Assessment of Retinotopic Rod Photoreceptor Function Using a Dark-Adapted Chromatic Perimeter in Intermediate Age-Related Macular Degeneration

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PURPOSE. We determine the feasibility of using a dark-adapted chromatic (DAC) perimeter to obtain dark-adapted static and dynamic rod function at multiple retinal locations, and compare these functional parameters between subjects with intermediate age-related macular degeneration (AMD) and normal controls.

METHODS. Perimetric dark-adapted retinal sensitivities for the 505 and 620 nm stimuli across 7 retinal locations within the central 12° were repeatedly measured after exposing to a single photobleach in 22 intermediate AMD subjects and 8 controls. The sensitivities for each stimulus at 20 minutes after bleach and the sensitivity difference between the stimuli were used to determine static rod function. Sensitivities for the 505 nm stimulus at various times within the initial 20 minutes after bleach were used to estimate the rod criterion time to determine rod function dynamics. The static and dynamic rod functional parameters were compared between AMD and control eyes.

RESULTS. Compared to the control eyes, AMD eyes had a reduction in retinal sensitivities for the 505 nm ($P < 0.001$) and 620 nm ($P < 0.001$) stimuli, a reduction in sensitivity difference ($P < 0.001$), and an increased in rod criterion time ($P < 0.001$). Region within the central 6° appeared to be the most defective and AMD eyes with reticular pseudodrusen (RPD) seemed to have worse function than eyes without RPD.

CONCLUSIONS. It is feasible to use a DAC perimeter to study dark-adapted static and dynamic rod-mediated function at multiple retinal loci. Static and dynamic rod function were abnormal in intermediate AMD and more so in eyes with RPD, particularly within the central 6° retina.

Keywords: age-related macular degeneration, dark adaptation, retina

A n effective early intervention for age-related macular degeneration (AMD) provides the best opportunity to improve quality of life and reduce the economic burden of the disease. As we move closer to having interventions that might slow the progression of early disease before vision is threatened, the need for an early biomarker of disease risk and progression becomes increasingly important.

Difficulty seeing in dim or nighttime conditions, and prolonged adaptation time when changing lighting conditions, is an often reported early symptom in patients with AMD, typically in the presence of good visual acuity (VA).[1,2] Parameters of dark adaptation, in particular the rod dynamic responses, have long been posited as a possible marker for AMD severity[3-6] but whether rod function dynamics can be used for the purpose of monitoring disease progression in a clinical trial setting remains uncertain. This would, at least in part, seem to be due to the unavailability of commercial devices capable of assessing retinotopic rod dynamic responses and the lack of data on the retinotopic variation in rod function dynamics in AMD. As AMD progresses, atrophy of the photoreceptors and RPE develop in discrete, focal areas; thus, it is postulated that testing rod function dynamics at multiple retinal locations will improve the detection of localized changes.

An ophthalmic instrument, the Dark Adapted Chromatic (DAC) perimeter (Medmont, Melbourne, Australia), has been designed to assess dark-adapted retinal function at multiple retinal locations. At each test point the stimulus can be presented with either a cyan (505 nm, 75 dB dynamic rage) or a red (620 nm, 50 dB dynamic range) color. This allows the ability to perform two-color dark-adapted perimetry to assess rod function at multiple retinal loci.[7] When multiple perimetric tests are performed after the eye is exposed to a photobleach, the data on changes in retinal sensitivity over time at multiple retinal loci could be used to determine the retinotopic rod function dynamics. In this study, we investigated the feasibility of using the DAC perimeter to obtain dark-adapted static and dynamic rod function at multiple retinal locations, and compared these functional parameters between subjects with intermediate AMD and normal controls.

