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RETINAL DISORDERS

Characterisation of reticular pseudodrusen and their central target aspect in multi-spectral, confocal scanning laser ophthalmoscopy

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Abstract
Background To analyse reticular pseudodrusen (RPD) in patients with age-related macular degeneration (AMD) using multi-spectral (MS), confocal scanning laser ophthalmoscopy (cSLO).
Methods cSLO images (blue fundus autofluorescence [FAF; exc., λ=488; em., λ=500–700 nm], near-infrared reflectance [IR; λ=820 nm], MS [blue reflectance (BR) λ=488 nm, green reflectance (GR) λ=515 nm, IR λ=820 nm], as well as colour fundus photographs (CFP) were taken of 200 eyes from 100 AMD patients suspected to show RPD on the basis of funduscopy or previous fundus imaging. FAF and IR images were graded by two independent readers. If both readers concordantly confirmed the presence of RPD in both modalities, eyes were subsequently also graded for RPD in MS, BR, GR, green-blue enhanced mode (GBE), and CFP. Besides, FAF, IR, and MS images were evaluated for the presence of a target aspect, which represents a common feature of RPD lesions.
Results The presence of RPD was confirmed using FAF and IR images by both readers in 130 eyes of 76 patients. In those eyes, both readers concordantly diagnosed RPD in MS images in 124 (95.4 %) eyes (BR: 52 [40.0 %], GR: 63 [48.5 %], GBE: 101 [77.7 %], CF: 27 [20.8 %]). Cohen kappa statistics revealed excellent inter-observer agreement for MS (0.95) and GBE (0.85), substantial agreement for BR (0.75), GR (0.78), and moderate agreement for CFP (0.59). A target aspect within RPD lesions was detected in 45 of 130 (35.0 %) included eyes using FAF and IR. The presence of a target aspect improved the recognition of RPD lesions in all modalities. If a target aspect was present, RPD were diagnosed in 45 eyes (100 %) using MS (GBE: 42 eyes [93.3 %], BR: 30 eyes [66.7 %], GR: 37 eyes [82.2 %], CFP: 17 eyes [37.8 %]). Using MS cSLO, a target aspect could be identified in 75 of 130 (57.7 %) included eyes.
Conclusions MS cSLO imaging is equivalent to FAF and IR in identifying RPD in AMD patients. Higher identification rates in BR and GR of those RPD lesions featuring a target aspect confirm the current hypothesis of RPD localisation and its progression further into the photoreceptor layers. MS seems to be more sensitive in identifying a central target aspect in RPD lesions compared to blue FAF and IR.

Keywords Age-related macular degeneration · Reticular drusen · Reticular pseudodrusen · Subretinal drusenoid deposits · Confocal scanning laser ophthalmoscopy · Multi-spectral confocal scanning laser ophthalmoscopy · Multi-colour confocal scanning laser ophthalmoscopy fundus autofluorescence · Infrared reflectance · Green reflectance · Blue reflectance

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Introduction

Reticular pseudodrusen (RPD) have been recognised as an additional phenotypic characteristic frequently observed in patients with age-related macular degeneration (AMD) [1–5]. Several studies have suggested that the prevalence of RPD is associated with a high risk of disease progression to late forms of AMD [6–8]. Additionally, Ueda-Arakawa and colleagues recently confirmed the connection between the ARMS2 risk allele and RPD in a Japanese population [9].

Given the growing importance of this AMD phenotype, reliant and exact imaging of RPD has become an important issue clinically, as well as regarding the further understanding of RPD pathogenesis and the design of future interventional trials in dry AMD. Unlike conventional soft and hard drusen that are readily seen in colour fundus photography (CFP), detection of RPD in CFP turned out to be unreliable [4]. With the development of multi-modal, high-resolution imaging, the identification of RPD has improved significantly. Recent studies have suggested that fundus autofluorescence (FAF), near-infrared reflectance (IR) imaging, and spectral-domain optical coherence tomography (SD-OCT) tremendously facilitate the identification of RPD and represent the most sensitive imaging modalities at present [2, 4, 10, 11].

