Structure-Function Analysis in Patients With Intermediate Age-Related Macular Degeneration

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PURPOSE. To examine the topographic correlation between retinal morphology and retinal sensitivity by mesopic and scotopic fundus-controlled perimetry (FCP) in eyes with intermediate AMD.

METHODS. Thirty-five eyes from 32 patients (mean age 70.9 years) and 29 age-matched controls prospectively underwent spectral-domain optical coherence tomography (SD-OCT) imaging. Mesopic (Goldman III, 200 ms, 4–2 strategy) and scotopic (Goldman V, 200 ms, 4–2 strategy) FCP with a 56-stimulus point grid was performed in AMD patients with the MP-1S. Thickness values of different retinal layers were measured at each stimulus point and compared, topographically corresponding to values in controls of similar age for pointwise structural-functional analysis.

RESULTS. The overall mean sensitivity in patients was 16.9 ± 3.0 dB for mesopic and 14.0 ± 3.7 dB for scotopic testing. Within the central 4° of the macula, reduced mesopic and scotopic sensitivity values were found (P < 0.0001). These findings correlated to central increasing retinal pigment epithelium–drusen complex (RPEDC) thickness and central decreasing outer nuclear layer (ONL) and photoreceptor (PR)-segments thickness (P < 0.0001, respectively). Structure-function correlations revealed that a reduction of mesopic and scotopic sensitivity was associated with increasing thickness of the total retina and the RPEDC and a decrease of the ONL and the PR-segments (P < 0.001, respectively).

CONCLUSIONS. Accumulation of sub-RPE material in patients with intermediate AMD is spatially associated to quantifiable structural alterations in various retinal layers and to corresponding retinal dysfunction. The topographic analysis of retinal thickness and retinal sensitivity will be helpful for a better understanding of the disease process and for the evaluation of new interventional approaches.

Keywords: fundus-controlled perimetry, microperimetry, scotopic, mesopic, MP-1S, drusen, age-related macular degeneration, SD-OCT, retinal imaging

AMD is one of the major causes for visual impairment in elderly patients.1–2 Drusen are a hallmark of both early and intermediate AMD.5–4 Numerous large drusen represent a risk factor for the progression to late AMD stages, that is, as geographic atrophy and/or choroidal neovascularization (CNV).5–2

Various studies have reported functional impairment in AMD patients beyond the reduction of best-corrected central visual acuity, including reading speed, low-luminance visual acuity, dark adaptometry, and fundus-controlled perimetry (FCP).6–12 For the latter, early studies showed localized reduction of mesopic sensitivity over drusen and pigmentary changes.13–14 Further developments of the MP-1S device (Nidek Technologies, Padova, Italy) led to the possibility of scotopic testing under dark-adapted conditions.15 A reduction of scotopic sensitivity was found in patients with hard and reticular pseudodrusen/subretinal drusenoid deposits.15–17 Furthermore, it has been shown that alterations of visual function in patients with early AMD might precede the development of late AMD stages.8,18–20

With the development of high-resolution imaging, an improved detection and monitoring of structural changes in different retinal diseases, including AMD, has become possible.21–24 Although retinal imaging appears to be an important tool for the assessment of efficacy and safety of new therapeutic interventions, there is an unmet need for robust, reliable, and meaningful tests that allow the direct assessment of functional impairment and that are also accepted by regulatory agencies, health technology assessment bodies, and payers. This also includes a better understanding about the impact of disease-specific morphological changes to measurable retinal sensitivity.

