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# Optical coherence tomography angiography to assess vascular remodeling of the choriocapillaris after low-fluence photodynamic therapy for chronic central serous chorioretinopathy

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ABSTRACT

*Background:* To evaluate the efficacy of optical coherence tomography angiography (OCTA) in identifying changes in the choriocapillaris layer after low-fluence verteporfin photodynamic therapy (vPDT) in patients affected by chronic central serous chorioretinopathy (CSCR).
*Methods:* Low-fluence vPDT was performed on 28 eyes of 27 patients with CSCR. All patients underwent the following tests at baseline and 6 months after treatment: best corrected visual acuity (BCVA), fluorescein angiography, indocyanine green angiography, enhanced depth imaging OCT and OCTA.
*Results:* Subretinal fluid was completely absorbed in 18 of the 28 affected eyes (64.3%) after low-fluence vPDT ("responders"), and incompletely absorbed in 10 eyes (35.7%) ("non responders"). BCVA was significantly improved ($p = 0.006$) whereas central foveal thickness and choroidal foveal thickness were significantly decreased ($p = 0.001$ and $p = 0.00$ respectively) 6 months after treatment in responders.
*Conclusions:* OCTA revealed a different pattern of vascular remodeling of the choriocapillaris between CSC patients who responded and those who did not respond to low-fluence vPDT.

## 1. Introduction

Central serous chorioretinopathy (CSC) is characterized by accumulation of serous subretinalfluid (SRF), which often causes retinal epithelium pigment (RPE) detachment that affects the inner choroid [1]. The acute form of CSC resolves spontaneously in 3–4 months with a good visual prognosis [2]. Chronic serous chorioretinopathy and recurrent forms affect older adults, and long-standing SRF leads to photoreceptor death and may result in a poor visual outcome [3].

A multimodal approach showed that choroidal vascular hyperpermeability is the main pathophysiological feature for the diagnosis of CSC [4,5]. Fluorescein angiography revealed leakage of serous fluid into the subretinal space as a result of breakage of the RPE functional barrier [4,6]. The consequent widespread exudation of dye seen in the mid-phase on indocyanine green angiography (ICGA) supports choroidal hyperpermeability in CSC patients [3,7]. Recent prospective studies showed that optical coherence tomographic angiography (OCTA) revealed an intensive choriocapillary flow pattern associated with vascular abnormalities of the choriocapillarislayer, namely capillary dilation and tortuosity, and signs of hypoperfusion in patients affected by CSC [8,9].

Verteporfin photodynamic therapy (vPDT), which reduces choroidal hyperpermeability and leakage, has been successfully used to treat CSC [10,11]. Safety-enhanced PDT protocols such as low-fluencevPDT, which reduces choroidal hypoperfusion, have proven to be more effective and safer than standard PDT in terms of visus, retinal sensitivity and functional outcome [12–14].

The aim of this study was to analyze vascular changes of the choriocapillaris layer after low-fluence vPDT with OCTA in the attempt to identify differences in choriocapillaris features between patients with complete resolution of SRF (responders) and patients with incomplete resolution of SRF (non responders).