Multi-spectral (MS) confocal scanning laser ophthalmoscopy (cSLO) is a novel imaging modality that combines three colour-selective laser images: IR, green reflectance (GR), and blue reflectance (BR) (MultiColour ™; Heidelberg Engineering, Heidelberg, Germany). The information of three confocal reflectance images is merged into one multi-colour cSLO image. As laser light of different wavelengths penetrates at different depths in the retinal tissue, structures of different retinal layers can be viewed in one resulting multi-colour image. Recently, Querques et al. firstly described the characteristics of RPD lesions in MS cSLO imaging [12]. Based on these findings, the purpose of our study was to quantify, in a larger patient collective, the actual ability of this new MS cSLO mode to visualise RPD lesions compared to the established modalities FAF, IR, and CFP. Furthermore, we quantitatively analysed the ability of MS cSLO imaging to identify the central target aspect that represents an important feature of RPD lesions [13].

Methods

Population

Participants were recruited from the medical retina clinic of the Department of Ophthalmology at the University of Muenster Medical Center. Patients were enrolled and imaging protocol was performed if funduscopy or previous retinal imaging in the past brought up the suspicion of RPD being present in one or both eyes. RPD are sometimes hard to identify due to media opacities, and the reticular pattern may appear subtle and difficult to distinguish from other retinal alterations when using only one imaging modality. Thus, all eyes were graded by two independent graders for the presence of RPD in FAF (Fig. 1b) and IR (Fig. 1c). Eyes were included in the further evaluation of MS cSLO only if both readers concordantly diagnosed RPD in both modalities. Identification of characteristic, yet sometimes subtle changes associated with RPD

