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# Macular microcirculation blood flow in patients with age related macular degeneration treated with photodynamic therapy and transpupillary thermotherapy

## *Mikrokrążenie plamkowe u pacjentów z AMD leczonych terapią fotodynamiczną i termoterapią przezrzeniczną*

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**Summary:**

**Purpose:** To assess the macular retinal and choroidal microcirculation blood flow in patients with exudative age related macular degeneration before and after photodynamic therapy (PDT) or transpupillary thermotherapy (TTT) with Doppler laser scanning (HRF – Heidelberg retinal flowmeter).

**Material and methods:** Thirty patients with exudative age-related macular degeneration were included in a prospective study. The diagnosis was established based on ophthalmic examination and fluorescein angiography results. In all cases the subfoveal choroidal neovascularization (CNV) was present. Control group consists of the fellow eyes with early stage of AMD (19 eyes) or with disciform scar (11 eyes). In 15 eyes with active CNV PDT was performed and in remaining 15 – TTT. In all cases the macular blood flow was measured with Heidelberg retina flowmeter (HRF) before therapy and then 1 week, 4 weeks and 10-12 weeks after treatment.

**Results:** At the baseline examination in a group of eyes with active CNV the mean values of macular blood flow were significantly higher comparing to the fellow eyes and reached respectively:  $678.6 \pm 125.0$  AU and  $298.4 \pm 79.2$  AU ( $p=0.001$ ).

Four weeks after treatment all eyes showed the reduction of macular blood flow comparing to the baseline values ( $p=0.001$ ). Ten to twelve weeks after laser therapy in all cases the increased macular blood flow was detected comparing to the previous examination ( $p=0.01$ ). During the follow-up period the macular blood flow in the fellow eyes were significantly lower than in treated eyes.

**Conclusions:** The measurement of macular blood flow using Doppler scanning laser (HRF – Heidelberg retinal flowmeter) may act as a non-invasive and useful diagnostic tool in assessment of CNV activity in patients with exudative age-related degeneration before and after PDT or TTT.

**Słowa kluczowe:** AMD, HRF, mikrokrążenie plamkowe.

**Key words:** Age related macular degeneration, Doppler laser scanning, macular microcirculation blood flow.

Age related macular degeneration (AMD) is a disease characterized by the presence of functional and morphological alterations in the retina, Bruch's membrane, the retinal pigment epithelium, the choriocapillaris and larger choroidal vessels in addition to changes in ocular perfusion (1). In patients with the early stage of AMD, with age-related maculopathy (ARM) many various vascular alterations have been reported: a raised number of ischemic retinal capillaries, reduction of choroidal blood flow, an increase in pulsatility and decreased velocity of the short posterior ciliary arteries, increased submacular choriocapillaris density with reduced density of large choroidal vessels (2,3,4).

There are many methods of non-invasive measurement of the tissue blood flow in the retina or choroid: color Doppler ultrasonography, Doppler velocimetry, the laser speckle method, pulsatile ocular blood flow technique (4). However, the evaluation of the macular microcirculation by these techniques has been difficult. Heidelberg retina flowmeter (HRF), which combi-

nes the technique of laser Doppler flowmetry with laser scanning technology, can measure the blood flow within the macular region. HRF allows to measure the tissue at the depth of  $300 \mu\text{m}$ , so measurements may have included the choroidal blood flow in the foveola, where the retina is very thin, approximately  $135 \mu\text{m}$  (1). It has been known, that perfusion alterations in retinal and choroidal capillaries within the macular region may play an important role in pathogenesis of AMD, and the dynamics of their changes may reflect the clinical course of the disease (2,5,6,7).

There is a scant number of publications about the evaluation of macular microcirculation blood flow in patients with exudative AMD and also there are only a few papers on ocular blood flow in patients with choroidal neovascularization (CNV) due to AMD after laser therapy.