## 2. Materials and methods

Twenty-eight consecutive eyes of 27 patients with chronic CSC were

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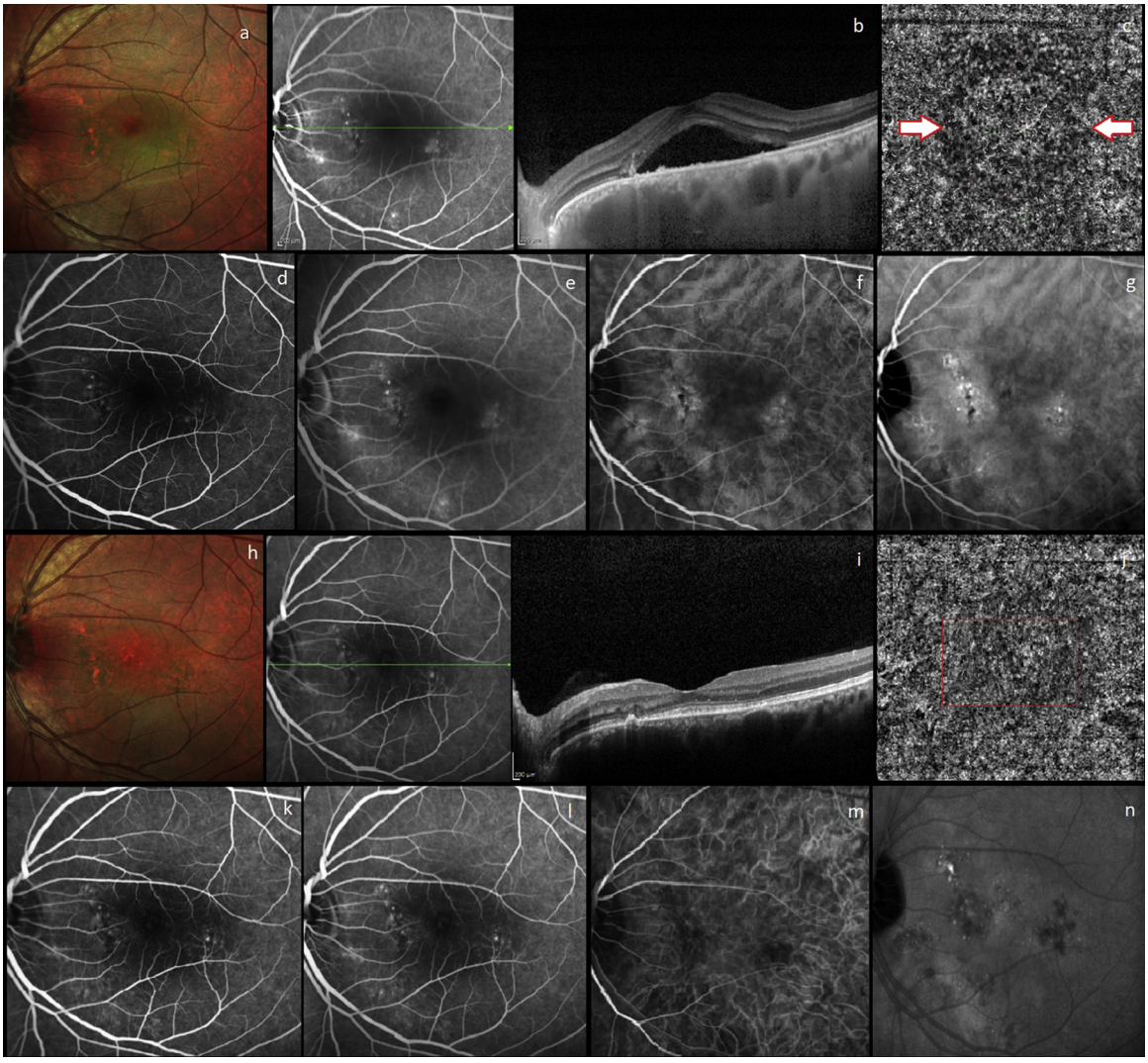


**Fig. 1. Multimodal imaging of the left eye of a 39 year-old male patient with chronic central serous chorioretinopathy at baseline and 6 months after low-fluence photodynamic therapy (PDT)**. (a,b) Baseline multicolor image and optical coherence tomography (OCT) B scan showing neurosensory retinal detachment and a thickening of the neuroretina in macular region before treatment. (c) OCT angiography (OCTA) (6 × 6 scan at choriocapillaris layer) revealing irregular flow pattern before PDT(between arrows). (d,e) Middle and late phase of FA before PDT showing uneven hyperfluorescence with minimal late leakage. (f,g) Indocyanine Green Angiography (ICGA) show dilated choroidal vessels with hyperpermeability areas in early-phase and moderately intense choroidal staining plaques in late-phase. (h–j) Multicolor fundus image 6 months after low fluence PDT ICGA-guided, OCT after treatment revealing a complete resolution of neurosensory retinal detachment and OCTA image showing a more regular flow pattern defined as narrow meshes pattern(inside rectangle area). (k–n) Early and late phase FA shows a reduction in leakege at posterior pole. Early-phase ICGA and late phase ICGA shows a decrease of choroidal vascular hyperpermeability and a reduction of extra-vascular leakage.

enrolled in a prospective study performed at the Eye Clinic of the University of Naples "Federico II", Italy, from October 2015 to October 2017. We excluded patients with evidence of choroidal neovascularization, previous focal laser treatment or PDT for CSC, and those with allergy or systemic contraindications to verteporfin or angiography dyes. All patients underwent a detailed ophthalmic examination: Best Correct Visual Acuity (BCVA), multicolor imaging, FA, ICGA, OCT and OCTA at baseline and 6 months after treatment. The study protocol was approved by the Institutional Review Board/Ethics Committee of the University of Naples Federico II and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients.

