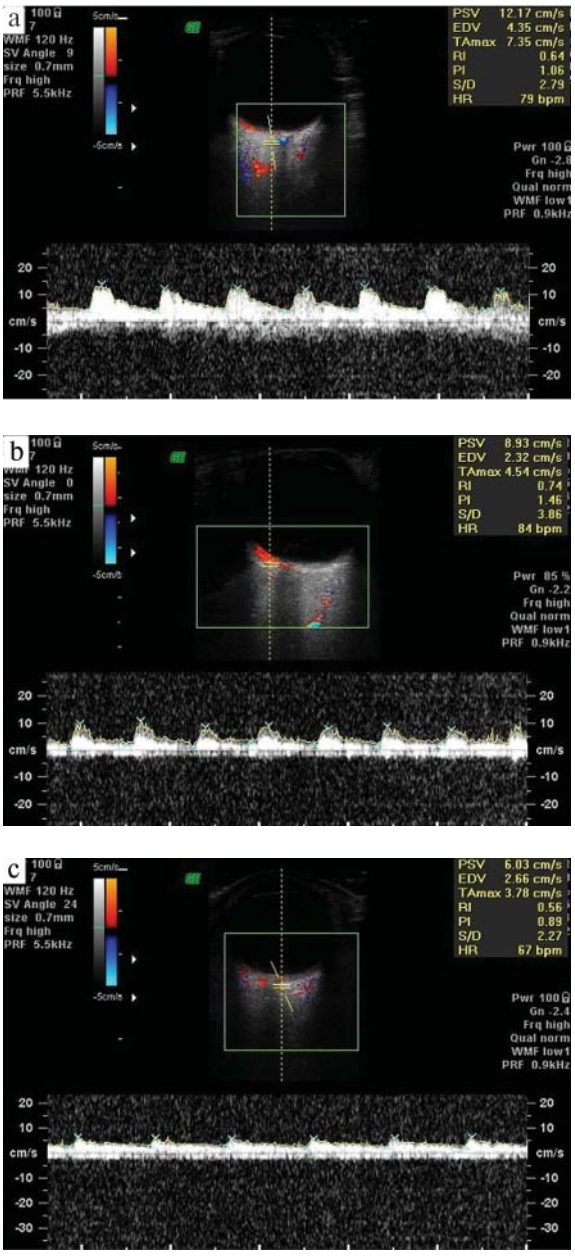

Fig. 5. **Doppler spectrum of blood flow in the sPCA.**

a — in patient with the early stage of RP (Vsyst = 12,17cm/s, Vdyast = 4,35см/с, RI = 0,64); b — in patient with the intermediate stage of RP (Vsyst = 8,93cm/s, Vdyast = 2,32cm/s, RI = 0,74); c — in patient with the late of RP (Vsyst=6,03 cm/s, Vdyast = 2,66 cm/s, RI = 0,56).

Author contributions:

Study conception and design — T.K., I.Z.

Acquisition and handling of data — I.Z., O.D., K.R., S.R.

Statistical analysis of data — I.Z., O.D.

Drafting of manuscript — T.K., I.Z., O.D., I.E., E.R.

Critical revision — T.K., I.Z., O.D., I.E., E.R.

The authors declare no conflict of interest.

REFERENCES

1 Shamshinova A.M. Pigmentnyj retinit, ili tapetoretinal'naja abiotrofija setchatki. Nasledstvennye i vrozhdennye zabolevanija setchatki i zritel'nogo nerva [Retinitis pigmentosa, or tapetoretinal abiotrophy] V kn.: pod red. A.M.Shamshinovoy [Hereditary and congenital retinal diseases] Moscow: Meditsina, 2001:134–151. (In Russ.).

2 Bird A. Retinal photoreceptor dystrophies. Am J Ophthalmol. 1995; 119:543–562.

doi:10.1016/S0002-9394(14)70212-0.

3 Langham M, Kramer T. Decreased choroidal blood flow associated with retinitis pigmentosa. Eye (Lond). 1990;4:374–381.

doi: 10.1038/eye.1990.50.

4 Grunwald J., Maguire A., Dupont J. Retinal hemodynamics in retinitis pigmentosa. Am J. Ophthalmol 1996;122:502–508.

doi: 10.1016/s0002-9394(14)72109-9

5 Falsini B, Anselmi G, Marangoni D, D'Esposito F, Fadda A, Di Renzo A, Campos C, Riva C. Subfoveal choroidal blood flow and central retinal function in retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2011;52:1064–1069.

doi: 10.1167/iovs.10-5964.

6 Cellini M., Lodi R., Possati G., Sbrocca M. et al. Colour Doppler sonography in retinitis pigmentosa: preliminary study. J Fr Ophthalmol. 1997;20(9):659–663.

7 Ma Y, Kawasaki R, Dobson L, Ruddle J, Kearns L, Wong T, Mackey D. Quantitative analysis of retinal vessel attenuation in eyes with retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2012;53(7):4306–4314.

doi: 10.1167/iovs.11-8596

8 Schmidt K. Ocular pulse amplitude is reduced in patients with advanced retinitis pigmentosa. Br J Ophthalmol. 2001;85(6):678–682.

doi :10.1136/bjo.85.6.678.

9 Beutelspacher S, Serbecic N, Barash H, Burgansky-Eliash Z, Grinvald A, Krastel H, Jonas J. Retinal blood flow velocity measured by retinal function imaging in retinitis pigmentosa. Graefe's Arch Clin Exp Ophthalmol 2011;249:1855–1858.

doi:10.1007/s00417-011-1757-y.

10 Akyol N., Kukner S., Celiker U., Koyu H., Luleci C. Decreased retinal blood flow in retinitis pigmentosa. Can J Ophthalmol 1995;30(1):28–32.

11 Cellini M., Strobbe E., Gizzi C., Campos E. ET-1 plasma levels and ocular blood flow in retinitis pigmentosa Can J Physiol Pharmacol. 2010;88(6):630–635.

doi: 10.1139/y10-036

12 Konieczka K., Flammer A., Todorova M., Meyer P., Flammer J. Retinitis pigmentosa and ocular blood flow. EPMA J. 2012;3(1):17–20.

doi:10.1186/1878-5085-3-17.

13 Zhang Y., Harrison J., Nateras O., Chalfin S. Decreased retinal-choroidal blood flow in retinitis pigmentosa as measured by MRI. Doc Ophthalmol 2013;126(3):187–197.

doi: 10.1007/s10633-013-9374-1.

14 Marmor MF, Fulton AB, Holder GE, Myake Y, Brigell M, Bach M. ISCEV standard for full-field clinical electroretinography (2008 update). Doc Ophthalmol. 2009;118(1):69–77.

doi:10.1007/s10633-008-9155-4