Special Issue

Retest Reliability of Mesopic and Dark-Adapted Microperimetry in Patients With Intermediate Age-Related Macular Degeneration and Age-Matched Controls

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Purpose. To determine the intrasession test-retest reliability of mesopic and dark-adapted fundus-controlled perimetry in patients with intermediate age-related macular degeneration (iAMD).

Methods. We conducted a cross-sectional study with 23 iAMD patients (67.3 ± 8.2 years; range, 50–85; 78% female) and 24 healthy controls (61.3 ± 5.2 years; range, 50–71; 50% female) using a modified MAIA microperimeter. All patients underwent duplicate mesopic (achromatic stimuli, 400–800 nm) and dark-adapted (red stimuli, 627 nm) microperimetry, using a grid of 33 stimuli over 14° of the central retina. Main outcome measure was the intrasession test-retest reliability for pointwise sensitivity (PWS).

Results. PWS test-retest reliability was good among mesopic and dark-adapted testing in both patients and controls (coefficient of repeatability of 4.4, 4.52, 3.96, and 4.56 dB, respectively). Mean mesopic sensitivity in patients was 2.62 dB lower than in controls ($P < 0.01$); mean dark-adapted sensitivity was 2.49 dB lower than in controls ($P < 0.01$).

Conclusions. The modified MAIA device allows for reliable mesopic and dark-adapted microperimetry in iAMD patients. We found that iAMD is associated with both reduced mesopic and dark-adapted retinal sensitivity.

Keywords: microperimetry, age-related macular degeneration, rod function, test-retest, variability

Patients with intermediate age-related macular degeneration (iAMD) often perform well in visual function tests under high-luminance and high-contrast conditions, whereas testing under dim light and low contrasts shows functional impairment.[1,2] Furthermore, iAMD patients commonly require high ambient light for tasks such as reading and report difficulties, especially in performing daily activities, under low-luminance conditions.[3–5] Several studies have demonstrated that early AMD and iAMD patients have impairment of rod-mediated dark adaptation.[6–9] However, high-luminance high-contrast best corrected visual acuity (BCVA) is the most widely used functional outcome measure in clinical trials, although it underestimates the disease extent and is a poor measure for progression.[10,11] Therefore, there is a lack of functional tests sensitive to disease severity and progression in iAMD.

A good way to detect functional deficits in early stages of AMD is to measure retinal sensitivity determined by fundus-controlled perimetry (FCP), also called "microperimetry" or "gaze contingent perimetry."[11–16] Studies have shown that functional deficits detected by FCP are correlated to retinal pigment epithelium (RPE) elevation, thinning of the outer segment thickness, and disruption of the second hyperreflective band on spectral-domain optical coherence tomography.[17–19] Impaired mesopic and scotopic sensitivity have been spatially correlated with the presence of both large soft drusen and focal abnormalities on fundus autofluorescence intensities.[20–22]

While there are multiple reports on mesopic function in iAMD, less information about scotopic and dark-adapted FCP is available.[11,23–26] One study in AMD patients with reticular drusen (RDR) revealed that rod function is more severely affected than cone function in retinal areas with RDR.[22] This study was conducted with a modified version (MP-1S) of the MP-1 microperimeter (Nidek Technologies, Padua, Italy). A disadvantage of the MP-1S is the limited dynamic range of the stimulus-presenting liquid crystal display of 20 dB.[27] Different neutral density filters must be used for different patients based on their respective visual function.[27]

Recently, a modified version of the macular integrity assessment microperimeter for scotopic testing (S-MAIA; CenterVue, Padova, Italy) has been developed. This device has two additional projection LEDs and the ability to reduce the line-scanning laser ophthalmoscope (SLO) laser power for scotopic testing. A study with a prototype has yielded good test-retest reliability for the S-MAIA in mesopic and scotopic testing in normal subjects as well as in patients with various retinal diseases.[28–30] The latest version of the S-MAIA features an increased dynamic range for scotopic testing (36 instead of 20 dB). As it is important to establish the quality of measurement in order to be able to interpret the data generated, we assessed test-retest reliability of mesopic and dark-adapted microperimetry with the S-MAIA in iAMD patients and investigated the difference for mesopic and scotopic retinal sensitivity in iAMD patients compared to persons of normal retinal health in the same age range.