### 2.1. Low-Fluence vPDT

Eligible patients underwent low-fluence PDT with intravenous infusion of verteporfin (Visudyne, Novartis AG, Bülach, Switzerland) for 10 min at a dose of 6 mg/m$^2$, followed by delivery of diode laser at 689 nm (Visulas 690S; Carl Zeiss Meditec Inc., Dublin, CA, USA). The laser parameters used were: a fluence of 25 J/cm2, a light dose rate of 300 mW/cm$^2$, a photosensitization time of 83 s and a spot size with a diameter 1000 µm larger than the greatest linear dimension of the choroidal exudation. Patients were advised to avoid exposure to sunlight for 48 h after treatment because of the risk of skin photosensitivity.

### 2.2. Outcome measures

BCVAwas measured at 2 m according the Early Treatment of Diabetic Retinopathy Study (ETDRS) visual logarithm of the minimum angle of resolution scale. Two masked experts (GC, MC) measured central foveal thickness (CFT) and choroidal foveal thickness. To measure CFT, on the OCT image, we placed a caliper on the inner and outer boundaries, which correspond respectively to the internal

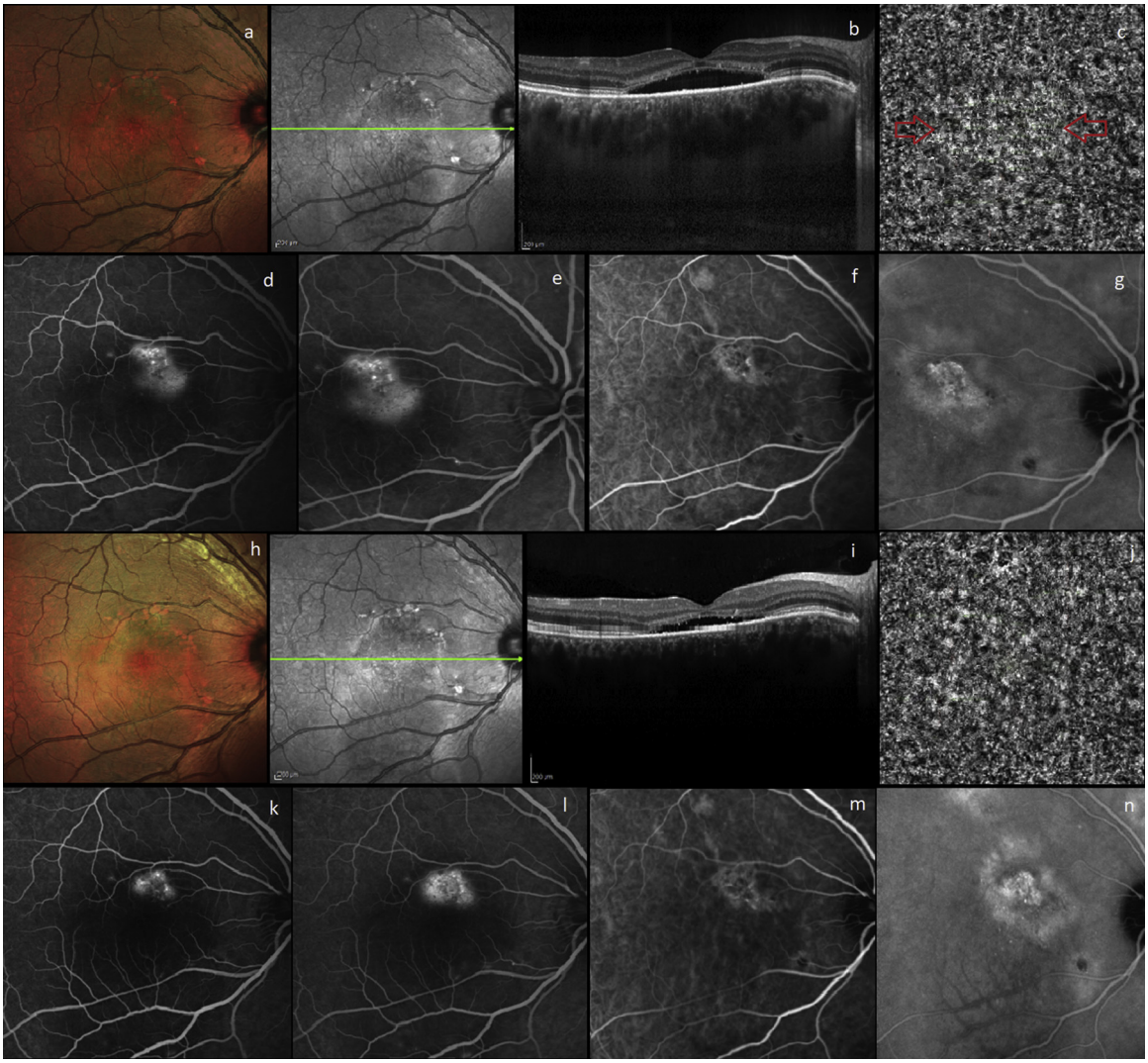


**Fig. 2. A Multimodal imaging of right eye of a 38 year-old man with chronic central serous chorioretinopathy treated with low-fluence photodynamic therapy (PDT) at baseline and after 6 months**. (a–c) Multicolor fundus image, optical coherence tomography (OCT) B scan showing the presence of subretinal fluid and a thickening of the neuroretina in macular region and OCT angiography (OCTA)(6 × 6 mm) that reveals an irregular flow pattern and a dilated aspect of choroidal vessels at baseline (between arrows). (d–g) Early and late-phase of fluorescein angiography (FA) showing a leaking area and Indocyanine Green Angiography (ICGA) findings revealing sites of hyperpermeability. (h–j) Multicolor fundus image 6 months after low fluence PDT ICGA-guided, OCT image after treatment revealing a persistent of subretinal fluid and OCTA image showing a persistence of abnormal flow pattern at choriocapillaris layer. (k–n) Middle and late phase of FA showing persistence of extravascular leakage and persistenceof late staining on ICGA.

**Table 1**
Demographic Characteristics of the Study Population.

| | Patients (n = 27) | Responders (n = 18) | Non responders (n = 9) |
|---|---|---|---|
| Age, years, mean (SD) | 47(11) | 45 ± 8 | 49 ± 12 |
| Sex, n (%) | | | |
| Males | 21 (77.7) | 12 (66.7) | 9 (100) |
| Females | 6 (33.3) | 6 (33.3) | 0 (-) |
| Duration of symptoms, months, mean (SD) | 14 (13) | 10 (6) | 20 (9) |

limiting membrane and the RPE /Bruch membrane. The choroidal foveal thickness was measured by EDI scan during which the caliper tool was placed between the two highlighted boundaries, namely Bruch's membrane and the outer surface of the scleral-choroidal junction.