METHODS

Participants with AMD were recruited from ongoing AMD studies at the Centre for Eye Research Australia (CERA). Control participants, recruited from friends or staff, volunteered for the study. In cases and controls the study eye was the eye with the best recorded VA. The research followed the tenets of the Declaration of Helsinki and informed consent was obtained from each subject following explanation of the various clinical tests. The study was approved by the Human
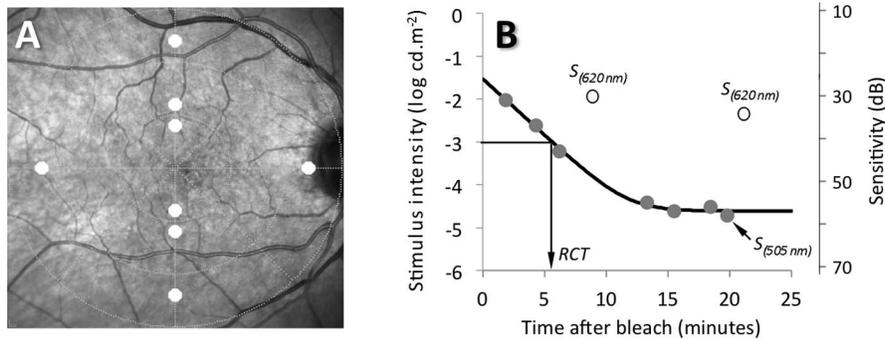
FIGURE 1. Dark-adapted chromatic perimetry test grid (**A**) and rod function measurements (**B**). Retinal sensitivities for the 505 nm (*filled gray circles*) and 620 nm (*open circles*) stimuli at various time points after bleach from a test location are shown in (**B**). Sensitivities of the 505 nm ($S_{[505\ nm]}$, approximately 20 minutes after bleach) and 620 nm ($S_{[620\ nm]}$, at approximately 7 and 21 minutes after bleach) stimuli were used to determine static rod function. An exponential decay function (*solid line*) was fitted to the sensitivity values of the 505 nm stimulus to estimate the rod criterion time (RCT).

Research and Ethics Committee of the Royal Victorian Eye and Ear Hospital.

Inclusion criteria required participants to be aged 50 years or over, with a best-corrected visual acuity (BCVA) of 20/40 (logMAR 0.30) or better in both eyes. Subjects with AMD had to have bilateral intermediate AMD according to the Beckman classification (defined as drusen $\geq$125 μm with or without pigmentary changes).[8] Control subjects were required to have no signs of AMD according to the Beckman classification (no visible drusen or pigmentary abnormalities)[8] or other retinal disease. The grading of the disease status was performed by an experienced, masked grader using color fundus photographs as well as spectral-domain optical coherence tomography (SD-OCT) and fundus autofluorescent (FAF) images to confirm that no signs of atrophy were present.[8] Subjects were excluded from the study if they had choroidal neovascularization, geographic atrophy, OCT, or FAF signs of atrophy or nascent GA,[9] and any other ocular disease that could compromise visual function, including glaucoma, significant cataracts ($\geq$2 score on the Age-Related Eye Disease Study [AREDS] cataract grading system[10]), diabetic retinopathy, amblyopia, history of previous eye surgery, and medications known to affect retinal function, such as hydroxychloroquine. In addition, subjects with medical conditions that could affect dark adaptation (such as liver disease[11] and renal disease[12]) also were excluded.

All participants underwent a comprehensive eye examination, night vision questionnaire, BCVA, low luminance visual acuity (LLVA) measurement, multimodal imaging and DAC perimetry.

Visual Acuity

Best-corrected visual acuity and refractive error were measured using a modified version of the Early Treatment of Diabetic Retinopathy Study protocol.[13] Following determination of the BCVA, a neutral density filter (2.0 ND) was placed in front of the study eye and measurement of LLVA was started immediately after the placement of the ND filter, as described previously elsewhere.[14–16] All measurements of VA were performed with best refractive correction. Low-luminance deficit (LLD) was calculated by subtracting LLVA from BCVA.[14] Visual acuity measures were recorded in terms of total numbers of letters read correctly.

Night Vision Questionnaire

A previously validated night vision questionnaire was administered to all participants to determine subjectively the level of night vision problems they experienced.[17]

DAC Perimetry

The Medmont DAC perimeter was used to obtain retinal sensitivity for the 505 and 620 nm stimuli in a completely darkened room. The test was performed monocularly on the study eye, with the fellow eye patched. Pupils were dilated with one drop each of 0.5% tropicamide and 2.5% phenylephrine. Testing took place only after pupil dilation was measured as being at least 7 mm diameter.

The perimetric test grid used in this study consisted of 8 test points located at 4°, 6°, and 12° on inferior and superior retina, 12° nasal and temporal retina (Fig. 1A). The test point at 12° on the nasal retina, however, subsequently was excluded from the analysis as it was located on the border of the optic nerve head. Spherocylindrical lens correction was inserted into a lens holder with the refractive correction set-up for a viewing distance of 30 cm. Fixation was monitored through use of an infrared-activated camera to observe the eye throughout testing.

