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DIAGNOSTIC VALUE OF OCT-ANGIOGRAPHY AND REGIONAL HEMODYNAMIC ASSESSMENT IN PATIENTS WITH RETINAL VEIN OCCLUSION

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✧ ***Introduction.*** Ischemic maculopathy is the main cause of irreversible vision loss due to retinal vein occlusion (RVO). Fluorescein angiography (FA), which is the "gold standard" for evaluating retinal capillary plexuses, does not allow for the visualization of separate intraretinal capillary networks. Optical coherence tomography angiography (OCT-angiography) enables the possible visualization of four capillary plexi and allows for the quantitative analysis of microcirculation to quantitatively estimate capillary network density and nonperfusion areas. ***Aim.*** To investigate microcirculation changes using OCT-angiography data and to compare the changes with opthalmoplethysmography indices in patients with RVO. ***Material and methods.*** The study included 12 patients with RVO. In all patients, a routine ophthalmic examination was performed, and ocular blood flow was estimated using FA, OCT-angiography, and ophthalmoplethysmography. ***Results.*** Ischemia in the macular area was detected in four patients (25%) according to FA results, and in eight (67%) according to OCT-angiography data. Compared with the unaffected eye, significant decrease in the density of both superficial and deep capillary plexuses as well as a decrease in "flow area" and enlargement of foveal avascular zone were observed. A significant close direct correlation was established between capillary density in the superficial capillary plexus ($r > 0.8$) and the deep capillary plexus ($r > 0.7$), choroidal thickness, and opthalmoplethysmography indices ($r > 0.6$). ***Conclusion.*** Compared with FA, OCT-angiography is a more sensitive method to detect macular capillary perfusion. In cases with RVO, the combination of the above mentioned methods with ophthalmoplethysmography allows for the comprehensive evaluation of regional hemodynamics.

✧ ***Keywords:*** retinal vein occlusions; ocular blood flow; retinal ischemia; capillary perfusion; OCT-angiography; ophthalmoplethysmography.

ИНФОРМАТИВНОСТЬ ОКТ-АНГИОГРАФИИ В СОЧЕТАНИИ С ИССЛЕДОВАНИЯМИ РЕГИОНАРНОЙ ГЕМОДИНАМИКИ ПРИ ОККЛЮЗИИ ВЕН СЕТЧАТКИ

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✧ ***Введение.*** Ишемическая макулопатия — основная причина необратимого снижения зрения при окклюзии вен сетчатки (ОВС). «Золотым стандартом» оценки ретинальной сосудистой сети является флюоресцентная ангиография (ФАГ), однако она не позволяет раздельно визуализировать интраретинальные сосудистые сплетения. Оптическая когерентная томография-ангиография (ОКТ-ангиография) даёт возможность визуализировать четыре капиллярных сплетения и позволяет проводить количественный анализ микроциркуляции с расчётом плотности капиллярной сети и зон отсутствия капиллярной перфузии. ***Цель:*** изучить у больных с ОВС особенности изменения микроциркуляции по данным ОКТ-ангиографии и сопоставить их с показателями офтальмоплетизмографии. ***Материалы и методы.*** В исследование включено 12 пациентов с окклюзией вен сетчатки. Всем пациентам проводилось стандартное офтальмологическое обследование с дополнительной

оценкой регионарной гемодинамики с помощью ФАГ, ОКТ-ангиографии и офтальмоплетизмографии. ***Результаты.*** У больных с ОВС по данным ФАГ ишемия в центральной зоне выявлена у 4 пациентов (25 %), а по данным ангиографии ОКТ — у 8 (67 %). При сравнении с непоражённым глазом выявлено значимое снижение плотности капилляров в поверхностном и глубоком капиллярных сплетениях, уменьшение зоны перфузии хориокапилляров и расширение фовеолярной аваскулярной зоны в глубоком капиллярном сплетении. Получена значимая тесная прямая связь между плотностью капилляров в поверхностном ($r > 0,8$) и глубоком ($r > 0,7$) капиллярных сплетениях сетчатки, толщиной хориоидеи и показателями офтальмоплетизмографии ($r > 0,6$). ***Выводы.*** ОКТ-ангиография является более чувствительным методом диагностики макулярной капиллярной перфузии по сравнению с флюоресцентной ангиографией. Сочетание обсуждаемых методов с выполнением офтальмоплетизмографии позволяет провести комплексную оценку регионарной гемодинамики при окклюзии вен сетчатки.

