Choriocapillaris Flow Signal Impairment in Sorsby Fundus Dystrophy

Kristina Hess\textsuperscript{a, b}, Kristin Raming\textsuperscript{a, b}, Martin Gliem\textsuperscript{c}, Peter Charbel Issa\textsuperscript{d, e}, Philipp Herrmann\textsuperscript{a, b}, Frank G. Holz\textsuperscript{a, b}, Maximilian Pfau\textsuperscript{a, f}

\textsuperscript{a}Department of Ophthalmology, University of Bonn, Bonn, Germany; \textsuperscript{b}Center for Rare Diseases Bonn, University of Bonn, Bonn, Germany; \textsuperscript{c}Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; \textsuperscript{d}Oxford Eye Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; \textsuperscript{e}Department of Clinical Neurosciences, Nuffield Laboratory of Ophthalmology, University of Oxford, Oxford, UK; \textsuperscript{f}National Eye Institute, Ophthalmic Genetics and Visual Function Branch, Bethesda, MD, USA

Keywords
Sorsby fundus dystrophy · Choriocapillaris · Bruch’s membrane · Optical coherence tomography angiography · Outcome measures · Clinical trials

Abstract

**Purpose:** The aim of the study was to quantify choriocapillaris (CC) flow alterations in early Sorsby fundus dystrophy (SFD) and to investigate the relationship of the CC flow deficits with the choroidal and outer retinal microstructure.

**Methods:** In this prospective case-control study, 18 eyes of 11 patients with early SFD and 31 eyes of 31 controls without ocular pathology underwent multimodal imaging, including spectral-domain optical coherence tomography (OCT), followed by deep-learning-based layer segmentation. OCT angiography (OCTA) was performed to quantify CC flow deficits (FDs). Differences in CC FD density between SFD patients and controls were determined, and the relationships with choroidal thickness, retinal pigment epithelium-drusen complex (RPEDC) thickness and outer retinal layer thicknesses were analyzed using mixed-model analysis. **Results:** SFD patients exhibited a significantly greater CC FD density than controls (estimate [95% CI]: +20.0%FD [13.3; 26.7], \( p < 0.001 \)) for SFD patients, even when adjusted for age. Square-root transformed choroidal thickness was a structural OCT surrogate of the CC FD density (−2.1%FD per \( \sqrt{\mu m} \), \( p < 0.001 \)), whereas RPEDC thickness was not informative regarding CC FD (\( p = 0.061 \)). The CC FD density was associated with an altered microstructure of the overlying photoreceptors (outer segments, inner segments, and outer nuclear layer thinning of −0.19 \( \mu m \), −0.08 \( \mu m \) and −0.30 \( \mu m \) per %FD, respectively, all \( p < 0.001 \)). **Conclusions:** Patients with early SFD exhibit pronounced abnormalities of CC flow signal on OCTA, which are not limited to areas of sub-RPE deposits seen on OCT imaging. Thus, analysis of the CC flow may enable clinical trials at earlier disease stages in SFD.

Introduction

Bruch’s membrane (BrM) is a pentalayer of extracellular components located between the choriocapillaris (CC) and retinal pigment epithelium (RPE). It constitutes a key interchange barrier for nutrients and waste between the systemic circulation and neuroretina [1]. Alterations of BrM have been identified in a variety of different dis-
ease entities, including age-related macular degeneration (AMD) and – more rarely – primary BrM diseases such as pseudoexanxthoma elasticum and late-onset retinal degeneration [2–4].

Sorsby fundus dystrophy (SFD; OMIM 136900) represents one of the primary BrM diseases. It is an autosomal-dominant inherited retinal disease caused by a mutation in the tissue inhibitor of metalloproteinase 3 (TIMP3) gene coding for the TIMP3 protein [3]. Physiologically, TIMP3 binds to several extracellular membrane-type matrix metalloproteinases, which play an important role in the homeostasis and turnover of extracellular matrix components [5]. TIMP3 can be found in BrM after secretion from the RPE. Mutant TIMP3 protein accumulates at the level of BrM, resulting in thickening, and is thus assumed to cause a diffusion barrier impairing the interchange across the CC-BrM-RPE complex [1, 6].