OCT angiograms were acquired with the Optovue RTVue XR Avanti system (Optovue Inc., Fremont, 2016.2.0.35 Software Version, CA, USA), based on split-spectrum amplitude decorrelation angiography. The instrument has an A-scan rate of 70,000 scans per second with a tissue axial resolution of 5 µm and a 15 µm beam width. Each B-scan contained 304 A-scans. Two consecutive B-scans were captured at a fixed position and extracted from each other to calculate decorrelation in the images. Motion correction was performed by acquiring two orthogonal OCTA volumes. The angiography data are reported as the average of the decorrelation values. A three-dimensional angiographic data cube was created by combining the horizontal and vertical scans with an algorithm, and blood perfusion was correlated to signal intensity. The software automatically segments the tissue into four vascular layers: inner and deep vascular retinal plexus, outer retina and choriocapillaris. We analyzed the choriocapillaris layer, defined as a vascular signal, by performing a 6 × 6 scan, 30 µm below the RPE-Bruch's membrane–complex.

### 2.3. Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (version 20.0 for Windows; SPSS Inc, Chicago, Ill, USA)

**Table 2**
Measurements at baseline and 6 months after low-fluence photodynamic therapy in all affected eyes, and in responders and non-responders.

| | Affected Eyes (n = 28) | | | Responders (n = 18) | | | Non Responders (n = 10) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Follow up | p-value[a] | Baseline | Follow-up | p-value[a] | Baseline | Follow up | p-value[a] |
| BCVA, logMar, mean (SD) | 0.11 (0.19) | 0.19 (0.12) | 0.002 | 0.11 (0.22) | 0.21 (0.11) | 0.006 | 0.1 (0.16) | 0.14 (0.13) | 0.102 |
| CFT, μm, mean (SD) | 324.75 (127) | 278.6 (84.6) | 0.025 | 345.8 (116.3) | 254.4 (53.9) | 0.001 | 318.8 (107.2) | 322.3 (112.7) | 0.173 |
| Choroidal Thickness, μm, mean (SD) | 365.3 (105.3) | 310.2 (88.7) | 0.000 | 359 (114.3) | 285.1 (81.7) | 0.000 | 376.7 (91.6) | 355.4 (84.5) | 0.284 |
| Angio-OCT Pattern, n (%) | | | | | | | | | |
| Dilated choriocapillaris | 28 (100) | 10 (25.7) | | 18 (100) | 0 (-) | | 10 (100) | 10 (100) | |
| Mesh Narrow | 0 (-) | 18 (74.3) | | 0 (-) | 18 (100) | | 0 (-) | 0 (-) | |

BCVA = best-corrected visual acuity; logMar = logarithm of minimal angle of resolution; CFT = central foveal thickness; OCT = optical coherence tomography; SD = standard deviation.
[a] Wilcoxon test.

using analysis of variance. A $P$ value of $< 0.05$ was considered statistically significant.Changes in variables over time in each groupwere evaluated with the Wilcoxon–Mann Whitney U test.