Methods

We conducted a cross-sectional study at the Department of Ophthalmology, University of Bonn, Bonn, Germany, from December 2016 to July 2017. The study was approved by the Institutional Review Board of the University Bonn (approval ID: 013/16). Written informed consent was obtained from all participants following an explanation of all tests involved. The protocol followed the tenets of the Declaration of Helsinki.

Twenty-three patients with iAMD and 24 age-matched subjects with normal retinal health were recruited from the AMD outpatient clinic, the self-help organization Pro Retina, and family members of patients. Inclusion criteria for the iAMD group were drusen greater than 125 μm and/or any AMD pigmentary abnormalities according to the classification system introduced by Ferris et al.[31] For the control group, inclusion criteria was BCVA of 20/20 tested using an autorefractor (ARK-560A; Nidek, Gamagori, Japan). Exclusion criteria for both groups were age <50 years, the presence of choroidal neovascularization (CNV), geographic atrophy, significant cataract, any corneal pathology that could compromise vision, amblyopia, glaucoma, diabetes, neurologic or systemic disease affecting vision, refractive errors >6.00 diopters (D) of spherical equivalent and >2.00 D of astigmatism. One eye of each patient (the one with the better visual acuity) was included in the study. If both eyes fitted the inclusion criteria and had the same visual acuity, the right eye was chosen. In addition to BCVA and microperimetry, spectral-domain optical coherence tomography raster scanning was performed using a 25° × 25°-scan field (49 B-scans, automated real-time mode 20 frames, centered on the fovea), as well as fundus autofluorescence and infrared photography (Spectralis OCT2; Heidelberg Engineering, Heidelberg, Germany).

All patients underwent two mesopic and two dark-adapted microperimetric examinations using the modified S-MAIA device with small breaks (maximum 5 minutes) between the examinations. Prior to testing, pupillary dilation was performed using 1.0% tropicamide, and instructions were given to all patients regarding how to perform the examination. For mesopic testing patients who were not dark-adapted, the room light was switched off just before each examination.

The MAIA performs fundus tracking using an SLO with a super-luminescent diode illumination with a central wave light of 850 nm for mesopic testing. An additional LED projecting red (627 nm) stimuli was used for dark-adapted testing. A customized stimulus grid was used that consisted of 33 points located at 0°, 1°, 3°, 5°, and 7° from fixation (Fig. 1). The grid was designed in a manner to provide a relatively regular sampling density throughout the macular region with an increased density toward the fovea. This foveal-weighted design allows covering lesions of interest in AMD with adequate density while minimizing the number of stimuli to keep the examination time as short as possible.

A 645-nm red ring of 1° diameter was used as target of fixation. For mesopic testing, achromatic stimuli (400–800 nm) were presented using a 4-2 staircase threshold strategy, while patients observed the fixation ring against a background of 1.27 cd/m^2. The dynamic range is 36 dB. For dark-adapted testing, red stimuli (627 nm) were presented, also using a 4-2 staircase strategy with a dynamic range for scotopic testing of 36 dB and no background illumination.

Second tests were performed using the follow-up mode. All examinations were performed by a single experienced examiner in a darkened room. Room light was switched off during the mesopic testing and briefly switched on before the follow-up examination. After the two mesopic tests, all patients underwent 30 minutes of dark adaptation while waiting in the examination room (light was switched off, light level <0.1 lux). Two dark-adapted tests were then performed using the same device but presenting red stimuli. In all patients, only the study eye was tested, while the fellow eye was covered with an eye patch.

Statistical Analysis

Test reliability was assessed by the frequency of false-positive responses, measured by presentations of suprathreshold stimuli to the optic nerve head (i.e., blind spot, Heijl-Krakau method), which was manually located before the presentation of the first stimuli. Any participants with false-positive responses of more >33% were excluded from analysis.[11]

The primary outcome measure was the pointwise sensitivity (PWS) intrasession test-retest reliability for the mean sensitivity of all test points for mesopic and dark-adapted retinal sensitivity testing assessed by the 95% coefficient of repeatability (CoR) as recommended by Bland and Altman.[32] The CoR represents a value for which 95% of the test-retest differences for the same subject are expected to lie, which can be interpreted as the measurement error of the instrument combined with the subjective variability. A larger value of CoR hence represents a greater degree of test-retest variability.

