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Original article

Circadian rhythms of ocular and systemic blood flow in patients with progressive primary open-angle glaucoma

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Abstract: Background — The significant role of hemodynamic factors in the pathogenesis of primary open-angle glaucoma (POAG) is now widely recognized. However, no studies have examined daily fluctuations in ocular and systemic blood flow in the context of endothelial dysfunction and their potential influence on the progression of glaucomatous optic neuropathy.

This study aimed to assess daily variations in ocular and systemic hemodynamic parameters in POAG patients, focusing on their association with endothelial vasodilatory capacity.

Material and methods — A total of 177 patients (350 eyes) were examined, including 99 patients with POAG (198 eyes; mean age 69.1±6.1 years), and 78 control subjects without glaucoma (152 eyes, mean age 68.2±5.8 years). To evaluate circadian variations in ocular and systemic hemodynamics, we assessed ocular pulse via electrotonosphygmography, peripheral blood flow in the upper and lower extremities using sphygmomanometry, and subfoveal choroidal thickness (SFCT), an indicator of choroidal blood filling, measured with the choroidal protocol on the OCT-HS100 device. All measurements were performed by a single operator at 08:00, 14:00, and 20:00 over three consecutive days, with standardized nutritional and physical activity protocols. Data were analyzed using correlation and multiple regression analyses.

Results — Our analysis of diurnal variations in ocular pulse and peripheral arterial blood flow (upper and lower extremities) revealed prominent, synchronized rhythmic oscillations in both glaucoma patients and age-matched controls. Peak blood flow velocities occurred in the morning hours, with lowest values observed in the evening. Patients with progressive glaucoma exhibited statistically significant reductions in pulse ocular blood flow and peripheral arterial perfusion, alongside elevated vascular resistance indices (PWV, CAVI, ABI, AI-R) compared to stable glaucoma cases and controls. Choroidal thickness variations demonstrated dependence on diurnal intraocular pressure (IOP) fluctuations. Vasodilatory capacity followed a circadian pattern in all groups, with maximal endothelial reactivity in the morning, progressive daytime decline, and minimal evening values. This decrease was significantly more prominent in progressive POAG (P-POAG) than in stable glaucoma or control groups.

Conclusion — The observed similarity in diurnal variations of ocular pulse parameters and peripheral vascular blood flow may reflect circadian rhythms in hormonal and metabolic activity. Notably, impaired ocular pulse characteristics and reduced peripheral blood flow — particularly during late evening hours — were associated with marked endothelial dysfunction. These findings suggest that such hemodynamic disturbances may serve as prognostic markers for glaucoma progression.

Keywords: circadian rhythms, perfusion pressure, ocular blood flow, endothelial dysfunction, primary open-angle glaucoma.

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Introduction

Primary open-angle glaucoma (POAG) is a multifactorial heterogeneous disease. Among ocular risk factors for disease

progression, elevated intraocular pressure (IOP) and its diurnal fluctuations remain the most extensively studied.

Studies from our country and abroad have established impaired ocular perfusion as a critical risk factor for POAG

development and progression [1-9]. Systemic circulatory alterations induce localized hemodynamic changes in ocular vessels, subsequently promoting degenerative processes affecting both the drainage system and optic nerve. Nevertheless, the underlying mechanisms of these hemodynamic disturbances and their precise role in glaucomatous optic neuropathy (GON) pathogenesis remain a subject of ongoing debate. There is still no consensus on the primary and secondary nature of these changes.

A number of researchers have emphasized the role of endothelial dysfunction (ED) in the progression of GON [10-16]. Vascular endothelial reactivity differs significantly between elderly patients with POAG and age-matched individuals without glaucoma.

In recent years, glaucoma has been considered as a systemic disorder involving neurohormonal dysregulation affecting multiple pathophysiological pathways, particularly through disturbances in metabolic and vascular homeostasis rhythms [17-19]. It has also been suggested that POAG may represent a primary ophthalmic condition capable of directly disrupting circadian process rhythmicity [20, 21].