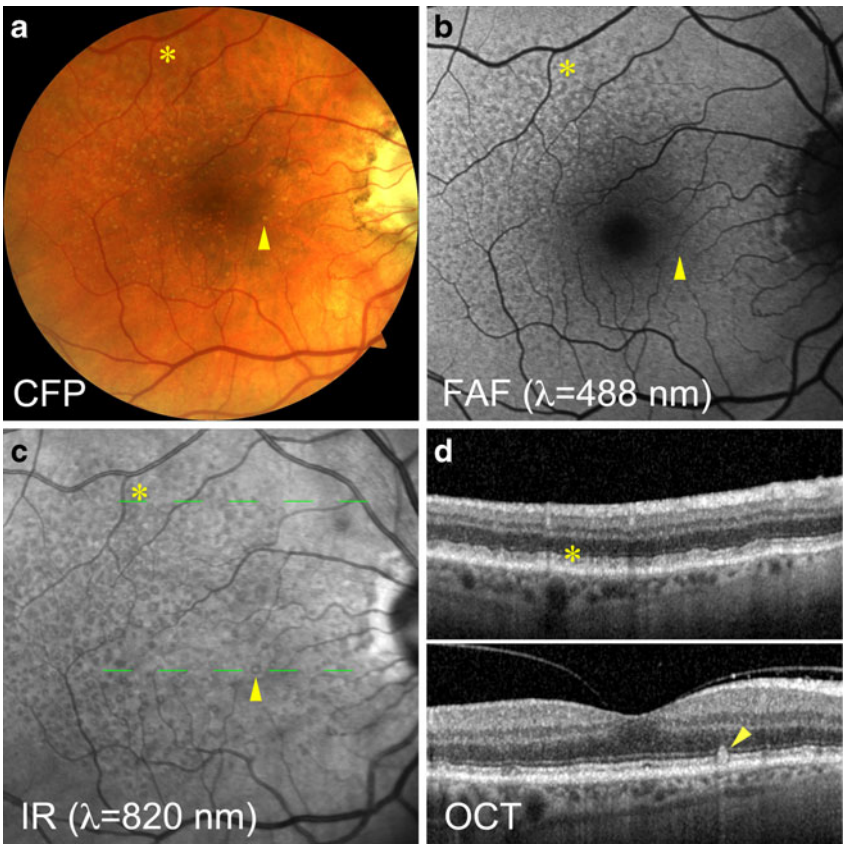

Fig. 1 **a-d** Multi-modal imaging in a patient with reticular pseudodrusen (RPD). Arrow heads mark an exemplary RPD lesion exhibiting a central target aspect within the lesion. Asterisks demonstrate an area affected by RPD lesions lacking central targets. **a** Colour fundus photography displays RPD as yellowish-pale lesions that may have a more punctate appearance closer to the fovea. **b** Confocal scanning laser ophthalmoscopy (cSLO) fundus autofluorescence (FAF) showing a hypofluorescent reticular pattern of RPD. **c** cSLO near infrared reflectance (IR) showing hyporeflective lesions. Green lines indicate the position of spectral-domain optical coherence tomography (SD-OCT) scans, shown aside. **d** SD-OCT scans show RPD of different stages; above lesions corresponding to stage 1 and stage 2, and below an RPD lesion corresponding to stage 3

requires good quality multimodal imaging and careful analysis. Nevertheless, retinal alterations such as soft or hard drusen may interfere with RPD detection despite sufficient image quality. If the two readers disagreed or if insufficient image quality did not allow a reliable grading of RPD presence, the eyes were excluded. Informed and written consent was obtained from all patients for imaging beyond routine.

Imaging

MS cSLO (Fig. 2a) is a novel imaging modality that combines three colour-selective laser images: IR at a wavelength of λ= 820 nm (Fig. 1c), GR at λ=515 nm (Fig. 2d) and BR at λ= 488 nm (Fig. 2c). The information of three cSLO reflectance images is merged into one MS image. Structures of different retinal layers imaged in three different reflectance images can be viewed and evaluated at the same time. Besides the standard composition of the three wavelengths in MS cSLO, it is possible to change the composition of the different wavelengths, i.e. the green-blue-enhanced mode (GBE), which emphasises the blue and green in the composition of the three wavelengths (Fig. 2b).

All patients underwent cSLO retinal imaging (Spectralis; Heidelberg Engineering, Heidelberg, Germany) including acquisition of IR (λ=820 nm), FAF (exc., λ=488 nm; em., λ= 500–700 nm), MS, and CFP (Zeiss FF450, Carl Zeiss Meditech, Berlin, Germany) (Fig. 1a) on the same day (see Table 1). cSLO imaging was performed with a minimum resolution of 768×768 pixels. The field of view was set at 30°×30° and centred on the macula. cSLO imaging was performed prior to an optional fluorescein angiography. For the current analysis, all recorded cSLO and fundus camera data were retrospectively evaluated for the presence of RPD. Additional data included demographics (age and gender) and stage of AMD in both eyes. AMD stage was defined as soft/hard drusen, geographic atrophy (GA) or choroidal neovascularisation (CNV) based on cSLO FAF and IR, and SD-OCT imaging. If CNV was suspected, fluorescence angiography was subsequently performed.

Eligible patients were listed in a standard spread sheet (Excel; Microsoft Inc., Redmond, WA). Corresponding imaging data were evaluated by two independent readers for definitive presence of RPD in IR, FAF, MS, BR, GR, GBE and CFP. Separately for each modality, eyes were classified as 'RPD present' only if both readers concordantly recognised the characteristic alterations of RPD in the corresponding modality, as described below. Furthermore, IR, FAF and MS cSLO images of RPD-affected eyes were evaluated for the presence of a target aspect in the centre of the lesions, as described by Querques et al [12, 13]. RPD-affected eyes were