The bivariate contour ellipse area (BCEA) was used for evaluation of fixation stability. It is the area of an ellipse (in degree) that covers either 63% or 95% of fixation points. After log transformation, the test-retest reliability was evaluated using the intraclass correlation coefficient (ICC) (after the Shapiro-Wilk test for normal distribution). Following this, retinal sensitivity in patients with iAMD and in persons with normal retinal health were compared using *t*-tests.

Statistical analyses were performed using the statistical software R.[33] Summary statistics (mean and standard deviation) were calculated for demographic and microperimetry performance data. Paired *t*-tests were used to compare the test duration and mean sensitivity between the first and second test. For comparison of mean sensitivity between the two persons group, an unpaired *t*-test was used. A P value < 0.05 was considered statistically significant.

Results

A total of 23 iAMD patients (67.3 ± 8.2 years; range, 50–85; 78% female) and 24 controls (61.3 ± 5.2 years; range, 50–71; 50% female) were included in the study. Twenty out of 23 iAMD patients had good BCVA of 20/25 or better, with the remaining three seeing at least 20/50. All controls had BCVA of at least 20/20. Nine patients were excluded from analysis because they did not match inclusion criteria (two patients with CNV, two patients with early AMD) or due to a false-positive response rate >33% (five individuals, three with iAMD and two healthy controls). Mean age of the five individuals with a high false-positive rate was 60.8 years, which did not significantly differ from the rest ($P = 0.39$). All patients and controls underwent the complete protocol, including duplicate mesopic and dark-adapted microperimetry. None of the persons had performed microperimetry previously.

Mean Sensitivity (MS)

For all testing types and in both groups the average MS was higher in the first test. In iAMD patients, the mean difference of MS between test 1 and test 2 was 0.22 dB in mesopic and 0.4 dB in dark-adapted testing. The difference between the two tests was greater in the control group with 0.41 and 0.38 dB, respectively. The difference was statistically significant ($P < 0.001$) (Table 1).