Diurnal variations in ocular hemodynamics across different glaucoma progression stages are of particular clinical interest, as well as the accompanying circadian fluctuations in peripheral arterial hemodynamics. Such comprehensive study is crucial to

determine whether the observed hemodynamic disturbances in POAG represent localized ocular manifestations or reflect a broader systemic vascular pathology.

This study aimed to examine diurnal fluctuations in ocular and systemic hemodynamic parameters in patients with POAG compared to age-matched controls without ocular pathology

Material and methods

Study cohort and design

A total of 177 patients (350 eyes) were examined, including 99 patients with POAG (198 eyes; mean age 69.1±6.1 years), and 78 control subjects without glaucoma (152 eyes, mean age 68.2±5.8 years). This hybrid prospective-retrospective cohort study adhered to the principles of the Declaration of Helsinki. The study was approved by the local ethics committee of the Tyumen Scientific Centre of Siberian Branch of the Russian Academy of Sciences (protocol No. 5 issued 01.05.2020).

Inclusion criteria were advanced POAG with IOP controlled by hypotensive therapy, and age between 65 and 75 years. Exclusion criteria were degenerative or inflammatory eye diseases, lower extremity peripheral artery disease, diabetes mellitus, other somatic pathologies (i.e., ischemic heart disease, arterial hypertension) if decompensated.

Table 1. Clinical characteristics of patients with stable glaucoma (S-POAG), progressive glaucoma (P-POAG), and control subjects

Variable	S-POAG n=53 Me [25%; 75%]	P-POAG n=46 Me [25%; 75%]	p 1-2	Control n=78 Me [25%; 75%]	p 1-3	p 2-3
	1	2		3		
General characteristics						
Gender, female (n, %)	32 (60%)	17 (37%)	0.01**	40 (51%)	0.425**	0.10**
Age, years	67.4 [60.1; 74.2]	69.6 [63.8; 79.1]	0.010*	66.7 [59.6; 71.8]	0.231*	0.351*
Clinical and morphofunctional characteristics						
IOP, mmHg	16.34 [12.3; 18.1]	21.84 [17.9; 24.3]	<0.001*	13.72 [11.2; 15.4]	<0.001*	<0.001*
Pperf., mm Hg	72.01 [70.1; 74.3]	58 [55.01; 61.24]	<0.001*	76 [74.01; 78.63]	0.032*	<0.001*
SAP MD, mean, dB (SAP)	-3.87 [-4.95; 2.74]	-7.22 [-8.85; -6.03]	<0.001*	-2.0 [-2.09; -2.17]	0.010*	<0.001*