Only limited data are available with regard to the refined topographic association of retinal dysfunction and localized structural changes as detected by high-resolution retinal imaging. For example, Wu et al.25 reported in a longitudinal analysis over 12 months in patients with early AMD and using a 37-stimuli point grid (Macular Integrity Assessment device [MAIA]; Center Vue, Padova, Italy) that mesopic sensitivity was reduced with increasing retinal pigment epithelium–drusen complex (RPEDC) layer thickness, looking at individual sectors.
of the Early Treatment Diabetic Retinopathy Study (ETDRS) grid. Further examinations revealed that spectral-domain optical coherence tomography (SD-OCT)-based changes, such as missing integrity of the external limiting membrane and the ellipsoid zone or a drusen-associated RPE elevation, might predict impairment in retinal sensitivity.25,26 Another study demonstrated that cone-mediated sensitivity was significantly associated with a BM (Bruch’s membrane)/RPE drusen complex volume.27 To the authors’ knowledge, no detailed structure analysis with high-resolution imaging and particularly scotopic FCP has been yet performed.

The aim of this study was the detailed pointwise correlation between retinal morphology and retinal sensitivity at 56 stimulus points by both mesopic and scotopic FCP in AMD patients with intermediate AMD.

METHODS

Participants

Subjects with large drusen (>125 μm) in the presence of intermediate AMD (“patients”) and participants of similar age (“controls”) were recruited at the Department of Ophthalmology at the University of Bonn, Germany. The study protocol complied with the Declaration of Helsinki and was approved by the local ethics committee (Ethik-Kommission, Medizinische Fakultät, Rheinische Friedrich-Wilhelms-Universität; Lfd. Nr.125/14). All participants provided informed written research consent after explanation of the study’s composition and the possible consequence of participation.

For inclusion, subjects had to be diagnosed with intermediate AMD in accordance with the classification system of Ferris et al.3 Furthermore, only subjects with clear media, a visual acuity of at least logMAR 0.2, and stable fixation to allow central visual function testing and retinal imaging were included. Exclusion criteria included any signs of geographic atrophy, CNV, diabetic retinopathy, glaucoma, inflammatory retinal diseases, and previous history of vitreoretinal surgery or laser treatment. If reticular drusen were present, the area was not larger than approximately 2 disc areas. If both eyes met the inclusion criteria, both were included. For controls, no signs of any ocular disease were allowed. Patients and controls with refractive errors > ±3 diopters spherical equivalent were excluded.

All participants received a complete ophthalmological examination, including best-corrected visual acuity assessment, slit lamp examination, and fundus biomicroscopy.

Retinal Imaging

Retinal imaging followed standardized operating procedures and following pupil dilatation with 1.0% tropicamide and 2.5% phenylephrine and was performed in patients and controls. High-speed combined and simultaneous confocal scanning laser optical coherence tomography (SLO) + SD-OCT imaging was performed using the Spectralis HRA+OCT (digital image resolution 768 × 768 pixels; Heidelberg Engineering, Heidelberg, Germany) device. The imaging protocol included color fundus photography, fundus autofluorescence (exc λ = 488 nm, em λ = 500–800 nm, minimum 15 frames), single horizontal and vertical combined cSLO+SD-OCT scans through the fovea (30°, automated real time [ART] minimum nine scans), and a raster SD-OCT scan (30° × 25°, ART minimum nine frames, 61 B-scan, distance 120 μm).

Quantification of Retinal Thickness

The automated segmentation of different retinal layers in the Heidelberg Eye Explorer (HEE) software (Heidelberg Engineering) was carefully reviewed and manually corrected, if indicated, in each of the 61 B-scans of the raster scan. According to previous publications, the individual retinal layers were defined as follows and demonstrated in Figure 1.1–3,28–32 The total retinal thickness was defined as the distance between the internal limiting membrane (ILM) to BM. The inner retina thickness was measured from the ILM to the outer plexiform layer (OPL). The ONL (outer nuclear layer) thickness was measured from the OPL to the external limiting membrane (ELM). In analogy to Sadigh et al.,29 the Henle fiber layer was counted toward the ONL. The thickness of the photoreceptors (PR) was determined from the ELM to BM. The PR-segments were defined from the ELM to the RPE layer. As previously described, the thickness of the RPE layer was defined from the apex of the RPE layer (including drusen material) to BM.25