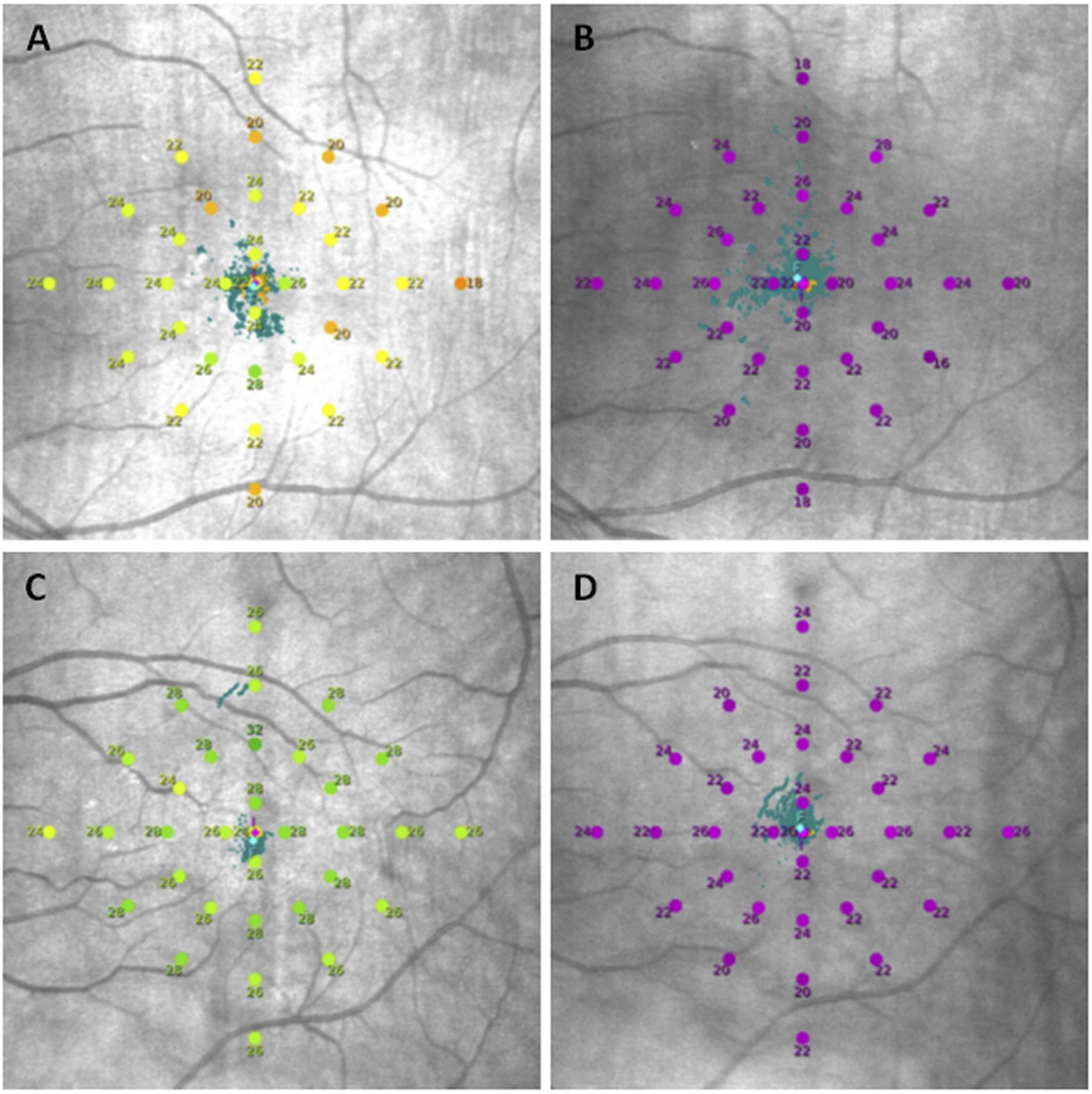

FIGURE 1. An exemplary report for mesopic and dark-adapted testing in iAMD patients and healthy controls. Each figure depicts the local retinal sensitivity of the patient superimposed on the SLO fundus photo. The numeric value represents the measured threshold in decibels. (**A**) Mesopic testing in iAMD. (**B**) Dark-adapted testing in in iAMD. (**C**) Mesopic testing in a control. (**D**) Dark-adapted testing in a control.

The pooled MS (first and second test) was significantly lower in iAMD patients compared to healthy controls as well as for mesopic and for dark-adapted testing ($P < 0.001$). The difference was slightly higher for mesopic testing: in iAMD patients, pooled MS was 23.01 dB (SD ± 3.3 dB) and in the control group 25.63 dB (SD ± 2.29 dB) (difference of 2.62 dB). For dark-adapted testing, the difference was 2.49 dB: the pooled MS in the iAMD group was 19.92 dB (SD ± 4.06 dB) versus 22.41 dB (SD ± 2.54 dB) in the control group. To provide detailed information we calculated the deviation in relation to the inter-eye variability in the control group (*z*-score), which also takes into account the variability in the control group. On average the mean mesopic retinal sensitivity was 1.09 SD lower than the mean of control eyes, while mean dark-adapted retinal sensitivity was 1.07 SD lower (Table 2). There was no difference of average MS between the different eccentricities in both groups for mesopic and dark-adapted testing. Table 1 shows the average MS for all eccentricities.

Test Duration

The pooled mean test duration (test 1 and test 2) was 4.25 minutes (SD ± 25.44 seconds) for iAMD patients and 4.2 minutes (SD ± 31.63 seconds) for controls in mesopic testing ($P = 0.04$) and 4.5 minutes (SD ± 28.43 seconds) and 4.41

Table 1. MS and SD Among Mesopic and Scotopic Red Testing in Cases and Controls in Both Testing Types