SAP PSD, mean, dB (SAP)	-4.8 [-4.98; -4.41]	-13.2 [-16.57; -10.45]	<0.001*	-2.0 [-2.87; -1.24]	0.005*	<0.001*
GCC Average, µm	89.97 [85.41; 93.75]	87.29 [78.24; 92.36]	0.0041*	99.14 [93.25; 102.74]	0.0106*	<0.001*
GCC Superior, µm	89.28 [84.85; 95.35]	86.39 [76.37; 91.42]	0.0002*	98.2 [93.74; 104.39]	0.0298*	<0.001*
GCC Inferior, µm	90.42 [85.65; 96.32]	87.01 [81.36; 92.84]	0.0019*	99.87 [64.39; 110.34]	0.0017*	<0.001*
Global Loss Volume mean, (GLV), %	7.03 [5.94; 9.17]	22.49 [19.57; 26.75]	<0.001*	5.52 [4.68; 6.87]	0.010*	<0.001*
Focal Loss Volume mean, (FLV), %	3.19 [2.94; 3.74]	10.79 [9.25; 12.14]	<0.001*	1.93 [1.57; 2.32]	0.010*	<0.001*
Subfoveal choroidal thickness (SFCT), µm	228.12 [199.85; 274.31]	221.07 [191.35; 233.41]	0.0236*	233.63 [214.65; 289.95]	0.128*	<0.001*
superior choroidal thickness, µm	231.12 [201.54; 281.12]	222.01 [192.74; 235.14]	0.0347*	234.27 [215.16; 288.85]	0.247*	<0.001*
lower choroidal thickness, µm	233.21 [202.74; 280.27]	220.11 [190.11; 233.05]	0.0241*	236.63 [215.74; 287.98]	0.824*	<0.001*
temporal choroidal thickness, µm	229.11 [201.05; 279.47]	221.54 [197.06; 230.82]	0.0872*	239.65 [219.31; 288.09]	0.214*	<0.001*
nasal choroidal thickness, µm	227 [206.04; 281.11]	219.98 [188.12; 229.36]	0.0974*	237.54 [211.01; 285.69]	0.187*	<0.001*
Ocular pulse parameters						
OPA, mmHg	0.97±0.73	2.0±0.33	<0.001*	0.71±0.21	0.043*	<0.001*
SIPV	2.04±0.18	1.8±0.4	<0.001*	2.20±0.15	0.0059*	<0.001*
IEIV, mm ³ /mmHg	1.35±0.54	0.71±0.12	<0.001*	1.41±0.32	0.010*	<0.001*
IBSA, mmHg/mm ³	12.10±0.64	14.2±1.42	<0.001*	7.72±0.13	0.051*	<0.001*
PBSA, mmHg/mm ³	0.91±0.19	1.22±0.76	<0.001*	0.76±0.11	0.0083*	<0.001*
Peripheral arterial hemodynamics						
CAVI	8.12 [6.85; 10.02]	6.28 [5.32; 7.01]	<0.001*	8.73 [7.32; 9.85]	0.005*	<0.001*
PWV, m/s	13.14 [10.2; 15.03]	17.21 [14.25; 21.97]	<0.001*	12.93 [10.3; 14.1]	0.008*	<0.001*
AI-R	0.91 [0.78; 1.03]	2.32 [2.19; 2.41]	<0.001*	0.8 [0.73; 0.92]	0.025*	<0.001*
ABI	2.02 [1.99; 2.11]	1.2 [1.01; 1.32]	<0.001*	2.38 [2.36; 2.49]	0.012*	<0.001*
Biological vessel age, years	68.4 [66.58; 69.54]	73.52 [71.65; 76.14]	<0.001*	65.5 [63.25; 66.85]	0.001*	<0.001*
Flow-mediated vasodilation						
FMV	6.8 [5.1; 7.6]	3.4 [2.6; 3.95]	<0.001*	8.12 [7.32; 10.2]	0.001*	<0.001*