Fundus-Controlled Perimetry

As previously described,16,33 mesopic and scotopic FCP of the central retina was performed in patients using the Nidek MP-1S device (Nidek Technologies). For both tests, a grid of 56 stimulus points, centered on the fovea, was used (Fig. 1). Initially, mesopic FCP was performed (Goldmann size III, 200 ms, 4–2 strategy, background luminance 1.27 cd/m², ring with a 3° radius and 1-pixel thickness as fixation target). Scotopic testing started with the filter selection examination (for identifying the appropriate neutral density filter), followed by two scotopic test runs (Goldmann size V, 200 ms, 4–2 strategy; background luminance 0.0032 cd/m², 5° radius and 1-pixel fixation ring) for each subject. To overcome the limited dynamic range of threshold values for scotopic testing with the current device, the filter selection examination was initially performed to establish the individual appropriate neutral density (ND) filter (0.0 log unit, 1.0 log unit, 2.0 log ND). As the comparison of test results between examinations that had been performed with different filters is currently difficult (no pure mathematical meaningful correction of sensitivity values possible), we enrolled only subjects in which the strongest filter (2.0 ND) was initially determined (i.e., the enrollment was limited to subjects with no or only mild scotopic dysfunction). Finally, only subjects with a mean difference of all stimuli points ≤3 dB between the two scotopic test runs were included. The second of the two scotopic examinations was then used for analysis.

Topographic Correlation of Localized Retinal Layer Thickness to Test Stimuli of Retinal Sensitivity

As previously described,33 thickness maps covering an area of 2° × 2° (total grid size 20° × 4°) were generated in the current available version of the HEE to measure the localized thickness of different retinal layers at the position of each of the 56 stimuli as placed by FCP. Using the fovea as orientation, the 20° × 4° grid was manually shifted several times to measure the localized thickness of the different retinal layers.

Statistical Analysis

Using the thickness data in each of the 56 stimulus points in controls, normed topographic thickness values of all retinal layers (total retina, inner retina, ONL, PR, PR-segments, and RPEDC) were determined for patients by subtracting the position-specific mean thickness value of controls and dividing by an overall estimation of the SD for the controls.

For scotopic and mesopic testing, the sensitivities at each stimulus point were corrected by subtracting the mean and dividing by the SD of the total retinal sensitivity in each eye.
account for the topographic differences in retinal structure and sensitivity, normalized data (i.e., $z$-scores) were analyzed. These represent the difference between the measured thickness or sensitivity value and the topographic normative thickness or sensitivity value divided by the corresponding normative SD.

To analyze the relation between the various thickness measurements and the structure-function correlation, mixed linear models were used, including the eye as random factor to account for the correlation of repeated measurements within one eye. The possible dependences due to the inclusion of both eyes for a few patients were not addressed in the model because the respective parameters would not have been reliably estimable due to low number of patients with both eyes measured ($n = 35$ eyes from 32 patients). In addition, multivariable models for scotopic and mesopic function were developed by stepwise procedures based on the improvement of the Bayesian Information Criterion. $R^2$ values were calculated following the suggestion of Nakagawa and Schielzeth. Further, the results for the central test points (within the central $4^\circ$) were compared with the peripheral test points, again using a mixed linear model approach with the eye as random factor.

Finally, the odds ratio for a local reduction of 5 dB and 10 dB in both mesopic and scotopic FCP testings in the presence of RPEDC, PR, and total retina thickening of $> 2$ SDs and ONL, PR-segments, and inner retina thinning of $> 2$ SD from healthy controls were estimated using a generalized mixed linear model. In a few cases, when the fit of the mixed model did not converge due to small numbers for one of the categories, odds ratios and $P$ values were derived from simple cross tabulations, ignoring the possible within-eye correlation.