Type of Testing	Eccentricity	MS, dB (SD) First Test	MS, dB (SD) Second Test	Test 1 − Test 2	Paired *t*-Test, 95% CI	
Cases ($n = 23$)						
Mesopic	Global	23.13 (3.3)	22.9 (3.3)	0.22	$P = 0.01$	0.05–0.4
	0°–1°	22.69 (3.91)	22.45 (3.75)			
	3°	23.53 (3.34)	23.35 (3.16)			
	5°	23.09 (3.0)	22.96 (3.02)			
	7°	22.2 (3.13)	21.9 (3.4)			
Dark-adapted	Global	20.17 (4.02)	19.66 (4.07)	0.4	$P < 0.001$	0.2–0.6
	0°–1°	18.66 (4.46)	18.41 (4.58)			
	3°	20.76 (4.24)	20.12 (4.48)			
	5°	20.23 (3.65)	19.83 (3.58)			
	7°	19.76 (3.05)	19.11 (3.08)			
Controls ($n = 24$)						
Mesopic	Global	25.84 (2.27)	25.43 (2.29)	0.41	$P < 0.001$	0.25–0.56
	0°–1°	26.27 (2.36)	26.02 (2.28)			
	3°	26.53 (1.93)	26.14 (1.91)			
	5°	25.25 (2.13)	24.78 (2.25)			
	7°	24.47 (2.01)	24.2 (2.01)			
Dark-adapted	Global	22.61 (2.48)	22.22 (2.58)	0.38	$P < 0.001$	0.2–0.56
	0°–1°	22.87 (2.73)	22.24 (3.41)			
	3°	23.07 (2.29)	22.8 (2.38)			
	5°	22.18 (2.19)	21.7 (2.19)			
	7°	21.56 (2.54)	21.32 (2.24)			

CI, confidence interval.

minutes (SD ± 28.74 seconds) in dark-adapted testing, respectively ($P < 0.01$). On average, control persons performed both tests faster than did patients with iAMD, while the difference was greater for dark-adapted testing. For mesopic testing, the difference was 2.62 seconds ($P = 0.04$), while for dark-adapted testing the difference was greater with 8.55 seconds ($P < 0.01$) (Table 3). In all persons and tests, mean test duration was significantly shorter in the second test ($P < 0.01$). The difference was greater in iAMD patients than in controls (18.52 seconds for mesopic and 14.13 seconds for dark-adapted testing in iAMD and 10.08 and 9.29 seconds for controls, respectively) (Table 4).

CoR and Limits of Agreement

The CoR was 4.4 dB for mesopic and 4.52 dB for dark-adapted testing in iAMD patients and 3.96 dB for mesopic and 4.56 dB in control persons. For mesopic and dark-adapted testing, the CoRs were in the same range across all eccentricities in both groups. Table 5 shows the CoRs for all eccentricities and Figure 2 the CoRs in the four quadrants.

The 95% limits of agreements (LoA) according to Bland-Altman statistics ranged in the iAMD group from −4.51dB (95% confidence interval [CI], −4.82 to −4.2 dB) to 4.97 dB (95% CI, 4.66–5.27 dB) for mesopic testing and −5.0 dB (95%, −5.35 to −4.65 dB) to 5.81 dB (95% CI, 5.46–6.15 dB) for dark-adapted testing. For the control group, the LoA was between −3.76 dB (95% CI, −4.03 to 3.5 dB) and 4.59 dB (95% CI, 4.32–4.86 dB) for mesopic testing and −4.44 dB (95% CI, −4.72 to −4.13 dB) and 5.21 dB (95% CI, 4.9–5.52 dB) for dark-adapted testing. Bland-Altman plots did not show correlations between the average and difference of MS of both groups in mesopic and dark-adapted testing (Fig. 3).

Stability of Fixation

After log transformation to reduce skew, the analysis of the stability of fixation revealed in the iAMD group low agreement between the first and the second test for mesopic and high agreement for dark-adapted testing (ICC values 0.274 and 0.863, respectively). In the control group with healthy persons, the analysis showed moderate agreement for mesopic and high agreement for dark-adapted testing with ICC values of 0.657 and 0.898, respectively.

Discussion

The modified S-MAIA device allows for a reliable assessment of mesopic and dark-adapted microperimetry in patients with iAMD and persons with normal retinal health in the same age range. Both mesopic and dark-adapted retinal sensitivity were reduced in iAMD patients compared to controls.

Our results are comparable to findings from previous studies, which found mesopic microperimetry to be a good functional test for patients in the early and intermediate stages of AMD.[26,34–38] Wu and colleagues[11] showed a pointwise CoR

Table 2. Pooled MS (First and Second Test) in Decibels and SD in Mesopic and Scotopic Red Testing

	MS, dB (SD) Cases	MS, dB (SD) Controls	Difference	Unpaired *t*-Test	*z*-Score
Mesopic	23.01 (3.3)	25.63 (2.29)	−2.62	$P < 0.01$	−1.09
Dark-adapted	19.92 (4.06)	22.41 (2.54)	−2.49	$P < 0.01$	−1.07