* Mann-Whitney U test; ** Pearson χ^2 test; Comparisons: p 1-2, S-POAG vs P-POAG; p 1-3, S-POAG vs controls; p 2-3, P-POAG vs controls.

Table 2. Diurnal variations in ocular pulse dynamics, peripheral arterial blood flow (upper/lower extremities), and choroidal thickness measurements

Variable	S-POAG n=53	P-POAG n=46	p 1-2	Control n= 78	p 1-3	p 2-3
	Me [25%; 75%]	Me [25%; 75%]		Me [25%; 75%]		
	1	2		3		
Clinical and morphofunctional characteristics						
Pperf. m	72 [70.5; 74.1]	64 [61.9; 66.3]	0.010*	76 [75.2; 78.3]	0.251*	0.005*
Pperf. a	70 [68.3; 71.9]	61 [59.8; 63.5]		75 [73.6; 76.8]		
Pperf. e	68 [66.1; 69.2]	58 [55.9; 59.1]		71 [69.3; 72.6]		
P (a-e)	0.01*	0.05*		0.184*		
SFCT m, μm	239.50 [215.1; 274.8]	233.63 [209.3; 244.8]	0.050*	233.77 [220.2; 288.1]	0.154*	0.001*
SFCT a, μm	232.46 [213.1; 266.4]	220.43 [201.7; 239.5]		249.50 [216.7; 271.4]		
SFCT e, μm	226.5 [211.2; 258.3]	211.02 [197.6; 228.7]		245.07 [213.8; 265.3]		
P (a-e)	0.006*	<0.001*		0.121*		
Ocular pulse parameters						
IEIV m, mm ³ /mm Hg	1.78 [1.71; 1.82]	1.244 [1.2; 1.3]	0.050*	2.5 [2.41; 2.54]	0.211*	0.010*
IEIV a, mm ³ /mm Hg	1.5 [1.47; 1.54]	1.144 [1.09; 1.19]		2.2 [2.14; 2.25]		
IEIV e, mm ³ /mm Hg	1.3 [1.26; 1.38]	0.9 [0.84; 0.95]		1.9 [1.83; 1.98]		
P (a-e)	0.108*	0.01*		0.241*		
Peripheral arterial hemodynamics						
PWV m, m/s	9.12 [8.8; 9.8]	16.7 [14.8; 17.9]	0.010*	8.12 [7.7; 8.9]	0.124*	0.050*
PWV a, m/s	15.2 [14.3; 16.2]	18.2 [17.1; 19.3]		11.2 [10.8; 11.7]		
PWV e, m/s	18.5 [17.8; 19.1]	21.04 [19.7; 22.4]		13.35 [12.5; 14.1]		
P (a-e)	0.02	0.001		0.002		
CAVI m	8.0 [7.84; 8.58]	10.45 [9.25; 11.36]	0.014*	6.0 [5.8; 7.56]	0.142*	0.001*
CAVI a	9.8 [8.64; 10.3]	11.11 [10.2; 12.63]		7.8 [7.03; 9.54]		
CAVI e	11.26 [9.85; 13.29]	13.1 [12.7; 15.6]		8.26 [7.99; 10.1]		
P (a-e)	0.01*	0.01*		0.003*		
ABI m	1.43 [1.39; 1.49]	1.12 [1.09; 1.15]	0.021*	1.53 [1.51; 1.55]	0.257*	0.011*
ABI a	1.34 [1.26; 1.39]	1.17 [1.14; 1.19]		1.52 [1.5; 1.58]		
ABI e	1.2 [1.11; 1.24]	0.84 [0.74; 0.91]		1.53 [1.48; 1.56]		
P (a-e)	0.009*	0.05*		0.008*		
AI-R m	0.97 [0.88; 1.1]	1.02 [1.0; 1.09]	0.018*	0.85 [0.8; 1.08]	0.251*	0.020*
AI-R a	1.1 [0.95; 1.13]	1.07 [1.01; 1.11]		0.92 [0.88; 1.1]		
AI-R e	1.11 [0.99; 1.15]	1.21 [1.18; 1.26]		1.08 [1.01; 1.12]		
P (a-e)	0.01*	0.01*		0.122*		
Flow-mediated vasodilation						
FMV m	7.7 [6.84; 8.8]	5.3 [4.2; 5.7]	0.020*	8.2 [7.5; 10.4]	0.191*	0.001*
FMV a	7.3 [6.3; 8.21]	4.6 [3.5; 4.93]		8.16 [7.4; 10.2]		
FMV e	6.8 [5.63; 7.96]	3.4 [2.1; 4.02]		8.12 [7.02; 9.85]		
P (a-e)	0.183*	0.015*		0.231*		

* Mann-Whitney U-test. m, morning values; a, afternoon values; e, evening values; p (a-e), p-value between afternoon and evening values.

Patients with glaucoma were randomized into two groups based on the rapidity of glaucoma progression. Morphofunctional verification of glaucoma progression was performed using changes in the retinal photosensitivity and Global Loss Volume index (GLV, %). These parameters were measured through static automated perimetry (SAP) with mean deviation (MD) analysis, as well as optical coherence tomography (OCT) data reflecting global retinal ganglion cell loss (GLV, %). Patients were followed every six months from 2019 to 2023.