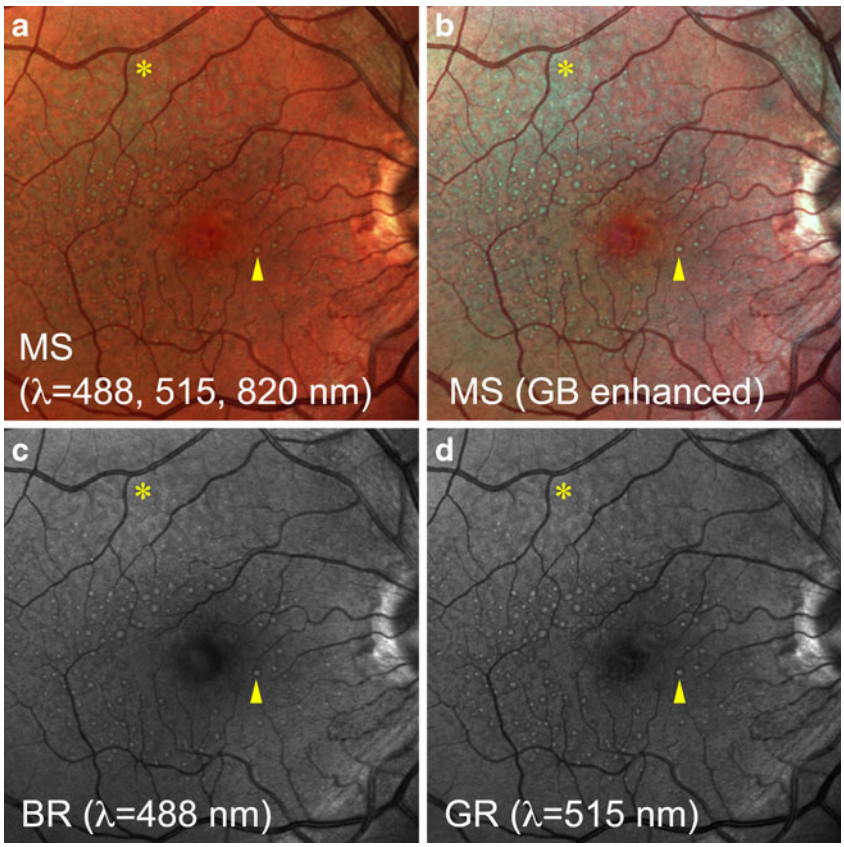

Fig. 2 **a-d** Multi-spectral (MS) confocal scanning laser ophthalmoscopy (cSLO) (**a**) MS cSLO shows greyish-yellowish lesions. If a target aspect is present, the centres of reticular pseudodrusen (RPD) show a round, yellowish core. Note that the target aspect in the centre of RPD lesions is revealed more clearly and distinctly than in corresponding IR and FAF images in Fig. 1. **b** The green-blue-enhanced mode displays rather greyish-greenish lesions with an accordingly greenish core at the centre of those RPD lesions that feature a target appearance. **c** Blue reflectance image (**d**) Green reflectance image

Table 1 Overview of the different imaging modalities employed

Abbreviation	Imaging modality	Wavelength [nm]
IR	Near infrared reflectance	820
FAF	Fundus autofluorescence	exc. 488; em. 500–700
BR	Blue reflectance	488
GR	Green reflectance	515
GBE	Green-blue-enhanced	488, 515, 820 (IR underemphasised)
MS	Multispectral	488, 515, 820
CFP	Colour fundus photography	-

regarded as displaying a target aspect if both readers concordantly recognised the characteristic alterations in at least three separate RPD lesions in the corresponding modality.

Using automated eye tracking and image alignment based on cSLO images, the software allowed the averaging of a variable number of single images in real time (ART [Automatic Real Time] Module; Heidelberg Engineering, Heidelberg, Germany). Scans were saved for evaluation after 50 frames had been averaged using the automatic averaging and eye-tracking feature of the Spectralis device. CFP was performed using a 30° lens focused on the macula. Photographs were viewed in the Zeiss Visupac 4.2 software (Carl Zeiss Meditech, Berlin, Germany). Heidelberg Eye Explorer software 1.6.4.0 (Heidelberg Engineering, Heidelberg, Germany) was used for viewing cSLO images.