Table 3. Pooled (First and Second Test) Mean Test Duration in Cases and Controls for Both Testing Types

	Mean Test Duration, s (SD)			
	Cases	Controls	Difference	Unpaired *t*-Test
Mesopic	255.3 (25.44)	253.62 (31.63)	−2.62	$P = 0.04$
Dark-adapted	273.23 (28.43)	264.68 (28.74)	−8.55	$P < 0.01$

for iAMD patients and controls of 4.12 and 3.74 dB, respectively, using mesopic microperimetry with the unmodified MAIA device with 37 test stimuli. These results were similar compared to the CoRs found in this study performed under mesopic conditions using 33 test stimuli (for iAMD 4.4 dB and for controls 3.96 dB).

A study by Pfau et al.[30] assessing test-retest reliability of scotopic microperimetry using the same modified S-MAIA device found CoRs of 4.75 dB for mesopic and 4.06 dB for dark-adapted testing in persons with normal retinal health. The CoRs were slightly higher than our findings for control persons. The perimetry grid with 49 testing points, resulting in longer test durations and a higher proportion of test points at eccentricities of 5° and 7°, may explain the difference in the CoR.

The assessment of dark-adapted microperimetry is more complex and time-consuming since it requires 30-minute dark adaptation in a room completely darkened. In total, the procedure is more prone to interference than is mesopic testing and requires good participant compliance. Due to the testing grid with 33 stimuli, we could keep test duration below 5 minutes for both mesopic and dark-adapted testing. This examination time was well accepted by patients and controls. In total, the whole examination procedure, including repeat testing and dark adaption time, took about 1 hour. The examination time for dark-adapted testing was about 20% longer than for mesopic testing in both groups. As the dark-adapted testing with red stimuli reflects rod and cone photoreceptor function, the longer reaction time might result from the lower stimulus intensities and the increasing recruitment of rod photoreceptors in this test.[30,39]

Nebbioso and colleagues[24] conducted a cross-sectional study to investigate the correlation between the presence of hard drusen only and a reduction in mesopic and scotopic retinal sensitivity measured with the Nidek MP-1S. They found that in patients with hard drusen, scotopic sensitivity was statistically significantly reduced, while mesopic sensitivity was not different. In our study both tests revealed reduced retinal sensitivity. The results showed no greater difference in dark-adapted testing between patients and controls than in mesopic testing (2.62 vs. 2.49 dB). However, in our study we included patients with iAMD, that is, a more advanced stage of AMD compared to Nebbioso and coworkers.[24]

Table 5. 95% CoR and 95% CI of 95% CoR

Type of Testing	Eccentricity	95% CoR, dB	95% CI of 95% CoR
Cases			
Mesopic	Global	4.4	0.15–8.66
	0°	4.6	−1.37–10.57
	1°	4.34	0.31–8.36
	3°	4.73	1.29–8.17
	5°	4.06	0.22–7.91
	7°	4.27	0.52–8.03
Dark-adapted	Global	4.52	0.19–8.8
	0°	3.15	−2.37–8.67
	1°	5.26	0.87–9.66
	3°	5.16	1.68–8.63
	5°	4.37	1.98–6.77
	7°	4.64	0.41–8.88
Controls			
Mesopic	Global	3.96	−0.73–8.65
	0°	4.41	−3.85–12.67
	1°	3.78	−0.39–7.95
	3°	3.9	1.44–6.67
	5°	3.72	1.42–6.02
	7°	3.9	0.23–7.72
Dark-adapted	Global	4.56	−0.52–9.66
	0°	4.65	−3.88–13.19
	1°	5.07	−0.44–10.58
	3°	4.65	1.36–7.94
	5°	4.29	2.27–6.32
	7°	4.16	0.39–7.93

In our study we found a slightly better MS for the first test and for mesopic compared to dark-adapted testing in cases and in controls. This finding differs from results in previous studies, which investigated test-retest variability, where a slight improvement in MS between the first and the second test was observed.[30,40] Wu and colleagues[11] demonstrated in their study a significant learning effect between the first and second examination of mesopic microperimetry with the MAIA. In our study, we could not confirm such a large learning effect. One explanation for the slightly better MS in the first test in our study could be the examination procedure: before scotopic testing, 30 minutes of dark adaptation in a completely darkened room is required, and thus fatigue can easily occur. Although we tried to keep the examination time as short as possible with a 33-stimuli grid, nevertheless it is a demanding testing procedure requiring patient concentration. In further examinations, longer breaks and higher motivation should be tested to assess both the impact of a learning effect as well as fatigue.