Before the measurement of retinal sensitivity, the study eye was bleached once with a customized Ganzfeld light source. The details of the bleaching device have been described in our previous publications.[18,19] In brief, the device was constructed in our laboratory comprising a tube with a translucent dome positioned inside the tube at the observer's end and a light source positioned at the other end with a 450 mm separation between the front surface of the light source and the back surface of the dome. The light source was a photographic flash (Mecablitz 45 CL-4; Metz-Werke GmbH & Co., Zirndorf, Germany). Only one flash was applied to the study eye and this flash level has been shown to bleach approximately 30% of rod photopigment (11 ms duration; 6.48 log scotopic troland seconds) and 10% of cone photopigment (5.66 log photopic troland seconds) with an 8-mm pupil.[18] This amount of pigment bleaching was the most efficient in the testing dark adaptation in AMD-affected individuals.[18] Recording of retinal sensitivity levels started approximately 30 seconds after bleaching and was completed during a single session of approximately 20 minutes (no more tests were commenced once 20 minutes elapsed from the time of bleaching though any test underway was completed). Dark-adapted sensitivities for the 505 and 620 nm stimuli were measured and the order of the measurements is shown in Figure 1B. For each participant, at least six perimetric tests using the 505 nm stimulus were performed within 20 minutes immediately after bleach to allow us to examine the rod function dynamics using the rod criterion time (RCT) parameter. At the conclusion of one perimetric test, subjects were given a break of approximately 45 seconds before being instructed to reposition themselves in

TABLE. Summary of Clinical and Demographic Characteristics of the Study Participants

Parameters	AMD, $n = 22$	Controls, $n = 8$	P Value
Age, y	71.5 ± 6.8	67.6 ± 5.5	0.143
BCVA, number of letters	87.82 ± 4.6	89.75 ± 3.3	0.219
LLVA, number of letters	72.41 ± 5.6	73.75 ± 3.5	0.445
LLD, number of letters	15.4 ± 3.4	16.0 ± 3.4	0.697
Cataracts, number of eyes, %	8 (36%)	3 (38%)	0.643
NVQ, raw score	18.23	15.50	0.229
AMD characteristics			
Pigmentary changes, number of eyes	9		
Reticular pseudodrusen, number of eyes	6		

NVQ, night vision questionnaire.

time to begin the next test 60 seconds after the completion of the previous one. Retinal sensitivity to the 620 nm stimulus was tested twice: once each at approximately 7 and 20 minutes after bleach. The changes in sensitivity between the first and second test using the red stimulus allowed us to assess the dark-adapted rod-mediated sensitivity to the 620 nm stimulus. A stimulus size of 1.73° (Goldmann size V) was used and the stimuli were presented with durations of 200 ms. Threshold was determined using the staircase threshold strategy. With respect to reliability indices, testing for false-positives was included in the test protocol. No single test returned a false-positive rate above 10%.

Imaging

All imaging was performed after the DAC perimetry was complete to ensure no bleaching of retinal photopigment occurred before the functional assessment. Multimodal imaging, including near infrared reflectance (NIR) imaging, FAF, and SD-OCT, was performed to detect the presence of reticular pseudodrusen (RPD). Color fundus photographs were taken for AMD grading.

Crystalline Lens Grading

Changes to the crystalline lens were assessed using slit-lamp microscopy and graded according to the AREDS classification scheme[10] by a single examiner (RF). This was performed on dilated pupils and at the end of all other testing, once again to prevent bleaching of retinal photopigment.

Analysis

Retinal sensitivities for the 505 and 620 nm stimuli at approximately 20 minutes after bleach (the last perimetric test for each stimulus) as well as the sensitivity difference between the 505 and 620 nm stimuli were used to compare the dark-adapted rod-mediated function between the study groups. The sensitivities for the 505 nm stimulus at various time points after bleaching were used to determine rod function dynamics by estimating the RCT using an exponential decay equation and the Solver function in Microsoft Excel, as described in detail previously.[18,20] Rod criterion time was defined as the time taken to reach a rod threshold value of -3.0 log units stimulus intensity using the modeled rod recovery curve (Fig. 1B).[21,22] The RCT was calculated for each test point (7 in total) for each eye, and the data were compared between the study groups. To compare the regional variation in different parameters of rod function, and to determine the sensitivities of the four parameters in detecting abnormal function in eyes with intermediate AMD, each parameter at each test point was converted into the number of standard deviations from normal (Z-score). This was to account for the difference in the variability of each functional parameter.