Definitions

RPD were defined as showing characteristic changes in the different modalities, as described below. Terminology of this entity has not been consistent in the past. In this study, we use the term "reticular pseudodrusen" according to the nomenclature by Arnold et al [1].

For FAF imaging, RPD were defined as a regular network of uniform round or oval shaped irregularities with a diameter ranging between 50 and 400 μm. Furthermore, lesions were characterised by a decreased FAF signal surrounded by mildly increased intensities [4, 14]. In IR imaging, RPD were identified as a pattern-like grouping of lesions varying in size with decreased reflectivity. For larger and more centrally located lesions, these images may be accompanied by a halo-like appearance exhibiting an increased IR signal in the centre, surrounded by a decreased intensity corresponding to RPD appearance in FAF [4, 14]. Querques et al. described this characteristic as a "target" aspect of RPD lesions in IR and FAF [13]. The morphologic explanation of this target appearance may be, according to Querques, an interruption of the inner segment/outer segment (IS/OS) boundary of the photoreceptors, as well as the presence of central lipofuscin-like material. In MS cSLO imaging, RPD appear as a network of greyish-yellowish lesions. If a target aspect is present, centres of RPD lesions show a round, yellowish core [12]. The GBE mode displays rather greyish-greenish lesions with an accordingly greenish core at the centre of those RPD lesions featuring a target appearance. RPD appear as a network of distinctive, irregular, hyperreflective lesions in GR and BR images, exhibiting an increased signal that may be surrounded by a decreased intensity if a target aspect is present. In CFP, RPD can be characterised as yellowish-pale or pale light, ill-defined networks of broad, interlacing ribbons that may appear slightly whiter or greyish compared with soft drusen, and may have a more punctate appearance closer to the fovea [4, 11] (Figs. 1 and 2).

Statistical methods

Data were compiled and analysed with a standard spreadsheet program (Excel; Microsoft Inc). Unweighted Cohen's kappa statistics were applied to assess for inter-observer reliability [15].

Results

Two hundred eyes from 100 AMD patients who were suspected to show RPD were included. In 130 eyes of 76 patients (53 females and 23 males, age 81.0±6.4 years), both FAF and IR images were concordantly graded by both independent readers as showing distinct RPD and were included in further evaluation. Besides RPD, 52 eyes (40 %) showed conventional soft or hard drusen; 41 eyes (31.5 %) were diagnosed as having a choroidal neovascularisation (CNV), and 37 eyes (28.5 %) presented with geographic atrophy due to AMD.

Using MS cSLO imaging, RPD were concordantly diagnosed in 124 (95.4 %) eyes. The GBE mode showed definite characteristic alterations in 101 (77.7 %) eyes. Single BR and GR images revealed the presence of RPD in 52 (40.0 %) and 63 (48.5 %) eyes, respectively. CFP showed distinct RPD lesions in 27 (20.8 %) cases (Fig. 3a).

For the analysis with each cSLO imaging modality, there was very good inter-observer agreement for MS (kappa value 0.95) and GBE (0.85), substantial agreement for both BR (0.75) and GR (0.78), and moderate inter-observer agreement for CFP (0.59) [15].

A target aspect in all RPD-affected eyes could initially be identified in 45 (35.0 %) eyes with either FAF or IR imaging. The presence of a target aspect improved recognition of RPD lesions in all modalities. If a target aspect was present, RPD were diagnosed in 45 eyes (100 %) using MS (GBE: 42 eyes [93.3 %], BR: 30 eyes [66.7 %], GR: 37 eyes [82.2 %], CFP: 17 eyes [37.8 %]) (Fig. 3b).

In comparison to IR and FAF, where the target aspect was recognised in only 45 eyes, screening for a target aspect in MS cSLO images showed a positive result in 75 eyes (57.7 %).