For dark-adapted testing, we found high ICCs for the BCEA, indicating high test-retest repeatability for the assessment of fixation stability. For mesopic testing, the ICC was low for iAMD patients and moderate for controls. However, absolute BCEA

Table 4. Mean Test Duration in the First and Second Test for Both Testing Types in Cases and Controls

	Mean Test Duration, s (SD)			Paired *t*-Test	
	First Test	Second Test	Difference	95% CI	*P* value
Cases					
Mesopic	264.56 (27.82)	246.04 (18.7)	18.52	16.87–20.16	$P < 0.001$
Dark-adapted	280 (25.77)	266.17 (29.21)	14.13	12.74–15.51	$P < 0.001$
Controls					
Mesopic	258.66 (34.8)	248.58 (27.2)	10.08	9.07–11.09	$P < 0.001$
Dark-adapted	269.33 (28.69)	260.04 (28.04)	9.29	7.86–10.71	$P < 0.001$

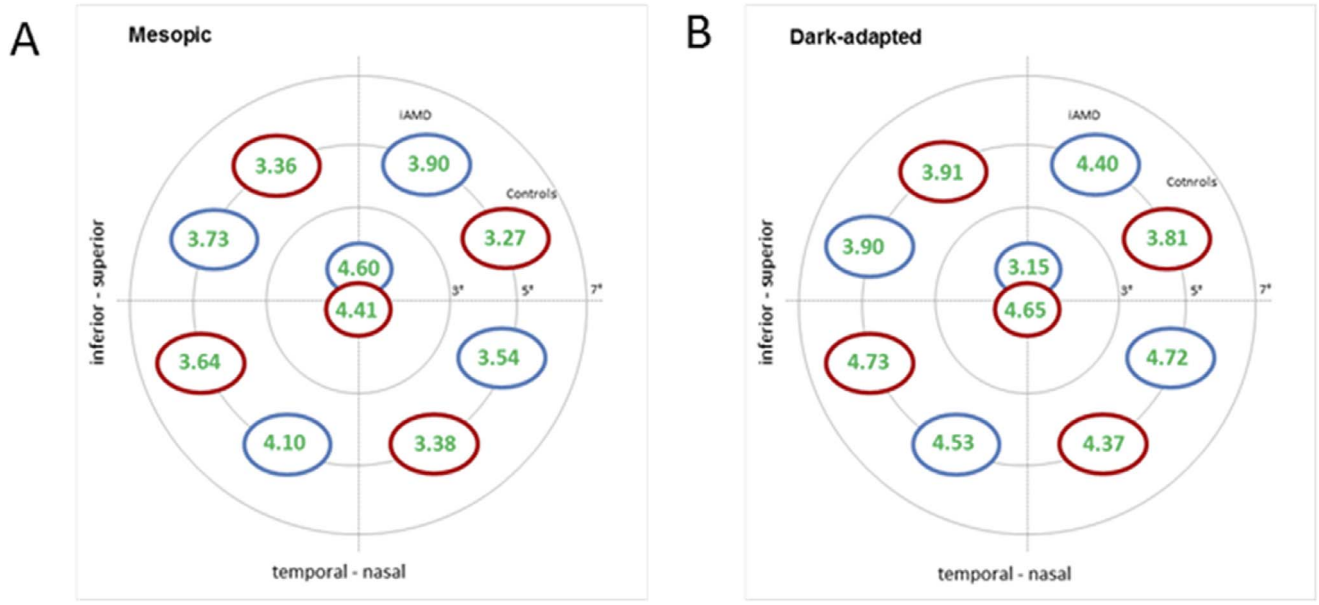

Figure 2. For (**A**) mesopic and (**B**) dark-adapted testing, 95% CoR in each quadrant and central in iAMD patients (*blue circles*) and controls (*red circles*)

was lower in all eyes for mesopic testing. Several previous publications have reported difficulties ensuring a stable fixation under scotopic conditions compared to mesopic conditions.[22,30,41] It would be conceivable that the different ICCs in our study result from a learning effect in fixation. Mesopic testing was always performed before dark-adapted testing.