RESULTS

A total of 22 subjects with intermediate AMD and 8 subjects with a normal fundus appearance participated in the study. A summary of clinical and demographic data of the participants is presented in the Table. Pigmentary abnormalities were present in 9 of the 22 (41%) AMD eyes. Six of the 22 (27%) AMD eyes had reticular pseudodrusen identified on SD-OCT and confirmed on either an NIR reflectance or FAF image. None of the control eyes had visible drusen or pigmentary abnormalities. No significant difference was detected between the AMD and control group for age, BCVA, LLVA, LLD, cataract/lens grade, and night vision questionnaire score ($P \geq 0.143$; Table). No subject had a presence of lens changes (or cataracts) greater than or equal to severity level 2.

Retinal sensitivities for the 505 and 620 nm stimuli at various retinal loci are shown in Figure 2. For the 505 nm stimulus, the mean retinal sensitivity at approximately 20 minutes after bleach was significantly reduced in the AMD group compared to the control group ($P < 0.001$). Post hoc analysis showed that the difference in retinal sensitivity between the AMD and control groups was significant for all test points ($P \leq 0.003$, Fig. 2). The reduction in retinal sensitivity was most prominent at retinal loci within the central 6°. For the 620 nm stimulus, there was a significant increase in retinal sensitivity between the first (measured on average 7.3 ±
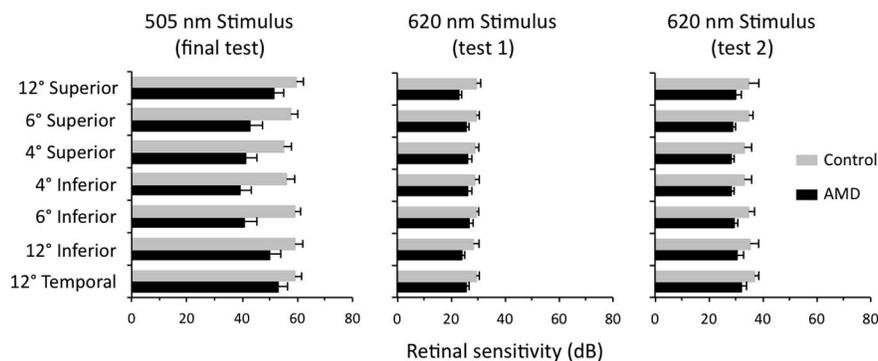

FIGURE 2. Mean retinal sensitivity for the 505 and 620 nm stimuli at various retinal loci. Eyes with AMD had a significant reduction in retinal sensitivity compared to the control eyes for both test stimuli and at all test locations ($P \leq 0.016$). *Error bars*: 95% confidence interval.
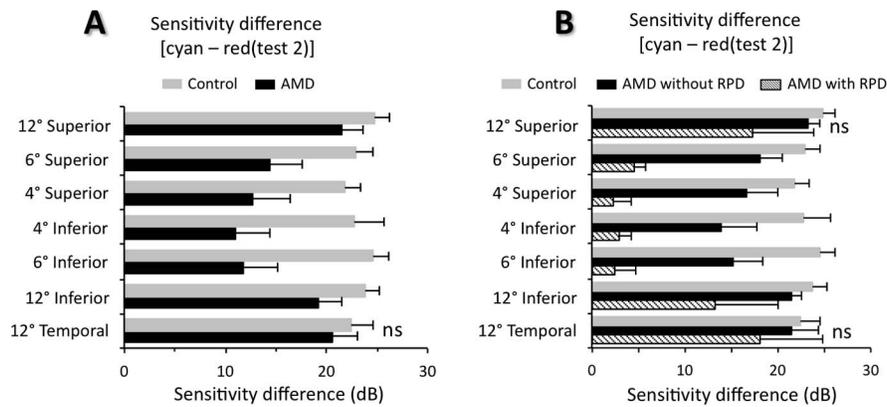
FIGURE 3. Mean sensitivity difference between the 505 and 620 nm stimuli at various retinal loci. The sensitivity difference was significantly reduced in AMD eyes compared to that of the control eyes at all retinal loci except the test point at 12° temporal retina (**A**). Subanalysis of eyes with AMD showed that eyes without RPD had a significantly greater sensitivity difference than eye with RPD in all retinal loci except the retinal locations at 12° superior and 12° temporal retina (**B**). *Error bars*: 95% confidence interval. ns, nonstatistical significance.