The group of patients with stable glaucoma (S-POAG) included 53 individuals (mean age 67.4±5.1 years) with a change in the MD index of no more than 0.5 dB/year and a decrease in GLV of no more than 2 % per year. This group comprised 32 women and 21 men. The group with progressive glaucoma (P-POAG) included 46 patients (mean age 69.6±7.9 years) with an MD index change exceeding 0.5 dB/year and a GLV reduction of more than 2% per year. This group included 17 women and 29 men.

All participants underwent comprehensive ophthalmic evaluation including visometry, ophthalmotonometry, biomicroscopy, and ophthalmoscopy. Visual field testing was performed using the Humphrey Visual Field Analyzer II-I Series (USA) with SITA-Standard 30-2 threshold testing. Intraocular

pressure was measured with the Icare ic 100 tonometer (TA011 model, Finland). Optic nerve head and macular ganglion cell analysis was conducted via RTVue-100 OCT (Optovue, Inc., USA) using ONH, 3D Disc, and GCC protocols. Subfoveal choroidal thickness (SFCT) was assessed using Canon OCT-HS100 (Japan) with choroidal protocol.

Ocular pulse blood flow was evaluated using the Glautest-60 tonograph (Russia) in sphygmometry mode, with intraocular vessel elasticity index (IEIV) calculated using the O. Frank formula (IEIV = systolic increase in pulse volume [SIPV] / ocular pulse amplitude [OPA]), representing systolic pulse volume increase per 1 mm Hg of ocular pulse pressure.

Arterial elasticity and vascular wall tone in the extremities were assessed using volumetric sphygmomanometry (VaSera VS-1000, Fukuda Denshi, Japan), measuring: pulse wave velocity (PWV), cardio-ankle vascular index (CAVI), ankle-brachial index (ABI), augmentation index (AI-R), and vascular biological age. Endothelial dysfunction was evaluated through reactive hyperemia testing (En Visor ultrasound, Philips, USA), with flow-mediated vasodilation (FMV) calculated as: FMV(%)=[(DRG-ID)/ID]×100, where DRG represents maximum hyperemia-induced artery diameter and ID indicates baseline arterial diameter.