For disease monitoring, dark adaptometry has been successfully used as a functional measure of the impaired trafficking across an altered BrM in SFD [7, 8], and likewise in AMD [9, 10]. However, psychophysical testing is relatively time-consuming. Regarding imaging biomarkers, quantification of BrM-RPE separation has been proposed in the context of SFD [11]. But the application of this metric as an outcome measure would systematically exclude early-stage SFD patients from clinical trials due to the absence of visible BrM-RPE separation on optical coherence tomography (OCT). However, exactly these patients could potentially benefit the most from a therapeutic intervention in the long run.

Therefore, this study aimed to investigate the impact of a diseased BrM in early stages of SFD on CC flow quantified by OCT angiography (OCTA). Moreover, we aimed to identify correlates of reduced CC flow on widely available structural spectral-domain OCT and to identify structural associations of reduced CC flow and overlying photoreceptor microstructure.

**Methods**

**Patients**

Patients with SFD were recruited between June 2019 and May 2020 from a dedicated clinic for inherited retinal diseases of the Department of Ophthalmology, University Hospital Bonn, Germany. This prospective single-center case-control study adhered to the Declaration of Helsinki. Institutional Review Board approval (Ethikkommission, Medizinische Fakultät, Rheinische Friedrich-Wilhelms Universität Bonn, Germany) and patients’ informed consent was obtained.

Inclusion criteria were the clinical diagnosis of SFD based on funduscopy, OCT, fundus autofluorescence (FAF), and functional testing, in conjunction with the presence of at least one pathogenic mutation in the TIMP3 gene. Furthermore, we only included eyes exhibiting early stages of SFD, defined as eyes without any quiescent or exudative neovascularization, no previous or current anti-VEGF treatment in the study eye and no areas of atrophy larger than half of the optic disc area (approx. 1.28 mm²) in analogy to late AMD defining criteria. Further exclusion criteria were additional retinal pathologies not associated with SFD, refractive errors > ±3 dpt, or ocular media opacities. Healthy eyes from age-similar subjects served as controls.

**OCT Acquisition and Processing**

All subjects and controls underwent a complete ophthalmological examination including refraction and best-corrected visual acuity testing, slit-lamp examination, and – after pupil dilation with 0.5% tropicamide and 2.5% phenylephrine – ophthalmoscopy as well as an extensive imaging protocol. This included spectral-domain OCT (30° × 25° volume scan with 121 B-scans), short-wavelength FAF, near-infrared reflectance images (all acquired with a Spectralis HRA-OCT 2, Heidelberg Engineering, Heidelberg, Germany), and color fundus photography (Zeiss Visucam, Oberkochen, Germany or Eidon confocal fundus camera, Centervue, Padua, Italy).

The spectral-domain OCT data were segmented using a customized, previously validated deep-learning pipeline [12]. Thickness maps for the choroid, RPE-drusen complex (RPEDC, ranging from BrM to the upper boundary of the RPE or subretinal drusenoid deposits), photoreceptor outer segments (OS), and inner segments (IS), as well as the outer nuclear layer (ONL), were generated [13]. The thicknesses of these layers were extracted for each ETDRS-grid subfield centered on the fovea.

**OCTA Acquisition and Processing**

OCTA was performed using a swept-source OCT device (6 × 6 mm OCTA scan, PLEX Elite 9000; Carl Zeiss Meditec AG, Jena, Germany). For OCTA images, the automated segmentation algorithm of the device was initially applied, followed by manual correction of the BrM (“RPE fit”) segmentation as needed. A 16-μm thick CC slab (+15 μm to +31 μm below “RPE fit”) was exported with the pre-set option of decorrelation tail artifacts removal [14].

OCTA images with severe artifacts (e.g., due to pronounced unstable fixation) or marked shadowing (e.g., floaters) were excluded from the analysis. First, all images were imported into FIJI (version 2.0.0, National Institutes of Health, Bethesda, MD, USA). We performed compensation of shadowing artifacts as previously described [15, 16]. Briefly, the CC-slab image was downsampled to 512 × 512 pixels from originally 1,024 × 1,024 pixels. Then the OCTA images were multiplied with the inverted, smoothed structural image (Gaussian smoothing with a sigma of 3 pixels) to compensate for shadowing effects.