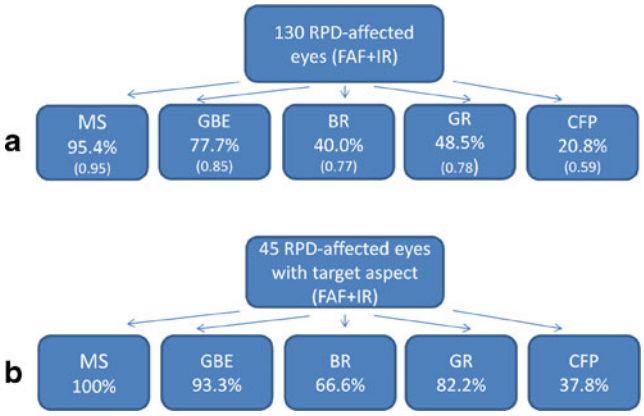

Fig. 3 a-b Flow diagram showing the prevalence of reticular pseudodrusen (RPD) in the study population by both confocal scanning laser ophthalmoscopy (cSLO) and fundus colour photography. FAF: cSLO fundus autofluorescence; IR: cSLO near-infrared reflectance; MS: cSLO multi-spectral; GBE: cSLO green-blue-enhanced; BR: cSLO blue reflectance; GR: cSLO green reflectance; CFP: colour fundus photography. **a** shows the results of RPD identification in the different modalities, in all included eyes that were initially graded as RPD-affected in both FAF and IR. Kappa values of inter-observer agreement between both readers are given in parentheses for each modality. **b** Of all 130 included RPD-affected eyes, 45 eyes were characterised as showing a target aspect. The chart shows the results of RPD identification in the different modalities in those eyes that showed a target aspect in either IR or FAF

Discussion

Laser light of different wavelengths penetrates to different depths into the retinal tissue. Accordingly, cSLO imaging using different wavelengths reveals details from different retinal layers. Most of the absorption of the blue light takes place in the inner part of the retina, while the green wavelengths penetrate a little deeper, showing elements like blood vessels and exudates, Most of the information of the infrared image originates from the outer retinal layers and the choroids (Fig. 4) [14].

Querques et al. firstly described the morphology of RPD lesions in MS cSLO imaging and found that lesions as well as their central target aspect appeared much more visible on IR and GR than in BR, which is in accordance with our data, suggesting that the morphologic substrate of RPD is localised between the RPE and the IS/OS boundary [12]. Additionally, we wanted to systematically determine the ability of the new MS cSLO mode to visualise RPD lesions compared to the established modalities in a larger patient collective and to evaluate the ability of MS cSLO imaging to identify the central target aspect.

In this study, MS cSLO imaging showed a high sensitivity and excellent inter-observer agreement in RPD detection based on previous lesion identification using FAF and IR, which may qualify MS cSLO as equivalent to FAF and IR in RPD detection. As IR at a wavelength of λ=820 nm is also included in the composition of MS cSLO imaging, this result may seem obvious. However, it proves that simultaneous IR, BR and GR imaging do not interfere in the visualisation of RPD lesions.

Inferior identification rates and inferior inter-observer agreement for BR and CFP in detecting RPD in comparison to FAF and IR are in accordance with previously reported data [4]. So far, RPD have not been systematically evaluated using GR; thus, a comparison with previous reports is not possible. In our evaluation, GR shows slightly better results in RPD