The aim of this study is the evaluation of macular retinal and choroidal microcirculation blood flow with Doppler laser

scanning (HRF – Heidelberg retinal flowmeter) in patients with exudative AMD treated with photodynamic therapy (PDT) or transpupillary thermotherapy (TTT).

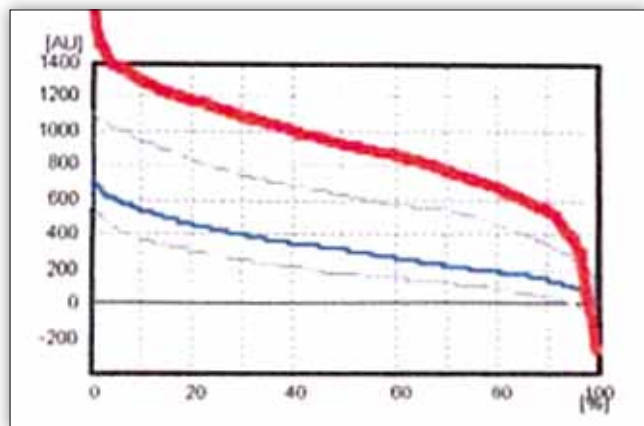
### Material and methods

Thirty patients with exudative age related macular degeneration were included in a prospective study. There were 13 males and 17 females, in age from 64 to 81 years, mean age:  $73 \pm 6.2$  years. The diagnosis was established based on ophthalmic examination and fluorescein angiography results. In each patient the exudative AMD was present in one eye; the subfoveal CNV was present, which in 17 cases was classic and in 13 – occult. The distance visual acuity in this group of eyes ranged



**Fig. 1.** The macular area  $10 \times 2.5^\circ$  within which the microcirculation blood flow was measured.

from counting fingers at the distance of 3 meters to 0.4. Control group consists of the fellow eyes with disciform scar (11 eyes) or with an early stage of AMD (age related maculopathy – ARM) that is characterized by the presence of drusen  $\geq 63 \mu\text{m}$  and/or RPE atrophy and/or RPE proliferation (19 eyes). The distance visual acuity in this group of eyes ranged from hand movements to 0.9.



**Fig. 2a.** Macular blood flow of the eye with active CNV qualified for PDT.

Based on qualification criteria in 15 eyes with active CNV PDT was performed; this group includes 11 eyes with classic CNV and 4 with occult CNV. In the remaining 15 eyes with classic CNV in 6 eyes and occult CNV in 9 eyes, not qualified for PDT because of a very large lesion size and visual acuity worse than 0.1 – TTT was performed.

Photodynamic therapy was performed using a diode laser with an emission wavelength at 689 nm (laser Opal, Coherent) and an intravenous injection of  $6 \text{ mg/m}^2$  BSA verteporfin (Novartis AG, Switzerland). The therapy was started 5 minutes after the infusion of verteporfin was completed.

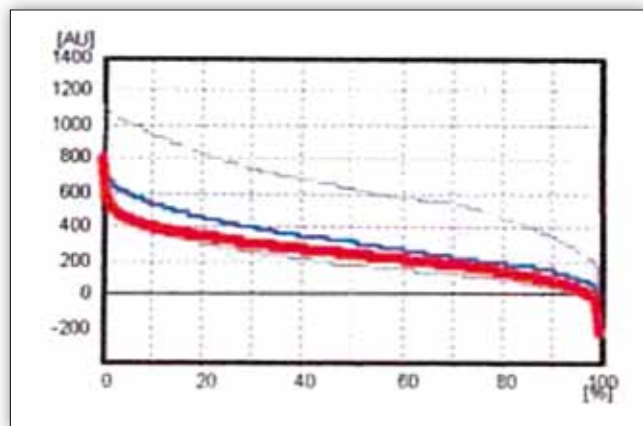
Transpupillary thermotherapy was performed with a diode laser with an emission wavelength at 810 nm (IRIS Medical Instruments, Mountain View, California, USA). In every case the diameter of a laser spot was established based on a largest linear diameter of CNV measured on fluorescein angiography to which  $1000 \mu\text{m}$  was added. The laser power for PDT was stable:  $50 \text{ J/cm}^2$ , but for TTT depended on laser spot size and ranged from 520 mW do 680 mW.