## 3. Results

At baseline, SRF was identified in 28 eyes of the 27 CSC patients enrolled in the study (21 men and 6 women) whose mean age was 47 years (range: 34–70 years) (Figs. 1a–g and 2 a–g). The disease was bilateral in 1 patient. The mean duration of symptoms was 14 months.The demographic characteristics of the study population are summarize in Table 1. All eyes underwent low-fluence vPDT using a mean spot size of 3134.5 ± 1089.5 μm. Table 2 shows the results obtained in responder and non responder patients at baseline and 6 months after treatment. Six months after low-fluence vPDT, SRF was completely absorbed in 18 eyes (64.3%) (responders) (Fig. 1h–n), and incompletely absorbed in 10 eyes (35.7%) (non responders) (Fig. 2h–n). In addition, 6 months after low-fluence vPDT, BVCA was significantly better than baseline only in responder patients ($P = 0.006$) although the difference between the two groups was not statistically significant ($P = 0.286$). The decrease in CFT and in choroidal foveal thickness was statistically significant six months after treatment only in responders.

In all 28 eyes with SRF, baseline OCTA scan of the choriocapillaris showed a high flow signal in the hyperpermeability zone,which was characterized by dilated choroidal vessels, and a low flow signal in the surrounding hypoperfusion area (Figs. 1c, 2 c). Six months after low-fluence vPDT, OCTA scan of the choriocapillaris showed a decrease of choroidal vascular hyperpermeability in the responder group together with complete resolution of SRF as witnessed by a “narrow mesh” pattern (Fig. 1j). These OCTA findings corresponded to a reduction of extravascular leakage in the treated area on early and late phase ICGA (Fig. 1m, n). OCTA images of the choriocapillaris in the non-responder group showed persistence of abnormal vessels and a heterogeneous flow pattern rather than a “narrow mesh” pattern (Fig. 2c–j).

## 4. Discussion

We used OCTA to evaluate vascular changes in the choriocapillaris layer in CSC patients after low-fluence vPDT in the attempt to identify differences between patients with complete resolution of SRF and patients with incomplete resolution of SRF. Previous OCTA-based studies demonstrated that choroidal abnormalities play a role in the pathophysiology of CSC and suggest that treatment targeting the choroidal circulation could be effective [8,15]. Fujita et al. analyzed the choriocapillaris layer in 6 eyes with CSC after half-dose PDT using OCTA and found that an initially no flow void in the area treated with PDT progressively decreased to a homogeneous aspect [16]. They assumed that PDT restored the normal choroid circulation by relieving pachychoroid-related compression. Xu et al., also using OCTA, identified choroidal hypoperfusionin 15.2% of 33 eyes affected by CSC 1 week after half-dose PDT, and a normal flow signal in 97% of eyes 3 months after treatment [17]. Also our results show that low-fluence vPDT induces vascular remodeling of the choriocapillaris and that this remodeling leads to recovery of circulatory decompensation.

We postulate that low power laser reduces short-term hypoxia by redirecting the flow into the hypoperfused choriocapillary network. Notably, improved choriocapillaris circulation with readaptation of vessels to the flow corresponded to a characteristic “narrow mesh” pattern. In non-responders, who did not undergo vascular remodeling of the choriocapillaris, the large pachychoroidal vessels led to irreversible ischemic damage of the choriocapillaris layer. We plan to continue to monitor these patients to see if they develop choroidal neovascularization. Therefore, further study is needed in order to compare treatment outcomes in terms of choriocapillaris changes and complications of half-dose PDT and low-fluence vPDT in early and long-term follow up.

In conclusion, OCTA revealed differences in the choriocapillaris between patients with complete resolution of SRF (responders) and patients with incomplete resolution of SRF (non responders) after low-fluence vPDT thereby improving the diagnosis and prognosis of CSC. Potential limitations of our study are the relatively low number of eyes examined in the responder and non responder groups, and OCTA images limited to a small area of the posterior pole that may be affected by movement and blinking of the eyes.

## Declarations of interest

None.

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