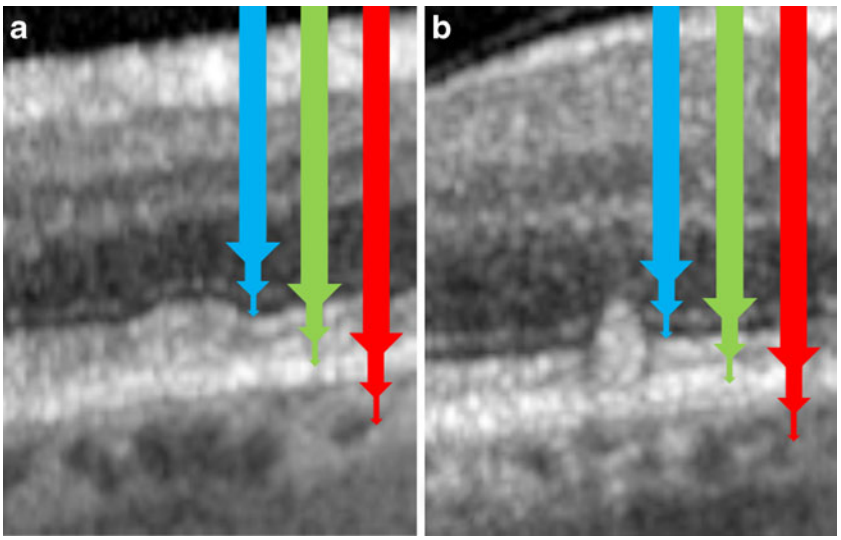

Fig. 4 a-b This figure shall exemplify schematically the penetration depth of light beams into the retinal tissue, dependent on their wavelengths. Illustration shows a high magnification of a spectral-domain optical coherence tomography scan depicting a reticular pseudodrusen lesion; stage two in **a**, and stage three in **b**. This simplified view of the penetration depth of different laser wavelengths shall reflect the results of RPD identification. Red arrow encodes for infrared reflectance at a wavelength of λ=820 nm, green for green reflectance at λ=515 nm and blue for blue reflectance at λ=488 nm

identification as well as inter-observer agreement compared to BR, which may be due to deeper penetration of green wavelengths. As described above, in the GBE mode, the blue and green wavelengths are accentuated in the composition of the three reflectance images at the cost of part of the infrared wavelength. The slightly inferior results for the GBE mode compared to regular MS cSLO in RPD identification may underline the importance of the infrared wavelength in detecting RPD lesions.

The fact that RPD can be detected in only nearly half of the eyes using BR and GR images may be due to the penetration depth of blue and green wavelengths. BR and GR may only be able to detect those RPD lesions that reach high enough into the retinal layers (Fig. 3)[14].

The reason for the appearance of the so-called target aspect, the isofluorescent centre of some lesions, has not been found yet. No histologic data exists so far providing an insight into the biologic substrate of centrally isofluorescent lesions. Possibly, the hyporeflective annulus might consist of deflected photoreceptors while the isoreflective centre consists of unphagocytosed photoreceptor outer segments. The target aspect is a consistent finding in patients with RPD. In our included patients, a target aspect within RPD lesions was detected in 35.0 % using FAF and IR, comparable to Querques et al. who report a prevalence of RPD stage 3 and 4 of 25.6 %, and an IS/OS boundary disruption of 34.6 % in all observed eyes [16].

Based on the theory by Querques et al., the target aspect can be recognised if the lesion has broken through the IS/OS boundary, i.e. if it has reached a certain height [13]. This theory can be supported by the high positive correlation between the presence of a target aspect in the centre of RPD lesions in IR and FAF on one hand, and RPD detection in BR and GR on the other hand. In other words, if a target aspect is present, it is more likely to detect RPD lesions in BR and GR. Querques and colleagues interpreted the target aspect as an interruption of the IS/OS boundary of the photoreceptors during the buildup of RPD lesions further into the photoreceptor layers, which correlates to RPD stage 3, according to the classification by Zweifel et al. and Querques et al [10, 13, 16]. This would also explain the absence of visualisation of the core in RPD lesions stage 1 and 2. The isoreflective and isoautofluorescent appearance surrounded by halos of reduced reflectance/autofluorescence in IR and FAF, respectively, may suggest the presence of centrally-located debris accumulating between the RPE and the outer plexiform layer [13]. Similarly, a hyperreflective signal in IR and a hyperautofluorescent signal in FAF, respectively, had been previously described for soft drusen due to lipoprotein-derived debris and RPE alterations [17]. In a study on FAF imaging in large, soft drusen, Landa et al. suggested that hypo- as well as hyperautofluorescent changes most strongly correlate, apart from drusen size, with the disruption of the overlying IS-OS layer. Similarly to the target aspect seen in RPD stage 3 lesions featuring an interruption of the IS/OS boundary, the status of the IS-OS layer appears to be equally important in large, soft drusen regarding their FAF imaging properties [18].