✧ ***Ключевые слова:*** окклюзии вен сетчатки; глазной кровоток; ишемия сетчатки; капиллярная перфузия; ОКТ-ангиография; офтальмоплетизмография.

BACKGROUND

Retinal vein occlusion (RVO) is among the major causes of irreversible visual loss. The main reasons for central vision loss are macular edema and ischemic maculopathy [2, 3]. S. Hayreh et al. allocated three groups of patients with retinal ischemia and classified RVO into ischemic and nonischemic types. Ischemic RVO is characterized by the presence of afferent pupillary defect, changes in electroretinogram and perimetry values, low visual acuity, and multiple deep intraretinal hemorrhages [1]. S. Hayreh found that 81% central retinal vein occlusions (CRVO) are of ischemic type, and the remaining 19% are of nonischemic type. In the case of hemiretinal RVO, the frequency of ischemic and nonischemic types was 78% and 22%, respectively.

Improvements in diagnostic capabilities have changed the RVO classification approach. Modern wide-field fluorescein angiography (FA) of the retina allows for the detection of extensive areas without capillary perfusion in 60%–80% of patients with RVO. Currently, it is possible to assess the area of ischemia, which is usually between 41 and 415 mm^2. Conversion of nonishemic RVO to ischemic CRVO occurs in approximately 5%–20% of cases [15, 24].

There are two types of ischemia: central and peripheral. Despite good visual function and the absence of afferent pupillary defect, patients with peripheral ischemia have an increased risk of proliferative disorders, which is determined by the size of areas without capillary perfusion [15, 20]. In 50% of cases, extensive areas without capillary perfusion at the periphery are associated with rubeosis iridis; in 5% of cases, they are associated with retinal neovascularization [21, 22]. Ischemic CRVO (ischemic maculopathy) is characterized by a significant and irreversible decrease in vision.

FA of the retina is the gold standard for the diagnosis of retinal perfusion [4]. It provides two-dimensional images with a wide-field visualization of blood flow. Main FA patterns include dye leakage, its accumulation, and the diffusion of the dye into the surrounding tissues [24]. FA requires an intravenous injection of fluorescent dye; therefore, it cannot be used in pregnant women, lactating women, children, or individuals with renal or heart failure. This method is limited to the detection of hemorrhages, which prevent photon excitation and emission with the emergence of hypofluorescent areas shielding the underlying structures. Another disadvantage of FA is its inability to allow separate visualization of the intraretinal vascular plexus [11, 15].

Optical coherence tomography angiography (OCTA) allows overcoming the limitations of FA. OCTA is a novel, noninvasive method for multi-layered visualization of retinal vessels and the optic disc without the need for a dye injection. OCTA registers changes in the amplitude of light reflected from red blood cells in a limited area within different layers of the retina and choroid. OCTA enables visualization of four capillary plexus areas: superficial retinal capillary plexus, deep retinal capillary plexus, outer layers of the retina, and choriocapillary plexus. It allows for the evaluation of microcirculation through the measurement of the capillary network density and areas without capillary perfusion. The OCTA technique has a number of limitations, such as relatively low axial resolution, which restricts the identification of small vessels, and a small scanning area, which restricts the detection of peripheral

ischemia. Artifacts are also quite common in OCTA; this occurs due to overlapping capillary plexuses or shadows of large vessels of the superficial plexus on the deep capillary network. Finally, OCTA allows for the assessment of only fluid motion through the vessels without visualization of the blood flow features; arteriovenous passage; and leakage, staining, and accumulation of the dye, which is important for detecting neovascularization, as well as the differential diagnosis of inflammatory and retinal vascular disorders [4, 15].

At present, OCTA is the only available multilayered visualization method for the estimation of capillary plexus with a possibility of quantitative evaluation of the blood circulation. OCTA allows for the identification of early stage ischemic maculopathy (first degree impaired macular perfusion) before it can be visualized using FA, or when these changes are shielded by hemorrhages. OCTA is widely used in patients with age-related macular degeneration, glaucoma, anterior ischemic optic neuropathy, and RVO. Existing data regarding this problem were primarily accumulated by foreign researches. Russian publications lack studies comparing OCTA results with the parameters of regional hemodynamics evaluated using ophthalmic plethysmography. The advantages of ophthalmic plethysmography include the ability to assess solely the eye component of the orbital blood flow, noninvasiveness, measurement of absolute values (μL), and the separation created between the results and the users [1].

This study aimed to investigate specific features of microcirculation changes in patients with RVO using OCTA and to compare these results with those obtained using ophthalmic plethysmography.