**RESULTS**

**Demographics**

Thirty-five eyes of 32 AMD patients (mean age 70.9 years; interquartile range [IQR] [66.9; 77.9], range 54.8–85.8; 20 males, 14 pseudophakic) and 29 eyes of 29 controls (mean age 75.3 years; IQR [69.7; 77.1], range 50.8–89.2; 10 males, 4 pseudophakic) were included. The median best-corrected visual acuity was logMAR 0.1 (Snellen equivalent 20/25) (IQR 0.0–0.1, range 0.0–0.2) for patients and logMAR 0.0 (Snellen equivalent 20/20) (range 0.0–0.0) for controls. All eyes of patients were classified as intermediate AMD according to the classification system of Ferris et al. 4

**Functional Analysis**

In patients, the overall mean sensitivity, calculated out of a total of 1960 stimuli of 35 eyes, was $16.9 \pm 3.0$ dB (SD) (range 0–20 dB) for mesopic and $14.0 \pm 3.7$ dB (range 0–20 dB) for scotopic testing, respectively. The total number of test points with threshold values at the lower dynamic range of the system ($\leq 4$ dB) was 13 for mesopic and 56 for scotopic testing. Within the upper dynamic range ($\geq 16$ dB), the total number of test points was 1478 for mesopic and 804 for scotopic testing.
The further analysis of FCP results showed that both mesopic and scotopic test results were reduced in the central 4° compared with the peripheral retinal areas (Fig. 2).

Under mesopic conditions, the mean of the corrected retinal sensitivity was 0.36 ± 1.17 dB (range 5.6–1.9) in the center and 0.14 ± 0.87 dB (range 3.3–2.9) in the periphery (P < 0.0001). Under scotopic conditions, the mean of the corrected retinal sensitivity was 0.86 ± 1.1 dB (range 4.6–1.7) within the central 4° and 0.34 ± 0.68 dB (range 3.0–2.5) within the periphery (P < 0.0001).

Topographic Analysis of Retinal Thickness Values in Patients

Figure 3 shows the topographic distribution of the average corrected thickness values for each layer in patients. This detailed analysis revealed that the thickness values in the central 4° were increased compared with the values outside the central 4° for the total retina (P < 0.0001), the RPEDC (P < 0.0001), and the PR (P < 0.0001). Decreased values for the center were found for the ONL (P < 0.0001) and the PR-segments (P < 0.0001). No statistically significant differences between central and peripheral areas was noted for the inner retina (P = 0.091). Supplementary Figure S1 demonstrates the corresponding box plots.

A detailed graphical analysis for the topographic correlations of the layer thickness for individual layers as compared with the thickness of the R PEDC, both for controls and patients, is shown in Supplementary Figure S2. Significant results were shown for all layers except for the inner retina in patients and the PR-segments in controls.

Pointwise Structure-Function Correlation

Pointwise structure-function correlation was performed in patients. The corrected thickness values at the site of each test point were correlated to the corresponding and corrected mesopic and scotopic sensitivity values (Figs. 4 and 5). With increasing thickness of the total retina, the PR, and the R PEDC, the mesopic and scotopic sensitivities were reduced (P < 0.001, respectively). The increase of 1 SD in R PEDC thickness led to a decrease of 0.15 dB SD in scotopic and 0.10 dB SD in mesopic function. A decrease in ONL and PR segments thickness correlated with a decrease of both scotopic and mesopic function (P < 0.001, respectively). Hereby, the decrease in ONL and PR segments thickness of 1 μm SD was correlated to the decrease of 0.25 dB SD in scotopic and 0.16 dB SD and 0.11 dB SD for mesopic function, respectively. For the thickness of the inner retina, no obvious correlation with both mesopic and scotopic sensitivity values was found.

Comparing the individual layers with significant correlations to each other, the slopes were consistently steeper for scotopic as compared with mesopic testing. For both mesopic and scotopic testing, the steepest slopes were determined for
ONL thickness changes, followed by similar slopes for PR, PR-segments, and RPE DC.

**Multivariable Analysis**

To further explore the impact of the different retinal layers on retinal function, we fitted multivariable models to the data. Potential explorative values were total retina, inner retina, ONL, PR, PR-segments, and RPE DC and information about the horizontal (nasal to temporal) and vertical (superior to inferior) position and the eccentricity within the eye.

