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# EVIDENCE AGAINST A CONTRALATERAL COATS PHENOTYPE BY OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

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**Purpose:** To evaluate the laterality of Coats disease by analyzing optical coherence tomography angiography features in affected, fellow, and control eyes.

**Methods:** Patients with Coats disease who underwent optical coherence tomography angiography were retrospectively reviewed. Healthy eyes of age-matched patients served as controls. Automated optical coherence tomography angiography determination of foveal avascular zone size and vascular density of superficial capillary plexus and deep capillary plexus was recorded.

**Results:** Thirty-four patients with Coats disease (13 with bilateral optical coherence tomography angiography) and 24 controls were included. The foveal avascular zone was larger in affected eyes compared with fellow eyes ($P$ = 0.004). Vascular density was decreased in affected eyes compared with fellow eyes in the superficial capillary plexus and deep capillary plexus whole images ($P$ = 0.047 and $P$ = 0.007) and in the deep capillary plexus at the fovea ($P$ = 0.001). Vascular density was significantly reduced only in the deep capillary plexus in Stage 1 or 2A patients but in both plexuses in patients with Stage 2B1. No differences were shown on foveal avascular zone and vascular density values between fellow eyes of patients with Coats disease and controls.

**Conclusion:** The foveal avascular zone is enlarged, and vascular density is decreased in affected eyes with Coats disease, but no differences are seen between fellow and control eyes, confirming the unilateral nature of the disease.

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Coats[1] disease is a rare, congenital condition predominantly affecting young men and characterized by retinal telangiectasia and exudation. Coats disease has been classically considered as a unilateral disorder, with 95% of cases affecting only one eye.[2] Presumed bilateral Coats disease should rule out systemic conditions, such as facioscapulohumeral dystrophy, leading to secondary Coats disease–like retinopathy.[2] More recently, with the advent of wide-field imaging, it has been suggested that Coats disease could be considered a bilateral condition because of the presence of peripheral vascular changes in fellow eyes.[3] Approximately 18% of fellow eyes of patients with Coats disease may show asymptomatic, non-progressive vascular abnormalities.[4] Importantly, such peripheral changes could also be observed in heathy eyes, complicating the interpretation of these findings.[5] The study of macular changes in Coats disease determined by optical coherence tomography angiography (OCTA) has yielded inconclusive results concerning the laterality of Coats disease.[6,7] Schwartz

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et al[6] have shown significant differences in vascular density and foveal avascular zone (FAZ) when comparing affected and fellow eyes. Conversely, Stanga et al[7] have suggested that fellow eyes of Coats disease carry quantitative foveal vascular alterations compared with control eyes.

The aim of this study was to evaluate vascular density and FAZ by OCTA in affected and fellow eyes of patients with Coats disease and age-matched controls.

## Methods

This study was designed in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Swiss Federal Department of Health (authorization CER-VD no 95/15). Patients diagnosed during childhood with unilateral Coats disease who underwent OCTA at Jules-Gonin Eye Hospital between June 2017 and June 2020 were retrospectively reviewed. Data collection included patient demographic characteristics and stage of Coats disease according to Shields et al[8] and Daruich et al[9] into Stage 1, telangiectasia only; Stage 2, telangiectasia and exudation (2A, extrafoveal exudation; 2B1, foveal exudation, without subfoveal nodule; and 2B2 foveal exudation with subfoveal nodule); Stage 3, exudative retinal detachment (3A1, extrafoveal subtotal retinal detachment; 3A2, foveal subtotal retinal detachment; and 3B, total retinal detachment); Stage 4, total detachment and secondary glaucoma; and Stage 5, advanced end-stage disease.

Fellow healthy eyes of unilateral retinoblastoma or congenital cataract patients who underwent OCTA during the same period served as control group.

Optical coherence tomography angiography images were acquired using the AngioVue Avanti RTVUE XR (Optovue, Inc, Freemont, CA) after disease stabilization. The scanning area was captured in 3 × 3 mm sections centered on the fovea, capturing both eyes of each subject. Automated AngioVue OCTA software determination of FAZ size and vascular density of superficial capillary plexus (SCP) and deep capillary plexus (DCP) of the whole image and at the fovea was recorded.