MATERIALS AND METHODS

This study included 12 patients with RVO (10 males and two females) with a mean age of 43 years (range, 22–61 years). CRVO was detected in five patients, whereas branch RVO was found in seven. All patients underwent standard ophthalmic examination with additional evaluation of hemodynamics using FA (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany) and OCTA (RTVue XR Avanti, Optovue Inc., USA), and ophthalmic plethysmography (ocular plethysmograph Optimed OP-A, Russia). OCTA was performed in a regimen HD Angio Retina 6 × 6 mm, with the assessment of vessel density, foveolar avascular zone in both superficial and deep retinal capillary plexuses, and flow area of choriocapillaris.

Data were analyzed using the IBM SPSS Statistics software. We calculated median values ($M \pm$) with their dispersions and the Spearman's correlation coefficient. We used median, minimum, and maximum to describe quantitative data. Statistical significance of the differences was evaluated by the Wilcoxon signed-rank test. Results were considered significant if $p \leq 0.05$.

RESULTS

Hemodynamic parameters of the eyeball are shown in the Table 1. The mean heart rate was 58 beats per min (range, 52–80 beats per min), systolic blood pressure was 121 mm Hg (range, 102–150 mm Hg), and diastolic blood pressure was 72 mm Hg (range, 54–91 mm Hg). The retinal thickness in the macular region and the thickness of the choroid did not differ between the two groups ($p = 0.286$ and $p = 0.906$).

CRVO was detected in four (25%) and eight (67%) patients using FA and OCTA, respectively. Comparison of parameters measured using ophthalmic plethysmography and OCTA revealed a direct correlation between vessel density in the superficial ($r > 0.8$) and deep ($r > 0.7$) retinal capillary plexuses, choroidal thickness, and parameters of ophthalmic plethysmography ($r > 0.6$).

OCTA allowed us to assess the vascular bed in patient S., who underwent kidney transplantation and in whom FA was contraindicated. Visual acuity in the affected eye was 0.4 and retinal thickness in the macular region was 165 μm. Ophthalmic plethysmography revealed reduced blood flow to the affected eye. OCTA showed an enlarged foveolar avascular zone and the presence of areas without capillary perfusion within the lower temporal arcade with an involvement of macular area in the superficial and deep retinal capillary plexuses (Figures 1 and 2). The nonperfusion areas corresponded to the areas with a decreased retinal photosensitivity according to the static automated perimetry (Figure 3). Identified areas without capillary perfusion helped us performing laser photocoagulation in ischemic areas.

The following example may illustrate the significance of OCTA in the detection of ischemic maculopathy. Patient P. was under medical observation due to post-occlusion retinopathy after CRVO which occurred eight months before. Visual acuity in the affected eye was 0.7, and retinal thickness in the macular region was 248 μm. Ophthalmic plethysmography revealed decreased parameters of regional hemodynamics with a significant interocular asymmetry. Lower values were detected in the affected eye.

Table 1

OCTA and ophthalmic plethysmography results in affected and unaffected eyes

Таблица 1

Показатели ОКТ-ангиографии и офтальмоплетизмографии на поражённом и интактном глазах

	Parameter	Eye with RVO			Eye without RVO			*p*
		Me	Min	Max	Me	Min	Max	
OCTA	vessel density in the superficial retinal capillary plexus	51.39	41.68	56.96	54.15	49.72	58.33	0.013
	vessel density in the deep retinal capillary plexus	52.97	44.84	65.83	62.36	50.09	65.08	0.004
	flow area of choriocapillaris	22.6995	19.329	23.014	23.012	22.273	23.215	0.003
	retinal thickness in the foveolar area	289.5	165	645	258	218	291	> 0.05
	retinal thickness in the entire macular region	878	603	1563	847	763	910	> 0.05
	retinal volume in all areas	5.7935	4.676	10.29	5.6025	5.249	6.169	> 0.05
	size of the foveolar avascular zone in the superficial retinal capillary plexus	0.302	0.11	0.862	0.258	0.104	0.516	0.248
	size of the foveolar avascular zone in the deep retinal capillary plexus	0.353	0.162	0.958	0.293	0.141	0.699	0.05
Ophthalmic plethysmography	pulse volume anterior segment, μL	0.85	0.36	1.39	0.9	0.33	1.4	> 0.05
	minute volume of systolic increase of the eyeball volume, μL	462.8	295.3	840.5	513.6	309.0	810.6	> 0.05