0.9 minutes after bleaching) and second (measured on average 21.5 ± 0.9 minutes after bleaching) tests. The mean retinal sensitivity for the first and second tests in AMD eyes was 25.2 ± 3.3 dB and 29.6 ± 4.0 dB ($P < 0.001$), and in control eyes it was 29.0 ± 1.8 dB and 34.7 ± 3.3 dB ($P < 0.001$), respectively. In the first and second tests, the retinal sensitivities of AMD eyes were significantly reduced compared to the control eyes at all test points ($P \leq 0.016$, Fig. 2).

The difference in retinal sensitivities between the 505 and 620 nm stimuli at various retinal loci is presented in Figure 3. The sensitivity difference was significantly reduced in AMD eyes compared to that of the control eyes at all retinal loci ($P \leq 0.009$) except the test point at 12° temporal retina ($P = 0.213$, Fig. 3A). To determine whether AMD eyes with RPD had worse sensitivity compared to AMD eyes without RPD, a subanalysis was performed within the AMD group. When AMD eyes were subdivided into those with or without the presence of RPD, AMD eyes without RPD had a significantly greater sensitivity difference than AMD eyes with RPD at all test points ($P \leq 0.027$) except the retinal loci at 12° superior ($P = 0.069$) and 12° temporal ($P = 0.287$, Fig. 3B) retina. Both AMD with and without RPD eyes showed the greatest reduction in sensitivity difference at test points within the central 6° of the retina.

Representative dynamic responses for the 505 nm stimulus from a control participant and two subjects with AMD are shown in Figure 4, and examples of retinotopic rod response dynamics of control, AMD, and RPD eyes are shown in Figure 5. The comparison of RCT between the AMD and control group is shown in Figure 6. The AMD group had a significant increase in RCT compared to the control group at all test

points ($P < 0.001$). It is worth noting that many of the AMD eyes, particularly in eyes with RPD, did not reach the rod criterion level even at 20 minutes post bleach. Again, retinal loci that had the greatest difference in RCT between AMD and control eyes were points in the central 6° of the retina (Fig. 6).

To explore the trend of retinotopic variation of various rod functional parameters the average number of standard deviations from normal (Z-score) for each functional parameter at each test point was calculated and the data are illustrated in Figure 7. The normative data were derived from the 8 control participants. Of the four functional parameters examined, the RCT and sensitivity difference parameters displayed the greatest retinotopic variations and the RCT parameter had the greatest Z-score.

DISCUSSION

This study demonstrated that it is feasible to utilize a Medmont DAC perimeter to study dark-adapted static and dynamic retinal function at multiple retinal locations during one test session. Our findings showed that static and dynamic rod function were abnormal in subjects with intermediate AMD compared to control participants of a similar age range, and particularly in AMD participants with RPD. The region within the central 6° of the retina had the greatest functional loss.

According to the rod and cone spectral sensitivity curves, the sensitivity to the 505 and 620 nm stimuli in normal eyes with complete dark adaptation is mediated by the rod system except for the fovea where only cones are present.[7,23,24] When there is an absence of rod function the sensitivity to the 505
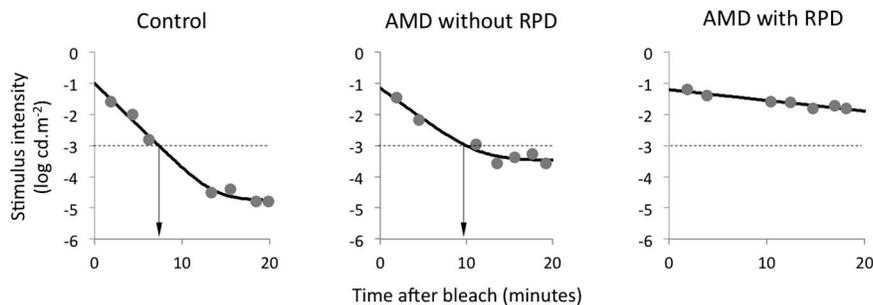