### Statistical Analysis

The Wilcoxon nonparametric test was used to compare vascular density and FAZ between affected and fellow eyes of patients with Coats disease. The Mann–Whitney nonparametric test was used to compare vascular density and FAZ between fellow and control eyes. Statistical analysis was performed on GraphPad Prism (version 9.1.0, GraphPad Software, La Jolla, CA). In all statistical comparisons, differences with a $P$ value inferior to 0.05 were considered significant.

## Results

Thirty-four patients with Coats disease (29 male patients and 5 female patients, mean age: 14 ± 8 years) were included. Of these, 13 patients had bilateral OCTA allowing the analysis between affected and fellow eyes. Twenty-four healthy eyes were included as controls (12 male patients and 12 female patients, mean age: 15 ± 10 years). In the Coats cohort, 2 patients had Stage 1, 4 Stage 2A, 8 Stage 2B1, 6 Stage 2B2, 5 Stage 3A, 4 Stage 3B, and 2 Stage 4 disease at diagnosis. Patients with bilateral OCT presented with Stage 1, 2A, and 2B1 at diagnosis. Foveal avascular zone values and vascular density in affected and fellow eyes of patients with Coats disease are reported in Table 1. The foveal avascular zone was significantly larger in affected eyes compared with fellow eyes ($P$ = 0.004) (Figures 1 and 2). Vascular density was significantly decreased in affected eyes compared with fellow eyes in the whole SCP and DCP images ($P$ = 0.047 and $P$ =

Table 1. Comparation of FAZ and Vascular Density by OCTA in Coats Disease–Affected Eyes and Fellow Eyes

| | Affected Eyes (AE) | Fellow Eyes (FE) | *P* Wilcoxon Test |
|---|---|---|---|
| No. of eyes | 13 | 13 | |
| FAZ | 0.28 ± 0.14 | 0.20 ± 0.10 | 0.004 |
| SCP | | | |
| Whole image | 47.91 ± 1.9 | 50.00 ± 2.8 | **0.047** |
| Fovea | 27.62 ± 6.8 | 28.86 ± 7.8 | 0.33 |
| DCP | | | |
| Whole image | 42.19 ± 6.7 | 52.45 ± 3.8 | **0.0007** |
| Fovea | 32.98 ± 8.4 | 40.65 ± 7.4 | **0.001** |