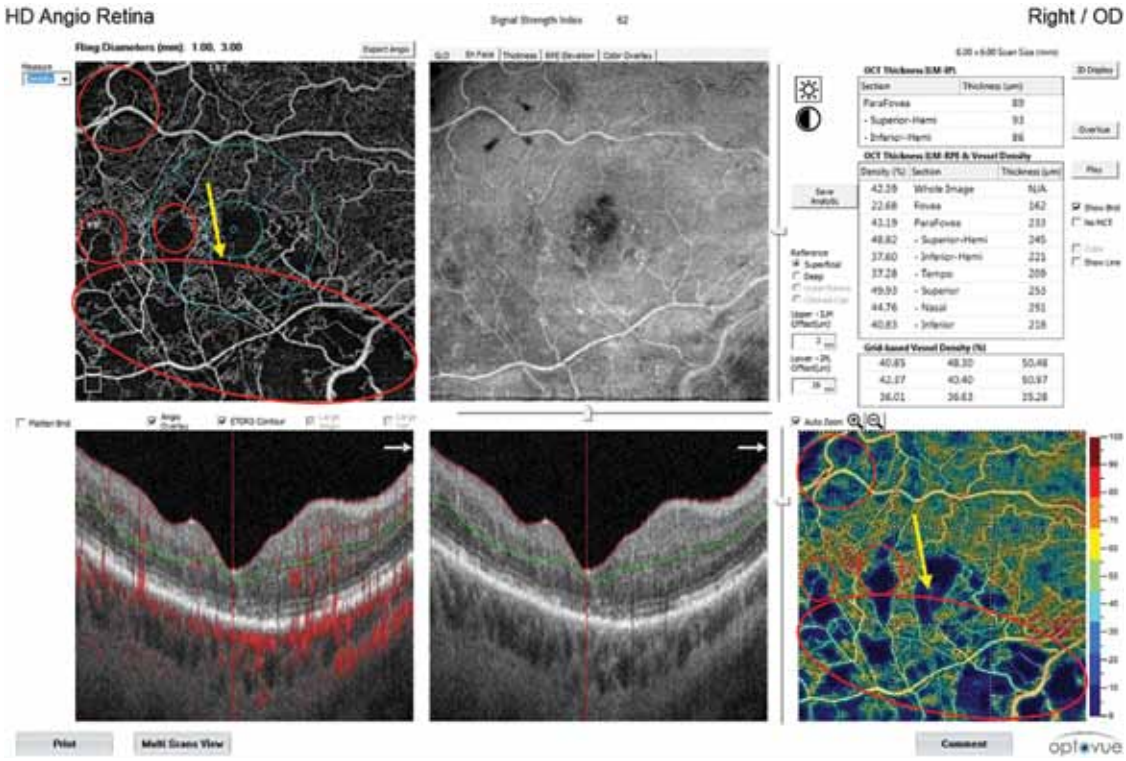

Fig. 1. Superficial capillary plexi density. Capillary network decreased density area, corresponding to the capillary non-perfusion area (oval) and foveal avascular zone enlargement (arrow) are shown

Рис. 1. Плотность капилляров в поверхностном капиллярном сплетении. Указаны зоны снижения плотности капиллярной сети, соответствующие участкам отсутствия капиллярной перфузии (овал), и расширение фовеолярной аваскулярной зоны (стрелка)