The tissue blood flow in the macular area was measured using a scanning laser flowmeter (Heidelberg retina flowmeter, Heidelberg, Germany). The measurement area included a zone of  $10 \times 2.5^\circ$ , that equals to  $2.8 \times 0.7 \text{ mm}$ . During each measurement the foveola was located in the central part of the scanned area (Fig. 1). The macular blood flow was measured before therapy and then 1 week, 4 weeks and 10-12 weeks after treatment. During each follow-up the measurements were performed in each eye at least 3 times.

The results of microcirculation blood flow were presented in arbitrary units – AU. The calculation of macular area capillary blood flow was performed with AFFPIA program (*automatic full-field perfusion image analyzer*). The results were statistically analysed using a t-Student test for independent trials. Level of significance was  $p \leq 0.01$ .

### Results

At the baseline examination in eyes with CNV qualified for PDT or TTT the mean values of macular blood flows were:  $678.6 \pm 125.0 \text{ AU}$  and  $702 \pm 168.0 \text{ AU}$ , respectively. In the fellow eyes the mean values of microcirculation blood flow in macu



**Fig. 2b.** Macular blood flow of the fellow eye with drusen and RPE changes.

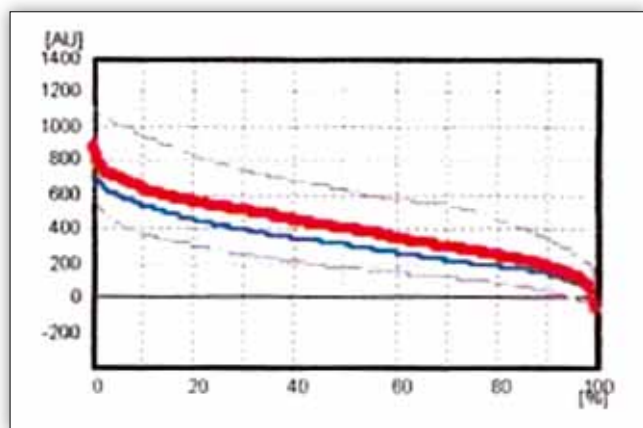


Fig. 3. Macular blood flow of the same eye 1 week after PDT.

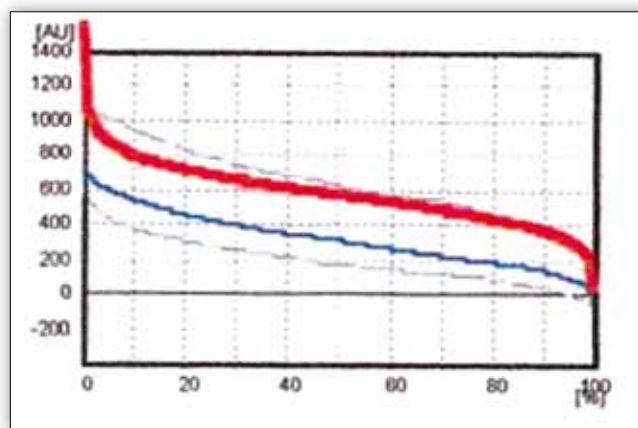


Fig. 4. Macular blood flow of the same eye 10 weeks after PDT.

lar area were statistically significantly lower:  $298.4 \pm 79.2$  AU ( $p=0.001$ ) (Fig. 2a,b).

In all treated eyes 1 week after therapy significantly decreased mean values of blood flow in macular region were recorded. In eyes after PDT the mean values of blood flow were:  $390.3 \pm 101.8$  AU and in eyes treated with TTT:  $360.71 \pm 121.2$  AU (Fig. 3).