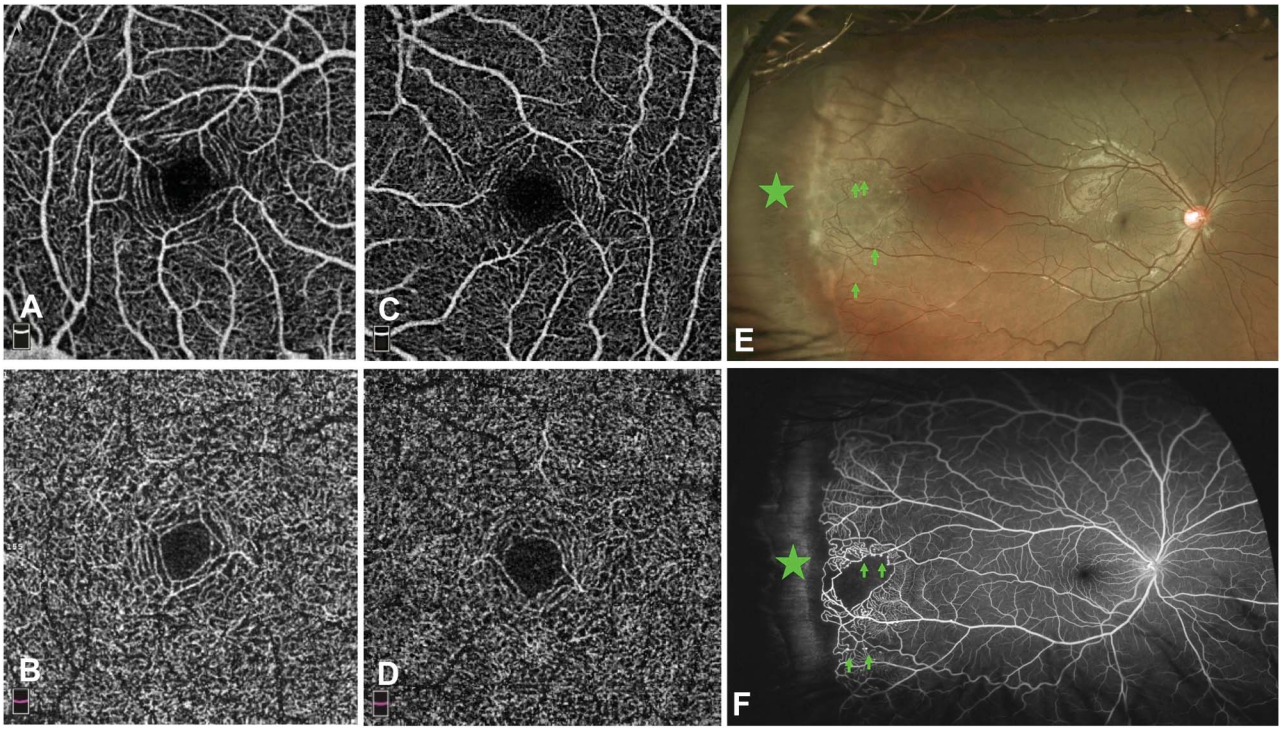


**Fig. 1.** Patient with Stage 1 Coats disease in the left eye compared with the right fellow eye. **A** and **B.** Optical coherence tomography angiography images of the fellow right eye showing the (**A**) SCP and the (**B**) DCP. Foveal avascular zone measured 0.15 $mm^2$. **C** and **D.** Optical coherence tomography angiography images of the Coats eye showing the (**C**) SCP and the (**D**) DCP. Foveal avascular zone measured 0.18 $mm^2$. Vascular density was reduced compared with the fellow eye mainly in the DCP. **E** and **F.** Ultra-widefield color fundus photography (**E**) and fluorescein angiography (**F**) of the left eye showing Stage 1 Coats disease with telangiectasias only (green arrows) without retinal exudation. Note a large temporal avascular area (green stars).

0.007, respectively). Vascular density at the fovea was significantly decreased in affected eyes compared with fellow eyes only in the DCP ($P$ = 0.001) (Figure 2). Subgroup analysis of patients according to the stage at diagnosis showed that affected eyes with Stage 2B1 had a significant decrease in vascular density in whole images in both SCP and DCP compared with fellow eyes. However, patients with Stage 1 or 2A Coats disease showed a significant reduction of the vascular density only in the DCP (Table 2). Comparative analysis of FAZ and vascular density showed no differences between fellow eyes of Coats disease and controls (Table 3) (Figure 2).

## Discussion

This study shows that FAZ is significantly enlarged and vascular density significantly reduced in eyes with Coats disease when compared with fellow eyes, especially in the DCP.

Similarly, Schwartz et al[6] have shown significant differences in vascular density and FAZ when comparing affected and fellow eyes. These authors have shown that DCP seems to be the first layer involved in the disease because decrease in vascular density was only observed in the DCP in Stage 2A Coats disease but in both plexuses, DCP and SCP (with the exception of the fovea level), in Stage 2B disease. We observed the same findings, thus confirming the implication of the DCP as a subclinical vascular macular phenotype in Coats disease. Interestingly, there was no difference in foveal SCP between affected and fellow eyes in both studies.

It has been suggested that DCP is more vulnerable than SCP to ischemia and other stress.[10] Superficial capillary plexus is connected to large retinal vessels; however, DCP is located in an area with lower oxygen saturation than the inner or the outer retina, which could explain the early loss of vascular density on the DCP in Coats disease. More severe DCP abnormalities have also been shown in other retinal vascular diseases, including diabetic retinopathy and retinal vein occlusion.[10] In retinal vein occlusion, the capillary disruption at the level of the DCP has been correlated with peripheral retinal ischemia, showing that peripheral abnormalities could be predicted by OCTA.[11] Similarly, the severity of diabetic retinopathy and the decrease of visual acuity have been also correlated with the loss of DCP on OCTA.[12]