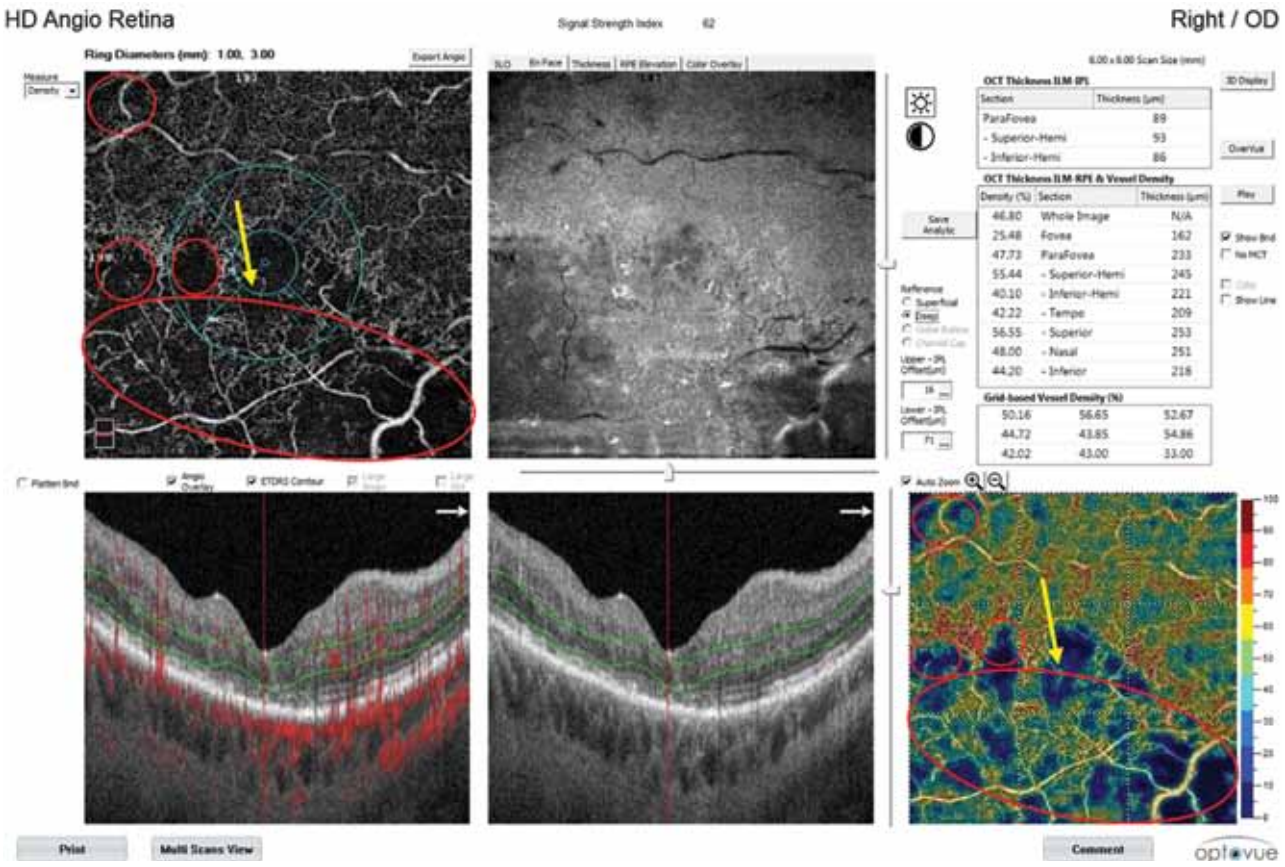

Fig. 2. Deep capillary plexi density. Zone of capillary network decreased density, corresponding to the capillary non-perfusion area (oval) and foveal avascular zone enlargement (arrow) are shown

Рис. 2 Плотность капилляров в глубоком капиллярном сплетении. Указаны зоны снижения плотности капиллярной сети, соответствующие участкам отсутствия капиллярной перфузии (овал), и расширение фовеолярной аваскулярной зоны (стрелка)

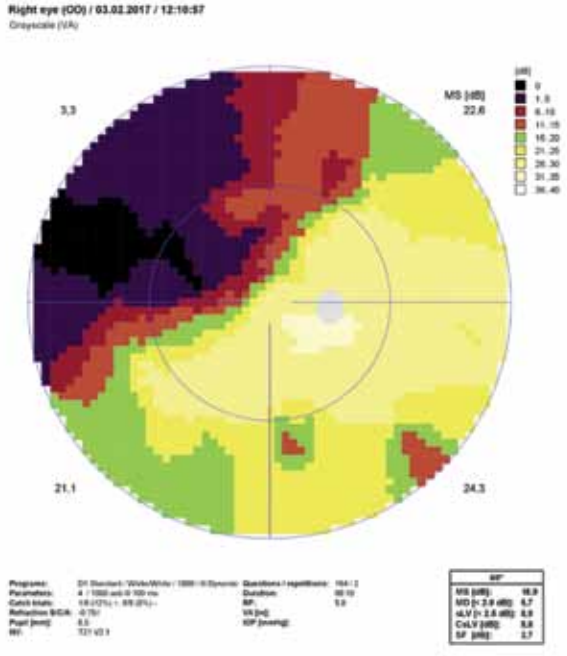

Fig. 3. Patient's S. SAP results. Decreased light sensitivity areas corresponding to the capillary non-perfusion areas are revealed

Рис. 3. Данные статической автоматической периметрии пациентки С. Выявляются зоны снижения светочувствительности сетчатки, соответствующие областям отсутствия капиллярной перфузии

FA showed restoration of previously absent capillary perfusion in the macular area (Figure 4). However, OCTA demonstrated an enlarged foveolar avascular zone and a decreased density of the perifoveolar capillary network with local ischemia in the superficial and deep retinal capillary plexuses, which was not visualized by FA (Figure 5 and 6).