Strengths of our study include the use of a highly standardized testing protocol for mesopic and scotopic testing

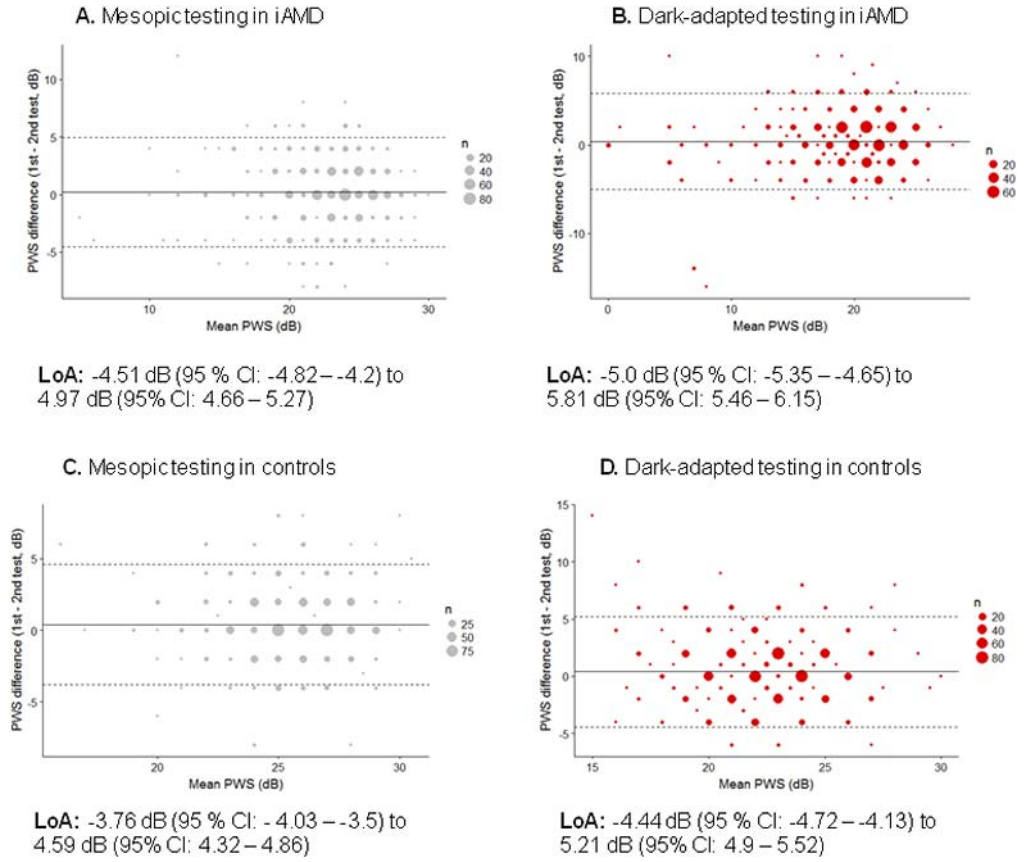

Figure 3. Bland-Altman plots for mesopic and scotopic red testing in cases (**A**, **B**) and in controls (**C**, **D**). The *x*-axis shows the mean PWS for each pair of repeated tests, the *y*-axis the PWS difference between the two tests (first test – second test). The overall mean is represented by the *central line*, and the 95% LoA are marked by the *upper* and *lower dashed lines*.

Investigative Ophthalmology & Visual Science

using a customized device performed by the same trained examiner as well as the comprehensive phenotyping of our participants. A possible limiting factor of our study might be the small study population. However, the sample was sufficient to demonstrate good reliability as well as differences in MS between the groups.

Another limitation is the fact that it is not possible to test exactly the same retinal locations with mesopic and dark-adapted testing. This is a limitation of the device, which allows for an exact overlap of the testing points in the follow-up mode within each testing mode, that is, mesopic or scotopic testing. The difference in the location of the testing points is very small ($<1^{\circ}$), thus it is unlikely to have an influence on the results. An additional limitation is the lack of assessment of intersession reliability days or weeks apart.

In conclusion, we found the modified S-MAIA device to yield highly reproducible mesopic and scotopic MS measurements in both iAMD patients and persons in normal retinal health. In addition, iAMD patients had lower MS on both mesopic and scotopic testing.

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