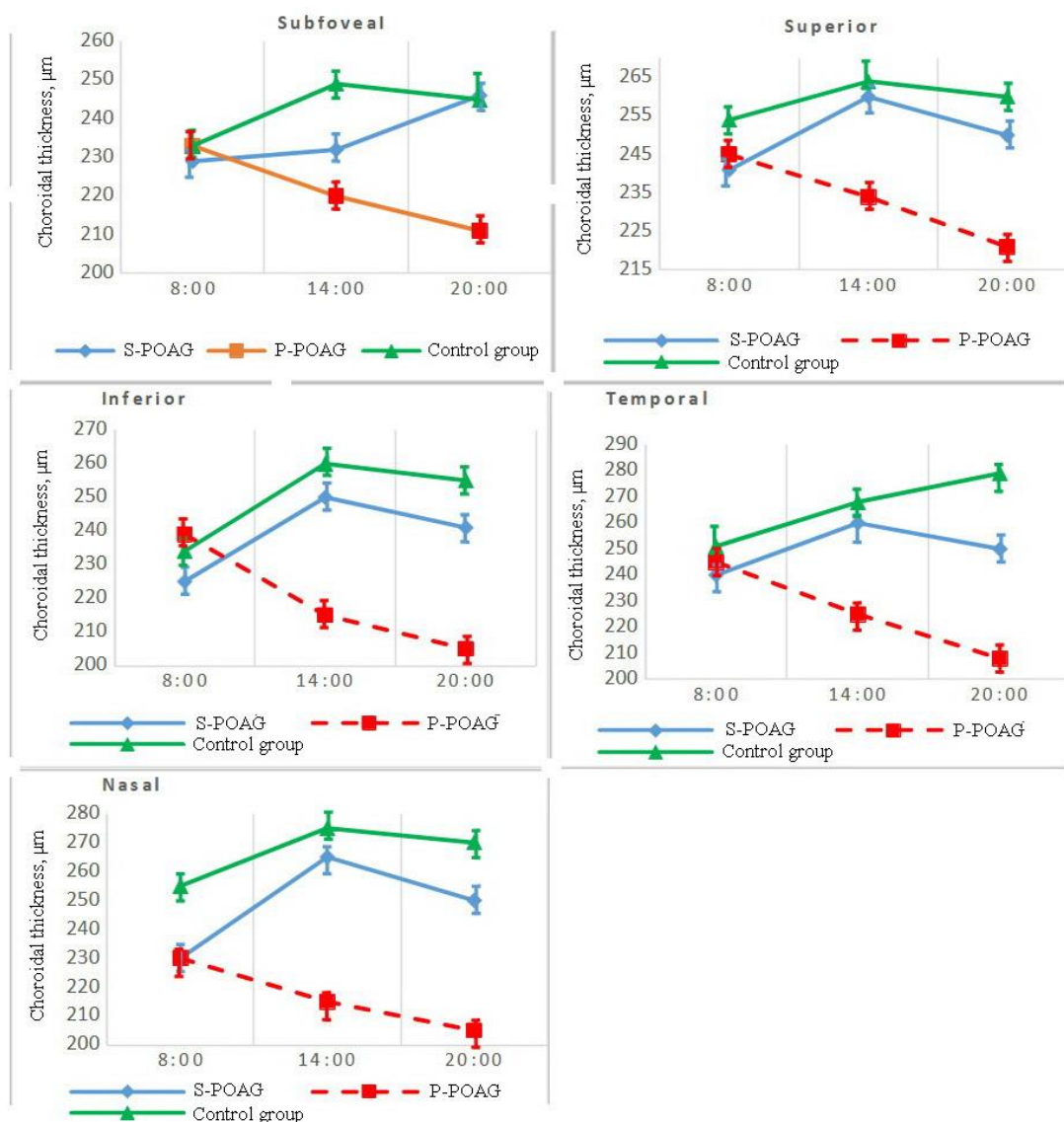


Figure 1. Circadian fluctuations in sectoral choroidal thickness.

Circadian monitoring was conducted at 08:00, 14:00, and 20:00 h over three consecutive days under standardized nutritional and physical activity conditions. Measurements included: (1) choroidal thickness, (2) ocular pulse parameters, (3) peripheral arterial hemodynamics (upper/lower extremities), and (4) flow-dependent vasodilation.

Data Analysis

Statistical analysis was performed using IBM SPSS 20 software. All tabulated quantitative data were presented as median with interquartile range – Me [25%; 75%]. Between-group comparisons used the Mann-Whitney U test for non-parametric data. Spearman's rank correlation coefficient was employed for ordinal variables. Categorical variables across two or three groups were assessed using Pearson's χ^2 test.

Results

The clinical characteristics of the study groups are summarized in [Table 1](#).

Patients with P-POAG were predominantly male ($p=0.01$) and older ($p=0.01$) compared to other groups. Key progression markers included: (1) reduced perimetric vision (MD and pattern standard deviation [PSD]: both $p<0.001$); (2) GCC thinning (average/superior/inferior $p<0.05$) with elevated FLV% and GLV% (both $p<0.001$); (3) higher IOP and lower perfusion pressure ($p<0.001$); and (4) significantly decreased choroidal thickness versus controls ($p<0.001$), unlike S-POAG cases which showed no difference.

P-POAG patients demonstrated distinct ocular pulse alterations: (1) higher OPA ($p<0.001$) but lower SIPV and IEIV (both $p<0.001$); and (2) elevated index of ocular blood supply adequacy (IBSA) and the parameter of ocular blood supply adequacy (PBSA, both $p<0.001$), reflecting decreased wall elasticity and increased blood flow velocity during disease progression.