DISCUSSION

Patients with RVO were found to have a decreased capillary density in the superficial and deep retinal capillary plexuses, reduced flow area of choriocapillaris, and an enlarged foveolar avascular zone in the deep retinal capillary plexus. Our results are congruent with those of foreign authors.

On average, the foveolar avascular zone should be 0.25–0.3 mm^2 in the superficial retinal capillary plexus and 0.49 mm^2 in the deep retinal capillary plexus [4, 16]. RVO is associated with a significant enlargement of the foveolar avascular zone (up to 0.76 mm^2 and 1.12 mm^2 in the superficial and deep retinal capillary plexuses, respectively), reduction of the capillary network density, and the emergence of capillary abnormalities, including

their destruction and appearance in areas without capillary perfusion.

Desolation of the perifoveolar capillary arcades correlates with the presence of peripheral ischemia [9]. More significant changes are observed in the deep retinal capillary plexus. V. Martinet et al. explain this by stating that large veins of the superficial retinal capillary plexus are directly connected with the deep retinal capillary plexus via transverse venules. An increase in intravascular pressure in large veins due to RVO induces rapid and significant elevation of hydrostatic pressure in the deep capillary network, as well as a reduction in retinal perfusion in the respective plexus areas, which explains why an increase in retinal thickness in the first stages of RVO occurs primarily due to the swelling of its outer layers. In addition, the superficial retinal capillary plexus is directly connected to retinal arterioles that have high perfusion pressure and oxygenation. These anatomical features make the deep retinal capillary plexus more vulnerable to ischemic changes in patients with RVO [17].

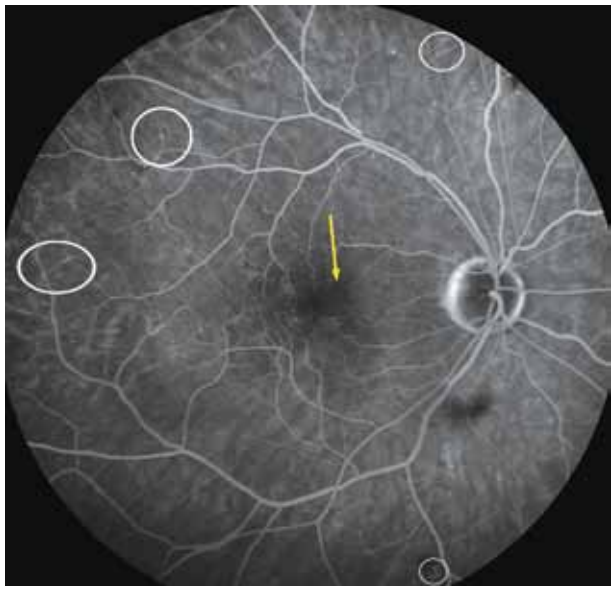

Fig. 4. FA results of patient P., late phase. Solitary microaneurysms on the periphery (ovals), enlargement of the foveal avascular zone (arrow) are shown

Рис. 4. Флюоресцентная ангиография пациента П., поздняя фаза. Указаны единичные микроаневризмы по периферии (овалы), расширение фовеолярной аваскулярной зоны (стрелка)