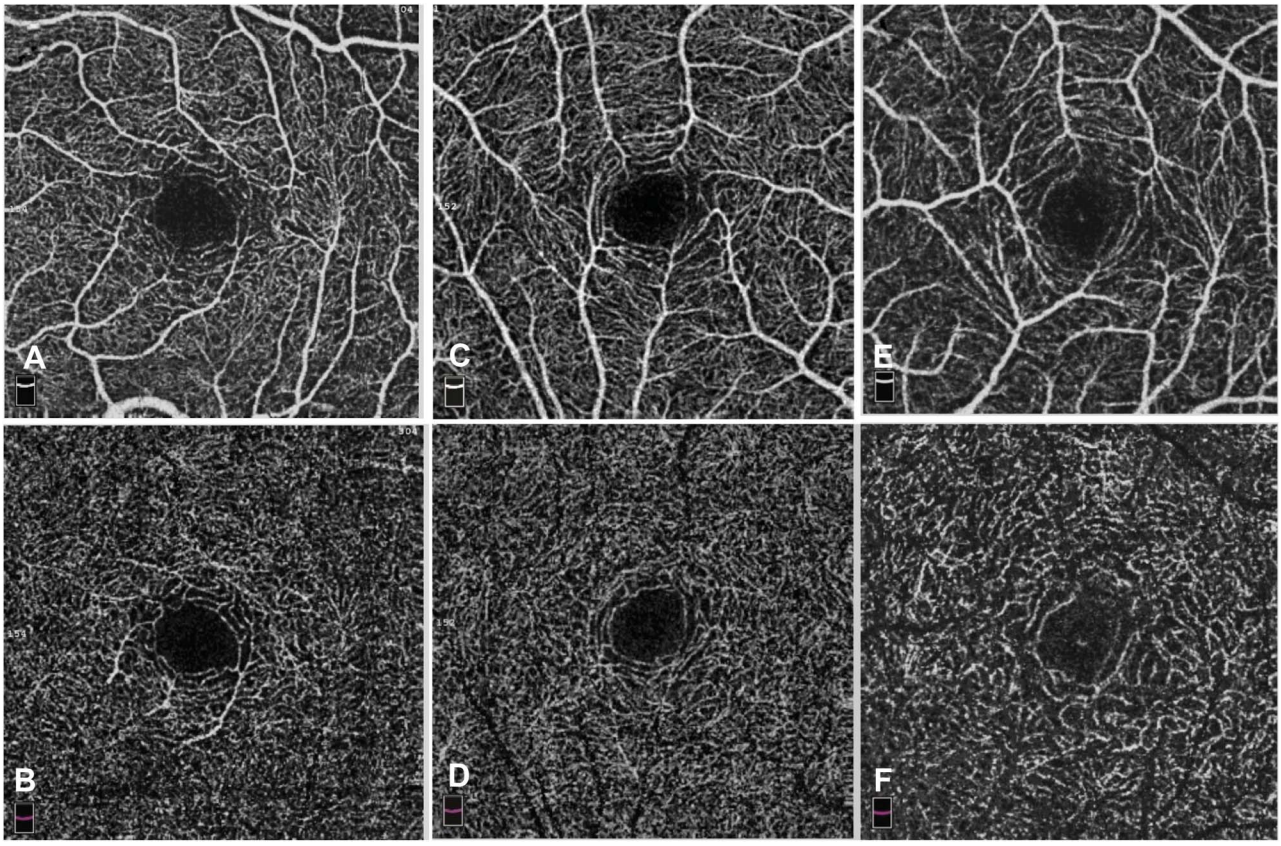


**Fig. 2.** Optical coherence tomography angiography images in control, fellow, and Stage 2B1 Coats disease eyes. Fellow eye differs from Coats disease eye, but not from a control eye. **A** and **B.** Superficial capillary plexus and the (**B**) DCP in a control eye. The FAZ area measured 0.22 $mm^2$. Density of SCP was estimated at 51.8 and density of DCP at 54.7 in the whole images. **C** and **D.** Superficial capillary plexus (**C**) and DCP (**D**) density in a fellow eye of Coats disease was 52.9 in the whole image. FAZ area measured 0.21 $mm^2$. **E** and **F.** Superficial capillary plexus (**C**) and DCP (**D**) in a Stage 2B1 Coats disease eye. The foveal avascular zone area measured 0.27 $mm^2$, density of the SCP was 45.7, and density of the DCP was 34.8.