The results of the multistep selection procedure are given in the Table. Scotopic function decreases with a decrease in PR segments thickness and an increase of RPE DC thickness. We also find a decrease of function toward the center of the eye and from inferior to superior. We found similar effects for mesopic function except that we did not find any evidence for the radial component.

The scotopic function seemed to be better explained than the mesopic function. We found marginal $R^2 = 0.333$ and 0.202, respectively, and conditional $R^2 = 0.479$ and 0.373, respectively.

The results of the odds ratio analysis are demonstrated in the supplement.

Figure 6 demonstrates the thickness of the individual retinal layers in an SD-OCT scan through several large drusen for one patient. The more central test points correlate with an increase in RPE DC and PR thickness, a decrease in ONL, inner retina, and (slightly) PR segments thickness and a reduced mesopic and scotopic retinal function.

**DISCUSSION**

The results of this study demonstrate that localized changes in retinal layer thickness are spatially confined to impairment in retinal sensitivity in patients with intermediate AMD. By performing a refined point-to-point correlation between findings based on high-resolution SD-OCT imaging and testing of both mesopic and scotopic retinal sensitivity, the results are in accordance with previous studies that have demonstrated a loss of retinal function in AMD patients beyond central visual acuity testing.8,14

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<th>Table: The Results of Multivariable Analysis</th>
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<td>marginal $R^2 = 0.202$, conditional $R^2 = 0.573$</td>
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FIGURE 3. Comparison of the central (within 4°) and peripheral corrected thickness values of the different retinal layers in patients.
We detected typical thickness changes of different retinal layers in AMD eyes as expected in the presence of large drusen and demonstrated in previous studies, particularly the increase in thickness of the RPEDC, the increase of the total retina and the decrease of the ONL, whereas the inner retina thickness showed only small alterations. It is well conceivable that the increase of RPEDC thickness may impair the integrity of the outer and inner segments as well as the cell bodies of the photoreceptors. Further, the reduction of the ONL and PR segments thickness itself may reflect morphological changes on the cellular levels and may be therefore well associated with photoreceptor dysfunction, reflected by reduction of both mesopic and scotopic retinal sensitivity testing. Although the results of the multivariable analysis are highly explorative, they fit very well to our expectations and the other findings. Interestingly, a decrease of PR segments thickness seems to be more significant than the decrease of ONL thickness. The scotopic function values seem to be better explained than the mesopic values. Further, the results of this study are in accordance with recent findings that demonstrated a correlation between an increase in RPEDC thickness with mesopic FCP using the MAIA device. Interestingly, another study found a correlation of photopic retinal sensitivity (background 31.4 asb [10 cd/m²]) and RPE+ outer segment volume but not between retinal sensitivity and ONL volume or area or volume of drusen. In contrast to previous studies, this study is not based on regionwise structure-function analysis (i.e., ETDRS segments), but pointwise analysis. Our analysis demonstrates

**Figure 4.** The structure-function correlation retinal layer thickness to mesopic (left column) and scotopic (right column) testing.
more pronounced changes for structural alterations than for retinal dysfunction. It appears conceivable that, initially, subtle structural changes are visible on high-resolution imaging but do not yet result in a decrease of retinal function. As these structural changes become more pronounced, a loss of retinal function as a result of damaged photoreceptors may then develop. Another explanation may be that retinal imaging is of a more objective nature as compared with functional testing, which is influenced by more potential confounding factors. Longitudinal data would be certainly needed to give more information about these interesting connections.

The greater structural and functional changes in the central 4° of the retina as compared with more eccentric areas not only further underscores the topographic correlation of structure and function, but also indicates the more severe disease manifestation in the parafoveal retina in intermediate AMD. This finding is in accordance with the observation that drusen and other typical AMD-related changes such as pigmentary alterations initially are typically located in this area.7,25 In addition, it is in accordance with previous findings by Curcio et al.,37 who reported of greater photoreceptor loss in the parafovea in association with greater rod than cone vulnerability in AMD disease. Finally, it would be in line with typical symptoms of AMD patients, such as reading difficulties, and underscores the importance of assessing parafoveal visual function in both natural history and clinical studies.