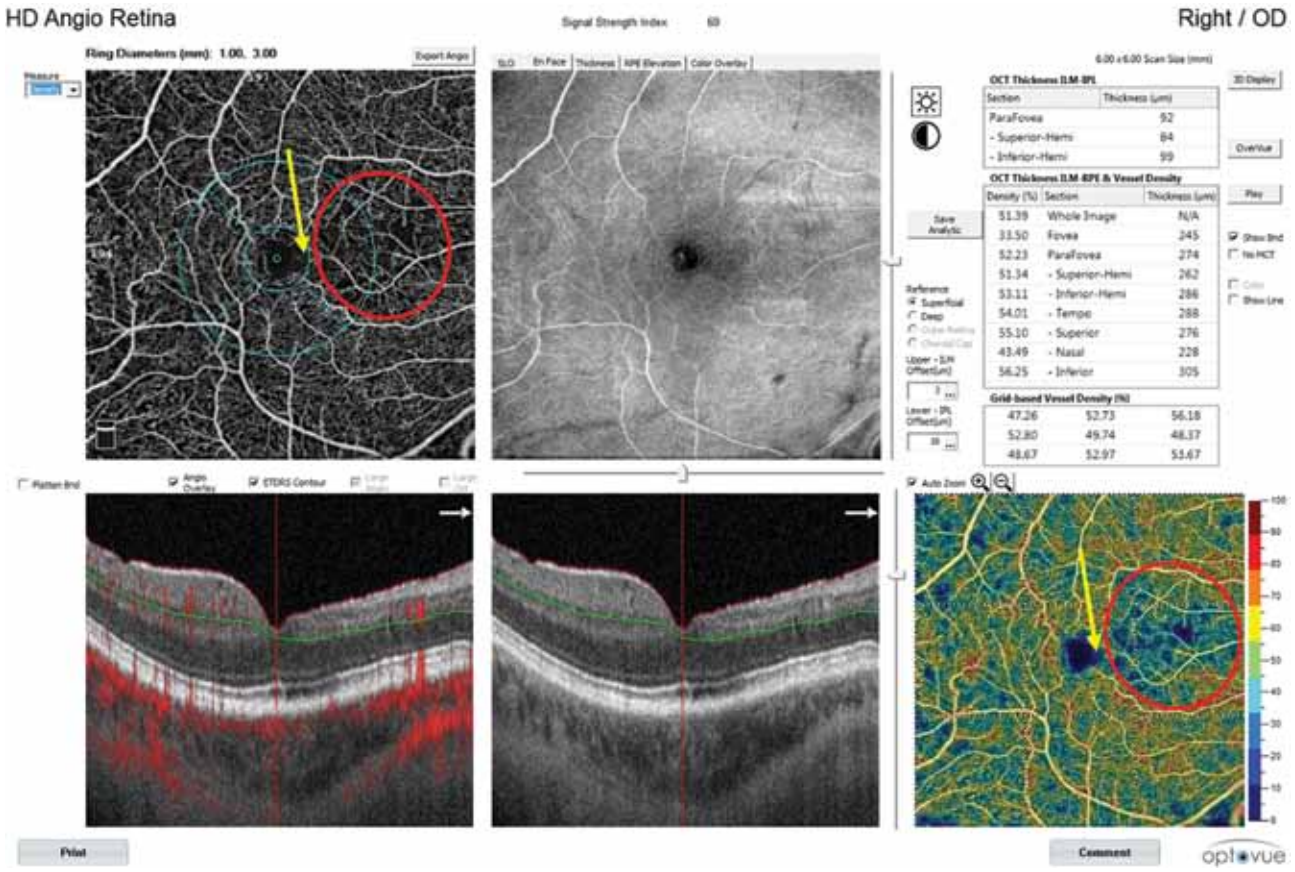

Fig. 5. Superficial capillary plexi density. Area of decreased density of the capillary network (oval) and foveal avascular zone enlargement (arrow) are shown

Рис. 5. Плотность капилляров в поверхностном капиллярном сплетении. Указаны зоны снижения плотности капиллярной сети (овал) и расширение аваскулярной зоны (стрелка)