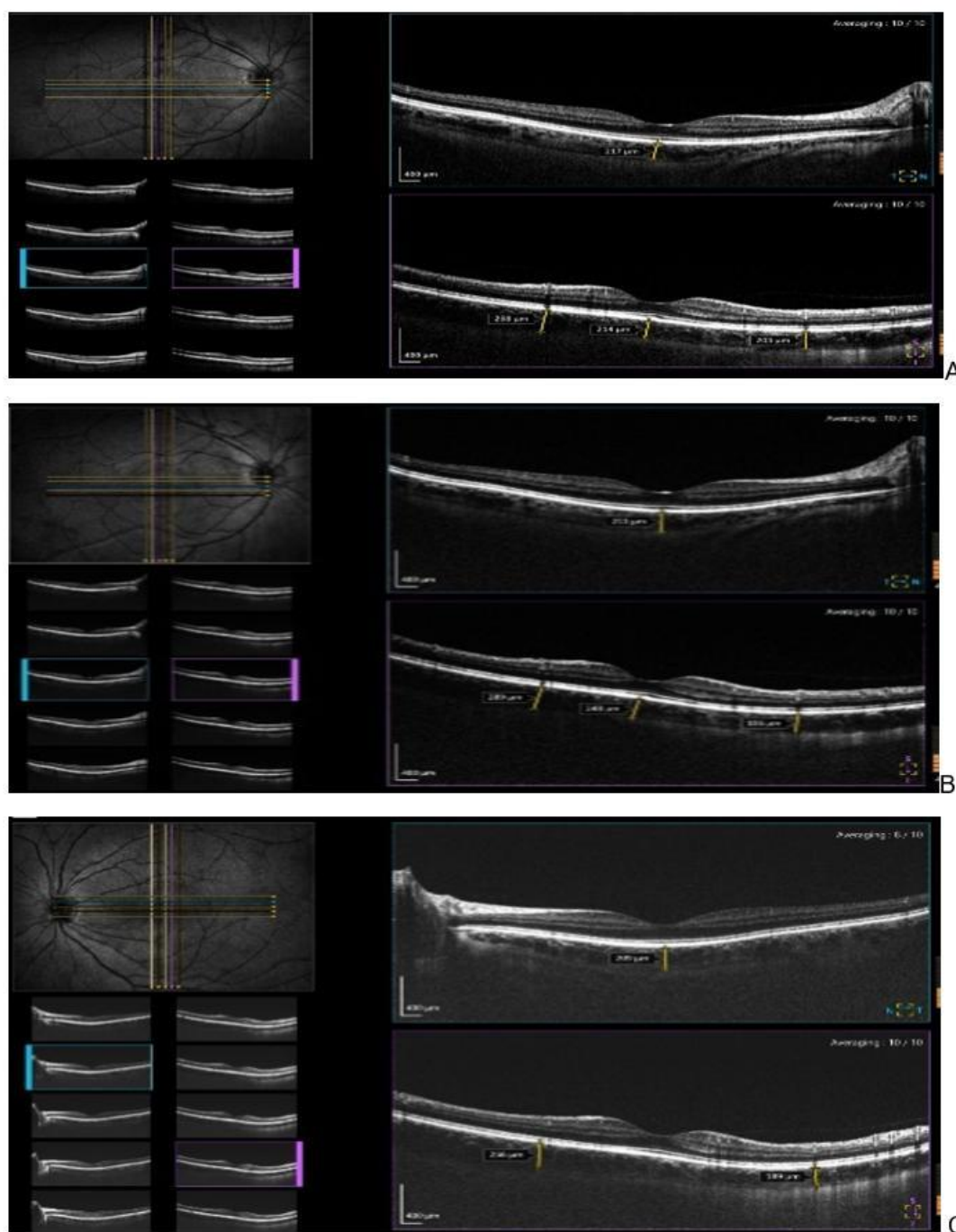


Figure 2. Diurnal changes in the choroidal thickness in patient P, 67 y.o., with P-POAG: A – choroidal thickness at 8:00: 229.50 µm; B – choroidal thickness at 14:00: 220.43 µm; C – choroidal thickness at 20:00: 211.02 µm.

When examining peripheral arterial hemodynamics, a decreased arterial elasticity, higher pulse wave velocity (PWV) and the resistance index, higher prevalence of arterial obstruction, and an increase in the biological vessel age were observed in patients with P-POAG.