Notably, we limited the inclusion to subjects in which the strongest (2.0 log unit ND) of the three different available ND
filters was determined during the filter selection examination. Although this setup allowed for a better comparison of threshold values between subjects, it can be assumed that subjects with marked scotopic dysfunction were not included in the current study from the beginning. In this context, it is also interesting to note that we did only include subjects with an area of reticular drusen of less than 2 disc areas in size. In this latter AMD phenotype, a marked scotopic dysfunction has been independently reported by different groups. 16,38 These observations are also in accordance with our previous study in patients with areas of reticular drusen in size of at least 2 disc areas and no signs of late AMD, in which the most common ND filter for scotopic FCP was the 1.0 log unit ND. 16 Moreover, Pfau et al.39 recently reported, using another FCP device, that rod function is particularly impaired as compared with cone function in patients with predominantly reticular drusen, whereas subjects with large drusen had similar rod and cone dysfunction.

The consistent finding that the slopes for scotopic sensitivity were steeper than for mesopic testing (Figs. 4 and 5) would suggest that rod function is more severely impaired as compared with cone function. This assumption would be in line with previous clinical studies and histopathological reports.16,40 However, we did not assess the central 1 degree from the fovea where the highest concentration of cones is present in the macula. Further, floor and ceiling effects of FCP testing need to be considered, particularly when using the MP-1S. Of note, there was a relatively high number of sensitivity values within the upper range for mesopic testing. This finding confirms previous studies that the dynamic range of the system is limited particularly with regard to detection of slight mesopic retinal sensitivity loss.11,25 Further improvements, such as the introduction of the MP-3 and other FCP devices, may overcome this limitation in the future.

This study has several other limitations. The number of patients was limited, and we did not include longitudinal data. Due to a limited dynamic range of the MP-1S device, ceiling and floor effects must be taken into account. In the Methods section, we reported the number of threshold values for both types of testing that were within 4 dB to the end of the lower and upper sensitivity range. In accordance with previous reports, the relative number of test points at the upper range were particularly high for mesopic testing (75%) and also, to a lesser extent, for scotopic testing (41%). It would be conceivable that very mild mesopic and scotopic sensitivity loss could not be measured, and therefore considered in the current structure-function analysis. The direct comparison of scotopic versus mesopic sensitivity loss is also limited, as the size of the test stimulus size varied between mesopic (Goldmann III) and scotopic (Goldmann V) testing. Together with the limited dynamic range, we would be therefore reluctant to estimate if any difference between rod and cone dysfunction could be determined with the current setup. Finally, the Goldmann size test stimuli were projected as circles, and thus...
the area for functional assessment did not totally match the squares that were used for localized retinal thickness measurements. A more-refined analysis strategy was not possible with the available version of the HEE. Strengths of the study include the standardized imaging protocol with dense SD-OCT volume scans, the pointwise evaluation of six different retinal layers, and the functional testing of both mesopic and scotopic settings.

In conclusion, we performed a refined structural-functional analysis in patients with intermediate AMD, using high-resolution SD-OCT imaging and both mesopic and scotopic FCP. By correlating localized thickness changes of different retinal layers to individual results of test stimuli, we could demonstrate that previously reported morphological changes of differential retinal layers in AMD eyes do have a functional impact on both rod and cone function. The topographic structural-function analysis does not only allow the detection of retinal dysfunction beyond best-corrected visual acuity evaluation, but would be particularly helpful for a better understanding of disease mechanisms and for the evaluation of new interventional approaches. Although this study evaluated quantitative changes in retinal layer thickness, we did not additionally assess qualitative morphological features like presence of hyperreflective dots or ELM integrity. The former are better determinable in an objective manner and also allow for direct correlation of quantitative parameters. The topographic mapping of stimuli to small qualitative changes would be also challenging. Future studies are required to investigate the benefits and limitations for structure-function correlation of subtle qualitative changes as detected by high-resolution imaging.

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