In this study, decrease in vascular density was observed in both plexuses in more severe stages of Coats disease, suggesting that peripheral Coats disease severity could be correlated with higher capillary loss at the macular level. However, because OCTA was not performed at diagnosis in this cohort, further studies are necessary to confirm this hypothesis. Finally, whether vascular density loss on OCTA is correlated with functional anomalies in Coats disease remains to be investigated. Although OCTA could be helpful at the early stages of the disease to quantitatively evaluate the macular microvasculature, fluorescein angiography remains essential to guide diagnosis, treatment, and follow-up in Coats disease where

Table 2. Comparation of FAZ and Vascular Density in Coats Disease and Fellow Eyes according to stage disease ≤ 2A or 2B1

| | Affected Eyes With ≤ 2A Stage | Fellow Eyes | *P* | Affected Eyes With Stage 2B1 | Fellow Eyes | *P* |
|---|---|---|---|---|---|---|
| No. of eyes | 6 | 6 | | 7 | 7 | |
| FAZ | 0.22 ± 0.1 | 0.15 ± 0.1 | 0.06 | 0.33 ± 0.1 | 0.24 ± 0.1 | 0.09 |
| SCP | | | | | | |
| Whole image | 49.57 ± 1.3 | 49.88 ± 3.7 | 0.69 | 46.49 ± 1.1 | 50.10 ± 2.2 | **0.03** |
| Fovea | 28.30 ± 8.4 | 29.87 ± 10.7 | 0.40 | 27.04 ± 5.8 | 28.00 ± 5.00 | 0.68 |
| DCP | | | | | | |
| Whole image | 47.48 ± 2.9 | 51.87 ± 4.0 | **0.046** | 37.66 ± 5.7 | 52.94 ± 3.8 | **0.01** |
| Fovea | 36.98 ± 7.6 | 43.65 ± 6.5 | **0.03** | 29.54 ± 7.9 | 38.07 ± 7.4 | **0.03** |

Table 3. Comparation of FAZ and Vascular Density by OCTA in Fellow Eyes of Patients and Controls With Coats Disease

| | Fellow Eyes (FE) | Control Eyes (CE) | *P* Mann–Whitney Test |
|---|---|---|---|
| No. of eyes | 34 | 24 | |
| FAZ | 0.22 ± 0.10 | 0.22 ± 0.08 | 0.78 |
| SCP | | | |
| Whole image | 49.73 ± 2.8 | 49.53 ± 3.4 | 0.92 |
| Fovea | 26.86 ± 6.1 | 24.31 ± 6.4 | 0.21 |
| DCP | | | |
| Whole image | 52.47 ± 4.3 | 54.05 ± 3.0 | 0.14 |
| Fovea | 38.90 ± 6.1 | 39.95 ± 6.2 | 0.50 |

vascular lesions are mainly located in the peripheral retina.

Foveal avascular zone and vascular density showed no differences between fellow eyes of patients with Coats disease and controls, confirming the unilateral nature of Coats disease, although close examination of the fellow eye in Coats disease should be performed because contralateral peripheral and central vascular abnormalities have been occasionally reported.[7,13] These lesions have been classified in some reports as bilateral Coats disease, yet they rarely included pathognomonic telangiectasia but rather unspecific vascular anomalies. Moreover, none of these described contralateral vascular lesions matches the classification of Coats disease. Stanga et al[7] have reported 14 fellow eyes disclosing a significant increase in the foveal vessel density of SCP when compared with 14 control eyes. However, affected eyes were not included in the analysis. In our study, we found that vascular density values on SCP are slightly increased at the fovea in both affected and fellow eyes of Coats patients compared with control eyes, but no statistically significant differences were shown. Contrary to Stanga et al, we have not observed differences in FAZ between fellow and control eyes.

The main limitations of this study are its retrospective nature and the small sample size resulting from the rarity of the disease. However, the series presented here is the largest analyzing OCTA in affected and fellow eyes in Coats disease and controls.

In conclusion, FAZ is enlarged and vascular density is decreased in affected eyes with Coats disease, enriching its vascular expressivity spectrum by a cryptic macular phenotype, but no differences are seen between fellow eyes and control eyes, confirming the strict unilateral nature of the disease.

**Key words:** Coats disease, laterality, optical coherence tomography angiography.

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