Flow-mediated vasodilation (FMV) assessment based on brachial artery reactivity testing showed a significant reduction in arterial vasodilation capacity in the P-POAG group ($p < 0.001$).

Diurnal variations in ocular pulse dynamics, peripheral arterial blood flow (upper/lower extremities), and choroidal thickness measurements are presented in [Table 2](#).

Evaluation of diurnal variations in ocular pulse and peripheral arterial blood flow demonstrated synchronized circadian rhythms in both glaucoma patients and age-matched controls. Optimal parameters were observed in the morning hours, followed by a gradual midday decline and a significant evening reduction.

Sectoral choroidal thickness variations are shown in [Figure 1](#).

In the S-POAG and control groups, sectoral SFCT was the highest at 14:00 ($p < 0.001$ vs other timepoints) across all sectors, while overall diurnal rhythm showed no significant changes ($p > 0.05$). In the P-POAG group, SFCT peaked during morning hours (08:00), with progressive thinning observed throughout the day (14:00→20:00; $p < 0.001$). This pattern was consistent across all choroidal sectors. These findings paralleled with decreased perfusion pressure and elevated IOP values during the late hours.

[Figure 2](#) illustrates characteristic choroidal thickness variations in a representative P-POAG patient during the day.

Circadian FMV patterns ([Table 2](#)) demonstrated 08:00 maxima, daytime decline, and marked 20:00 reduction (P-POAG>S-POAG>controls, $p < 0.001$).

In P-POAG, FMV correlated strongly with CAVI ($r = -0.682$) and PWV ($r = -0.594$), moderately with ABI ($r = 0.488$), while IEIV showed weaker associations (CAVI: $r = -0.311$; ABI: $r = 0.378$).

Discussion

Our findings revealed a significant decrease in ocular blood flow parameters. These results correspond with numerous studies on this subject [22,23]. Notably, this study provides the first evidence of concurrent peripheral hemodynamic deterioration in progressive POAG, demonstrating: prolonged aorto-tibial pulse wave velocity (PWV), increased augmentation index (AI-R), elevated arterial stiffness (CAVI), and more prevalent lower extremity arterial stenosis. These changes likely reflect more advanced atherosclerotic vascular changes in progressive POAG patients [24-27].

All groups showed rhythmic daily fluctuations in ocular and peripheral hemodynamics, FMV and choroidal thickness. In patients with P-POAG, the lowest ocular and peripheral hemodynamics parameters, a decreased FMV and vascular patency, and elevated AI-R were observed in the late evening.

While S-POAG patients and controls showed maximal choroidal thickness at 14:00, P-POAG cases exhibited: (1) 08:00 peaks, (2) progressive daytime thinning (14:00→20:00), and (3) an inverse rhythm to IOP fluctuations (morning nadir/evening peak) [28].

Novel correlations linked peripheral hemodynamics to both endothelial dysfunction (FMV) and ocular vascular elasticity (IEIV).

The principal limitation of this study relates to its 12-hour observation window (08:00-20:00), imposed by outpatient facility constraints. Comprehensive 24-hour monitoring would provide insight into nighttime fluctuations in measurements and would allow to identify possible phase shifts.

Conclusion

The identified triad of (1) impaired ocular/systemic perfusion, (2) elevated vascular resistance, and (3) endothelial dysfunction during glaucoma progression mandates incorporation of atherosclerotic risk assessment into clinical management protocols.

Furthermore, observed circadian variations in choroidal/hemodynamic parameters require rigorously timed measurements for reliable longitudinal evaluation.

Authors' contribution

Study design and concept – Malishevskaya T.N.; data processing – Malishevskaya T.N., Gubin D.G., Filippova Yu.E.; Renziak E.V., Zakharova E.K., text writing – Malishevskaya T.N., Filippova Yu.E., Renziak E.V., Zakharova E.K.; editing – Malishevskaya T.N., Gubin D.G.

Ethical approval

This cross-sectional study complied with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Conflict of interest

The authors declare no conflict of interest.

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