Subsequently, automatic local thresholding was performed with the Phansalkar method using a radius of 4 (reported in the main manuscript), and 8 pixels (reported in the supplement), corresponding to approximately 50 and 100 μm, respectively, to extract flow signal deficits (FDs) as proposed previously [17–19]. Last, an ETDRS-grid was centered on the fovea to extract the density of FDs of the outer, inner, and central ETDRS subfields.

The CC directly under large superficial retinal vessels was excluded from the analysis as previously described to exclude severe shadowing and projection artifacts [20].
ORCC image, which shows superficial vessels, was imported to FIJI. The MaxEntropy threshold was applied to visualize only superficial retinal vessels of first and second-order (Fig. 1). The identified areas were excluded from the analysis. The density was calculated with the remaining area (after exclusion of the regions with overlying first and second-order retinal vessels) of the respective ETDRS subfields. ETDRS subfields with any atrophic areas as seen on OCT imaging and FAF were excluded from the analysis.

Statistical Analyses
The statistical analysis was performed using the software environment R (version 3.2.0; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were described using the mean and standard deviation, and categorical variables were analyzed using frequency tables. A p value < 0.05 was considered significant. Mixed-effects models with patient ID as random effects term were used to account for the hierarchical nature of the data (eyes nested in patients as random effects term).

First, we investigated the association of age and group (SFD patients vs. control) as the explanatory variables with the FD density as the dependent variable. Subsequently, we examined the association of structural indicators (choroidal thickness or RPEDC thickness), the position of the ETDRS subfield, and an interaction term between these variables as explanatory variables and with FD as the dependent variable. Last, the association of FD density (this time as explanatory variable) with photoreceptor laminae integrity (e.g., ONL, IS, and OS thickness as dependent variables) was examined.

Results

Cohort Characteristics
Eighteen eyes from 11 patients (47.3 ± 11.9 years, range 28–61 years, 7 female) with a median [IQR] best-corrected visual acuity of 0.0 logMAR [−0.1; 0.1] and 31 eyes from 31 age-similar controls (52.4 ± 19.4 years, range 21–82 years, 13 female) were included in this study. A total of 5 ETDRS subfields from 3 eyes were excluded from the analysis due to small atrophic foci.

Four eyes of 2 patients did not show any fundus alterations on multimodal imaging, while 14 eyes from 9 patients showed soft drusen and irregularities of the photoreceptor layers (ONL thinning, hyporeflective outer, and inner segments). Five eyes of 3 patients additionally exhibited reticular pseudodrusen.
Choriocapillaris FDs

According to mixed-model analysis, the diagnosis SFD (estimate [95% CI] +20.0%FD [13.3; 26.7], p < 0.001 for SFD patients), and age (+0.25%FD per year [0.08; 0.42], p = 0.004) were significantly associated with the CC FD density (Table 1). The highest FD density was found in the inner temporal, inner inferior, and inner superior ETDRS subfields (online supplementary Figure S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000520931). An interaction term between SFD and age (e.g., indicating a steeper increase in CC FDs in patients compared to controls) did not further improve the model goodness-of-fit, although such a trend could be surmised in Figure 2.

Structural Indicators of CC FDs

Choroidal thickness was significantly lower in patients compared to controls (age-corrected estimate [95% CI] −70.7 µm [−126.3; −15.1], p = 0.013 for SFD patients, Fig. 3a). Moreover, choroidal thickness showed a similar spatial pattern among all subjects with the thinnest cho-roid in the outer nasal ETDRS subfield.

Square-root transformed choroidal thickness and the CC FD density exhibited a significant association (slope estimate [95% CI] −2.11%FD per √µm [−3.08; −1.13], p < 0.001, Fig. 3b). The slope for the association varied in dependence of the ETDRS subfield. The association of CC FDs with choroidal thickness was curvilinear (Fig. 3b), but followed a linear trend after square-root transformation of the choroidal thickness. This means, there was only a minor association of CC FDs and choroidal thickness among eyes with normal to high choroidal thicknesses. But among eyes with thin choroidal thicknesses, the association of CC FDs and choroidal thickness was relatively steeper. In contrast, the RPEDC thickness was not significantly associated with the CC FD density (p = 0.061), although it was significantly different between the control subjects and SFD patients (estimate [95% CI] +3.74 μm [1.10; 6.83], p = 0.006 for SFD patients, Fig. 3).