Four weeks after treatment all eyes showed the reduction of macular blood flow comparing to the baseline values ( $p=0.001$ ) and they reached:  $359 \pm 108.7$  AU in eyes treated with PDT and  $371.45 \pm 111.9$  AU in eyes treated with TTT. In the third follow-up examination performed 10-12 weeks after laser therapy significantly increased values of macular blood flow were detected in treated eyes as compared to the previous results. These values were as follows:  $608.7 \pm 124.6$  AU in eyes after PDT and  $512.4 \pm 101.3$  AU in eyes after TTT ( $p=0.01$ ) (Fig. 4).

During the whole follow-up period the mean values of macular blood flow in the fellow eyes were significantly lower comparing to the treated eyes.

The mean values of macular microcirculation blood flow in patients with CNV treated with PDT and TTT and in fellow eyes during a 3-months follow-up period are presented in table I.

**Discussion**

It has been known that alterations of ocular circulation both retinal and choroidal play an important role in ethiopathogenesis of AMD. It has been documented that in patients with an early stage of AMD; with age related maculopathy which is

characterized by the presence of soft drusen and RPE changes and also in eyes with geographic atrophy the decreased retinal capillaries blood flow is observed. The more advanced stage of the disease the more increased values of tissue ocular blood flow are present, what is suggestive for ischemia as an important factor in development of AMD (8,9,10). Chen et al. in eyes with CNV showed increased values of ocular pulsatile blood flow while in eyes with disciform scar its reduction was observed (11). In our material in eyes with drusen and/or RPE changes and in eyes with disciform scar we also found lower mean values of macular blood flow using the HRF comparing to the eyes with an active CNV. We have found only one publication about the assessment of ocular blood flow measured with the pulsatile ocular blood flow technique in patients with AMD treated with TTT (11). In our study we evaluated the changes in macular blood flow in two groups of eyes; treated with PDT or TTT. We noted decreased values of macular blood flow 1 and 4 weeks after laser therapy. In a follow-up examination performed 10-12 weeks after treatment the mean values of macular microcirculation blood flow in both group of treated eyes significantly increased. Our results are similar to those presented by Chen et al. however it is worth to underline that in both studies two different methods of assessment of ocular blood flow were used (11).

Both PDT and TTT lead to obliteration of pathological vessels within the CNV. In TTT the mechanism is associated with thermal effect, while in PDT with activation of photochemical reactions, that lead to damage of endothelial cells and activa-

Follow-up examination	Mean blood flow values (AU) in eyes treated with PDT	Mean blood flow values (AU) in eyes treated with TTT	Mean blood flow values(AU) n fellow eyes
0	$678.6 \pm 125.0$	$702.0 \pm 168.0$	$298.4 \pm 79.2$
1 <sup>st</sup> week	$390.3 \pm 101.8$	$360.71 \pm 121.2$	$330.9 \pm 103$
4 <sup>th</sup> week	$359.0 \pm 108.7$	$371.45 \pm 111.9$	$280 \pm 88.8$
10-12 <sup>th</sup> week	$608.7 \pm 124.6$	$512.4 \pm 101.3$	$302 \pm 93.8$

Tab. I. The mean values of macular microcirculation blood flow in patients with CNV treated with PDT or TTT and in the fellow eyes during a 3-months follow-up period.

tion of clotting cascade. It has been known that recanalization of CNV after PDT is observed in about 94% of cases within 12 weeks after treatment. This phenomenon is thus indicative that PDT does not eliminate the vasoactive factors.

The increased values of macular blood flow in eyes with active CNV was the result of detection by Doppler scanning laser the increased density of choroidal vessels in submacular region forming the CNV. The obliteration of pathological vessels within CNV after PDT or TTT was correlated with the reduction of macular blood flow.

The measurement of macular retinal and choroidal microcirculation blood flow in patients with exudative age related degeneration before and after PDT or TTT with Doppler scanning laser (HRF – Heidelberg retinal flowmeter) may act as a non-invasive and useful diagnostic tool in assessment of CNV activity.

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