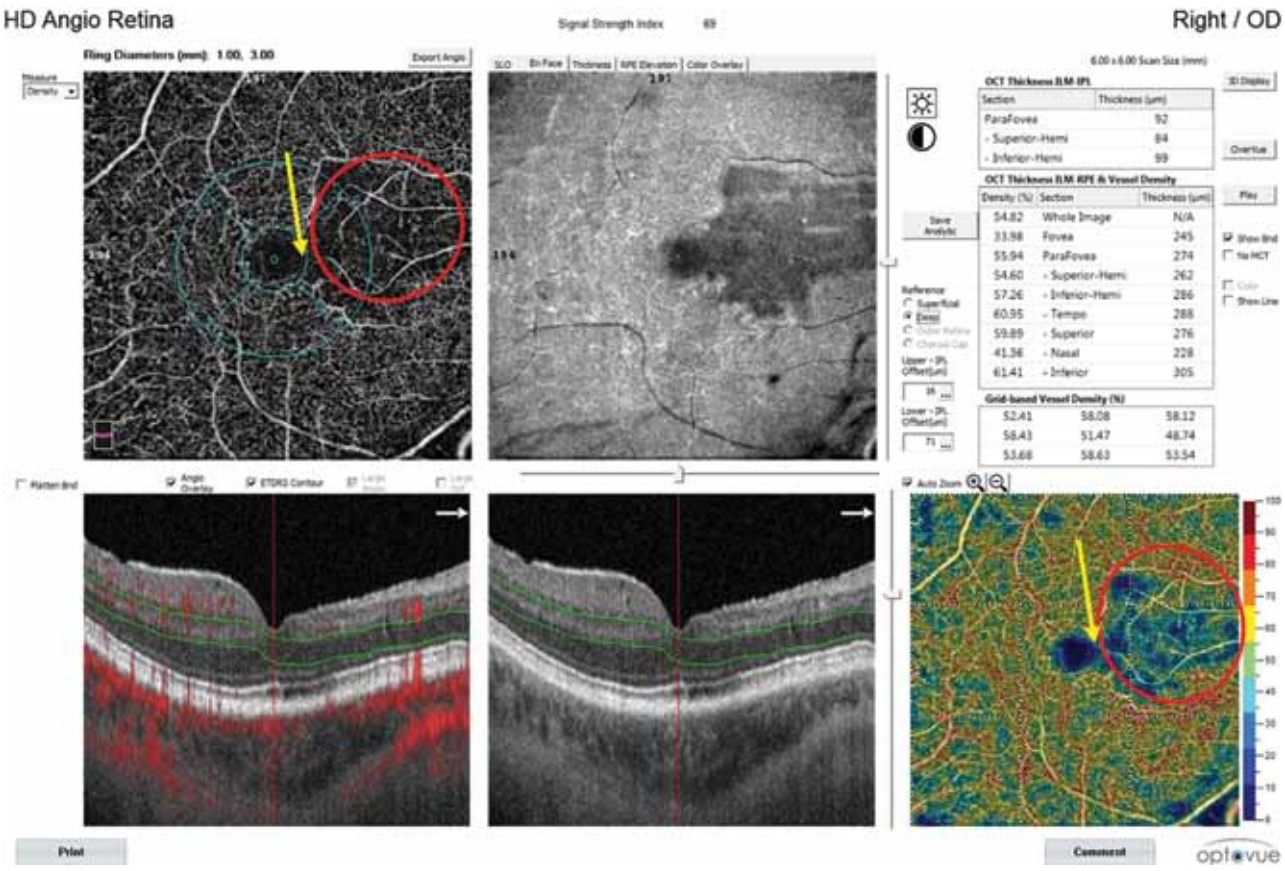

Fig. 6. Deep capillary plexi density. Area of the capillary network decreased density (oval), not visualized with FA, and foveal avascular zone enlargement (arrow) are shown

Рис. 6. Плотность капилляров в глубоком капиллярном сплетении. Выделены зоны снижения плотности капиллярной сети (овал), которые не визуализировались при проведении флюоресцентной ангиографии, и расширение аваскулярной зоны (стрелка)

CRVO is characterized by more significant microcirculatory changes, which are associated with higher concentrations of vascular endothelial growth factor [4, 5]. N. Suzuki et al. [25] found that therapy with angiogenesis inhibitors reduces the size of areas without capillary perfusion, and that the number of intravitreal injections is directly proportional to the improvement in hemodynamics.

The correlation between the studied plethysmographic parameters and the results of OCTA may indicate the involvement of choroid in the pathological process. Changes in choroidal blood flow in patients with RVO were not thoroughly studied. Diabetic retinopathy, which is similar to RVO in terms of its pathogenesis, is characterized by reduced blood flow to the eyeball in the early stages and an increased blood flow in the late stages, and this is detected using continuous tonometry [12]. Our sample was too small to be divided on the basis of disease duration. The detected values of choroidal blood flow significantly varied among patients, and high variability of plethysmography parameters prevented us from drawing unambiguous conclusions. Asymmetry of blood flow between eyes did not exceed 10% in 56% of cases. It was above 15% in one patient. It was higher in the affected eye than in the unaffected eye.

CONCLUSION

While our study has several limitations, such as limited sample size and a relatively small number of tested parameters, the novelty of OCTA, its non-invasiveness, and its clear advantages in terms of evaluation of the retinal capillary plexuses at different levels make it highly valuable for clinical practice. Additional information on the involvement of the macular area at early stages of RVO will help treating ophthalmologists in choosing a correct treatment strategy and predicting the possibility of visual acuity improvement. Ophthalmic plethysmography allows assessing the involvement of choroidal hemodynamics in the pathological process; however, despite the clear advantages of OCTA, FA is still necessary to accurately assess visual changes and to identify areas without capillary perfusion at the periphery of the fundus.

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