Querques et al. alternatively mention the confocal imaging technique as an explanation for the visibility of a target aspect, saying that the core of RPD may only be visible when the confocal laser beam is directly focused on the centre or the bottom of the lesion [13].

The target aspect that was previously reported in FAF and IR is also visible in MS images, as described above. Interestingly, by using MS images, a target aspect could be detected in more RPD-affected eyes in comparison to IR and FAF images, which suggests that MS may be a more sensitive tool for identifying a target aspect in RPD lesions. This could be explained by the fact that MS cSLO imaging merges information about RPD lesion architecture from three different wavelengths that obtain their information from three different retinal layers, which may result in a more comprehensive depiction of the RPD lesion. Figure 1 illustrates the more distinct appearance of the target aspect in MS compared to FAF and IR.

Volume SD-OCT imaging with a high number of scans does not necessarily ensure depiction of exactly the centre of RPD lesions in order to judge the lesion's true height. RPD themselves are quite small alterations and their centres that exhibit the target aspect are even smaller. The current Spectralis device features an axial resolution of 7 μm. Thus, even when setting the distance between SD-OCT scans as close as possible, the centre of RPD lesions may be located between two scans, and, consequently, an RPD lesion stage 3 may be misinterpreted as a lesion stage 1 or 2. Besides, clinical routine does currently not allow recording of such a closely-spaced volume scan due to limited capacities in time and data storage. Therefore, MS cSLO appears to represent a more sensitive and applicable tool for the identification of target aspects within RPD lesions. This may become more relevant if future investigations further reveal the predictive value of RPD itself, as well as the target aspect within RPD lesions regarding the progression of AMD. Thus, including MS cSLO imaging in the design of future epidemiologic and interventional studies in the field of dry AMD seems reasonable.

MS cSLO is certainly not able to completely substitute other modalities for imaging dry AMD; however, it does represent an additional tool to reliably identify RPD and central targets in RPD lesions in AMD patients. Regardless of the target aspect in cSLO, simultaneous SD-OCT obviously remains essential to diagnose RPD lesions based on the subretinal localisation [10].

Our data's validity is limited by the number of included patients. In addition, our patients did not only show RPD. Apart from RPD lesions, patients also presented with different phenotypic alterations due to AMD, like CNV, GA and

drusen. We adhered to the imaging protocol as strictly as possible; however, image data acquisition was not performed in a reading centre setting. The cSLO multi-colour device records images of different wavelengths at the same time, therefore, image quality is readily comparable for MS, BR, GR and GBE. The study design did not allow us to prove a superiority of MS cSLO in RPD identification compared to FAF and IR. As MS cSLO is a new technique, the aim of this study was primarily to show a non-inferiority of MS cSLO in RPD identification in comparison to the established methods, and not to address how to improve overall visibility of RPD in general. The study focuses mainly on the target feature of RPD, which is an important but not the only morphologic aspect of these lesions.

In conclusion, our findings suggest that MS cSLO imaging is equivalent to FAF and IR in detecting RPD in AMD patients. Higher identification rates in BR and GR of those RPD lesions featuring a target aspect, as compared to RPD lesions without a target aspect, confirm the current hypothesis of RPD localisation and their progression towards inner retinal layers. Additionally, MS seems to be more sensitive in identifying a target aspect in RPD lesions compared to FAF and IR.

Conflict of Interest F. Alten, Heidelberg Engineering, Novartis; C.R. Clemens, Heidelberg Engineering, Novartis, Bayer; P. Heiduschka, Novartis; N. Eter, Heidelberg Engineering, Novartis, Bayer, Sanofi Aventis, Allergan, Bausch and Lomb>

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