Association with Overlying Photoreceptor Integrity

The thicknesses of the three OCT laminae corresponding to the retinal photoreceptors were all inversely associated with the underlying CC FD density (i.e., thinning of these layers was evident in eyes with a greater FD density). Specifically, OS thickness was associated with a univariate estimate of −0.19 μm per %FD (−0.22; −0.16; p < 0.001). IS thickness showed a comparable association with −0.08 μm per %FD (−0.09; −0.06; p < 0.001), as well as ONL thickness (−0.30 μm per %FD [−0.40; −0.19], p < 0.001). There was no significant association of the FD density

Table 1. Final multivariable mixed-effects model for CC flow deficits

| Predictors       | Estimates, % CI | p value |
|------------------|-----------------|---------|
| Intercept        | 18.96 9.39; 28.52 | <0.001  |
| Group (patient)  | 20.02 13.34; 26.71 | <0.001  |
| Age, per year    | 0.25 0.08; 0.42  | 0.004   |
| SD (intercept)   | 4.43            |         |
| SD (intercept)   | 8.47            |         |
| SD (observations)| 2.87            |         |
| Random effects   |                |         |
| σ²               | 67.99           |         |
| τ₀₀ eid:id       | 19.58           |         |
| τ₀₀ id           | 71.74           |         |
| ICC              | 0.57            |         |
| N_eid            | 49              |         |
| N_id             | 42              |         |
| Observations     | 435             |         |
| Marginal R²/Conditional R² | 0.375/0.733 |         |
with the inner retinal thickness ($-0.14 \mu m$ per %FD, $p = 0.150$, Fig. 4). Clinical examples of patients in different disease stages are shown in Figure 5.

**Comparison across OCTA Processing Methods**

When using the pre-set slab of the device (+29 $\mu m$ to +49 $\mu m$ below RPE fit), the results were congruent, showing the same significant differences between the groups (however, with different absolute values). Further, when processing the images with a Phansalkar radius of 8 pixels, the results – regarding the difference between SFD patients and controls – were again consistent (online suppl. Table 1).

**Discussion**

To the best of our knowledge, this is the first study investigating CC alterations using OCTA in patients with SFD. Our findings demonstrate a significantly in-
creased CC FD density indicative of impaired CC flow in patients with SFD. This observation was evident even when adjusting for age. Moreover, an increased CC FD density is associated with thinning of the photoreceptor layers on OCT. Our findings highlight that SFD-associated alterations of BrM result (directly or indirectly) in the degeneration of the CC and outer retina.

**Fig. 4.** Association of CC flow deficit and structural alterations. All three outer retinal layer thicknesses representing photoreceptor integrity (y-axis, OS shown in panel (a), IS shown in panel (b), ONL shown in panel (c) show marked thinning with increasing FD density (x-axis). Every data point represents one ETDRS-grid sub-field of a patient or control. The analysis accounted for repeated measurements within each patient. CC, choriocapillaris; OS, photoreceptor outer segments; IS, photoreceptor inner segments; ONL, outer nuclear layer, FD, flow signal deficit.

Color version available online
The increased CC FD density was present in eyes with no or only a mild phenotypic manifestation on color fundus photography, indicating that CC changes may represent an early structural marker for BrM abnormalities. Possibly, the previously observed multilobular hypofluorescence in indocyanine green angiography in the central retina of patients with SFD without visible fundus changes reflect the same underlying loss of CC perfusion (cf. Fig. 7 in reference [21]). In principle, this is compatible with the histopathological description of extensive CC loss in SFD [22]; however, CC density for clinically unremarkable retinal regions has not yet been reported. In other BrM diseases like AMD, CC alterations have been demonstrated even in regions without overlying retinal atrophy [23, 24]. In pseudo-xanthoma elasticum, characteristic CC alterations on late-phase fluorescein and indocyanine green angiography are pathognomonic and helpful to establish the underlying diagnosis [25].

Biologically, the CC FDs in SFD are most likely a secondary phenomenon, given that TIMP3 is primarily expressed by the RPE [26]. However, it is unclear whether the CC flow deficit is merely a response to an altered RPE (i.e., reduced secretion of pro-angiogenic factors), or...
whether an interchange barrier between the RPE and CC drives subsequent CC degeneration [22, 26, 27].

Overall, FD density exhibited a wider range in SFD patients than controls, indicating inter-individual differences due to a multifactorial process. Higher variabilities in the group of patients might occur due to additional non-SFD related systemic risk factors (e.g., hypertension), different severities of specific TIMP3 mutations, and/or potential unquantified impacts of SFD at the level of the CC and choroid.

In our study, CC FDs were significantly correlated with choroidal thickness. An increased CC FD density was pronounced for choroidal thicknesses of 200 μm or less. Accordingly, the choroidal thickness may serve as a surrogate for sub-RPE/CC perfusion. Previous studies in patients with BrM diseases, including SFD and pseudoxanthomaa elasticum, indicated an inverse association between disease severity and choroidal thickness [28, 29]. In contrast, RPEDC thickness as a measure of the amorphous deposits found between the basement membrane of the RPE and the inner collagenous layer of BrM was not associated with the CC FD density. Estimating disease severity based on RPEDC thickening, as recently suggested for SFD and autosomal-dominant drusen [11], may thus be unsuitable for quantifying the disease severity in early stages. Moreover, CC degeneration appears to be more widespread than (visible) alterations at the level of the RPEDC.

Last, our findings indicate that an impaired CC-BrM complex is associated with degeneration of the overlying photoreceptors. Specifically, we showed a negative correlation of the CC FD density with the overlying ONL, IS, and OS thicknesses. This thinning of the outer retinal laminae most likely represents downstream degeneration of photoreceptors due to RPE dysfunction and possibly chronic local deprivation of vitamin A [7, 30].

Early CC changes highlight that efficacy of therapeutic interventions may be subject to a time window. It was previously demonstrated in SFD and other diseases of BrM such as AMD and pseudoxanthoma elasticum that oral intake of high dosages of vitamin A might improve rod-mediated dark adaptation [7, 31, 32]. Given the herein observed loss of CC with age and the associated microstructural alterations of photoreceptors, earlier rather than later treatment may be warranted. Otherwise, the residual CC density and photoreceptor degeneration may limit the therapeutic efficacy and, thus, the visual outcome of a vitamin A supplementation. Similar consideration would apply to emerging therapeutic strategies targeting BrM, including subthreshold laser therapy to induce RPE matrix metalloproteinase expression [33] and apolipoprotein A-I mimetics for lipid clearance [34].

Limitations of this study include the relatively small sample size, which constitutes a common challenge in rare diseases. The variability of choroidal thickness in the normal population has been addressed by adjusting for age and excluding patients with higher refractive errors. Quantitative analysis of CC FDs is affected by the slab selection and thresholding/binarization approach [33, 34]. Thus, we evaluated a slab that is thinner and closer to RPE-fit than the proprietary algorithm in addition to the pre-set slab of the PlexElite and considered different radii for Phansalkar thresholding [15]. Although different slab definitions may have altered the absolute values, the differences between patients and controls remained statistically significant with all 3 methods. CC FD data were summarized using the well-established ETDRS-grid. Other patterns with smaller regions-of-interest could potentially highlight more subtle relationships between outer retinal integrity and CC.

Conclusion

Our findings indicate an association between changes in the BrM-RPE complex and rarefication of CC flow, associated with a phenotype with various similarities to AMD. This adds evidence for interdependent roles within the CC-BrM-RPE complex and underscores the importance of BrM and the choroid as pathogenic factors for disease development and progression of diseases involving BrM abnormalities, including AMD.

Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board of the University Hospitals Bonn, Approval Number: 316/11. Informed consent was obtained by all participants.

Conflict of Interest Statement

K.R., M.P., and K.H.: Heidelberg Engineering: nonfinancial support, Carl Zeiss MedicTec AG: nonfinancial support, CenterVue: nonfinancial support. K.H.: financial support for presentations held for Novartis GmbH. M.G.: employee of Boehringer Ingelheim, Ingelheim am Rhein, Germany equity owner of F. Hoffmann-La Roche Ltd. Basel, Switzerland. P.C.I.: consultant for Gyroscope and Inozyme, received research support from Heidelberg Engineering and travel support from Bayer; principle inves-
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Author Contributions

K.H. and K.R. contributed to data assessment; K.H. and M.P. contributed to data processing, statistical analysis, and manuscript preparation; M.P. and F.G.H. contributed to supervision; P.C.I., M.G., and P.H. contributed to review of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary Material files. Further inquiries can be directed to the corresponding author.

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