FIGURE 4. Representative response kinetics for the 505 nm stimulus after bleach from control and AMD subjects. Subjects with AMD and without RPD had an increased RCT, whereas AMD subjects with RPD did not reach the criterion level (*dotted line*) even 20 minutes after bleach. All plots are responses from the test point at 6° superior retina.
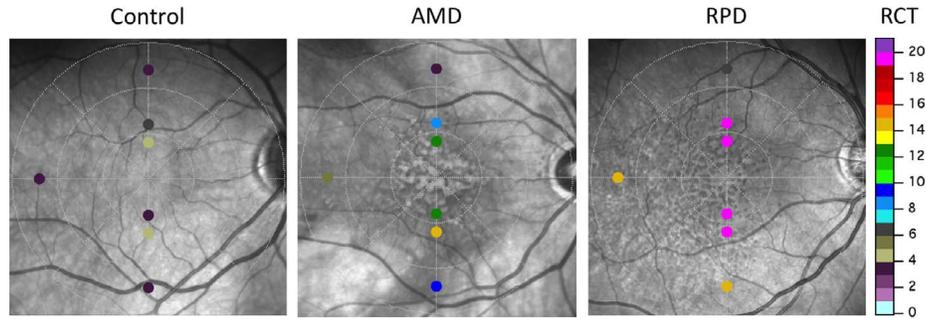
FIGURE 5. An example of retinotopic rod response dynamics of control, AMD, and RPD eyes. The RCT (minutes) was markedly increased in the AMD and RPD eyes compared to the control eye. In eye with RPD, four test points within the central 6° did not recover to the criterion level even 20 minutes after bleach.

and 620 nm stimuli is mediated by the cone system. In the early stages of disease when rod function is reduced the but cone function is normal, it is likely that the sensitivity to the 505 nm stimulus still is mediated by rods but the sensitivity to the 620 nm stimulus is mediated by cones (i.e., mixed mediation). As the rod thresholds are elevated in such conditions, the sensitivity difference between the 505 and 620 nm stimuli is expected to be reduced. In this study, we found that the sensitivity difference was significantly reduced in AMD eyes and more so in eyes with RPD, suggesting the presence of abnormal rod function in these eyes. These findings were supported by the rod kinetic data, which showed a significant increase in the RCT in eyes with intermediate AMD, particularly in eyes with RPD. Our results were in agreement with earlier studies that reported abnormal rod function dynamics in subjects with intermediate AMD, although these previous studies only tested dark adaptation kinetics at a single retinal location.[5,18,19,25,26] In addition, our findings also supported those of Flamendorf et al.,[21] which showed abnormal rod function dynamics, demonstrated by a delayed RCT, in eyes with RPD compared to eyes without RPD. However, our data further showed that the locations within the central 6° had a greater abnormality than the retinal locations 12° from the fovea. As our test protocol is not sensitive to detect changes in cone function, we are unable to comment on the involvement of the cone system in this study, although we have reported previously abnormal cone function in eyes with intermediate AMD using a flicker perimeter, microperimeter, and multifocal electroretinography.[27,28]

Among the four dark-adapted functional parameters examined, the RCT had the greatest Z-score. This indicated that the RCT either has the least variability and/or that it is the most affected parameter in AMD eyes compared to control eyes. Thus, the RCT may potentially be a clinically useful parameter for detecting changes in photoreceptor function in eyes with intermediate AMD compared to normal, as previously reported by others.[4,22]

The data from this study also increased our understanding on the retinotopic variation in static and dynamic rod function in AMD subjects with or without RPD. Regional variation in rod function was most noticeable in the sensitivity difference and RCT parameters. It also is notable that individually, many of the AMD subjects had multiple retinal areas for which rod function was not significantly different from the control for that location, yet other locations were several standard deviations away from normal. This variation in adaptation is, indeed, of great interest and warrants longitudinal studies to determine whether these areas with abnormal rod function are at a higher risk of progression compared to more normally functioning areas.

The strength of the current study is the demonstration of the ability to test rod static and dynamic function on the same system, at the same retinal areas, and to do so at multiple retinal locations in one session by a single examiner. To our knowledge, this study is the first to show that rod function dynamics vary across multiple retinal locations in subjects with
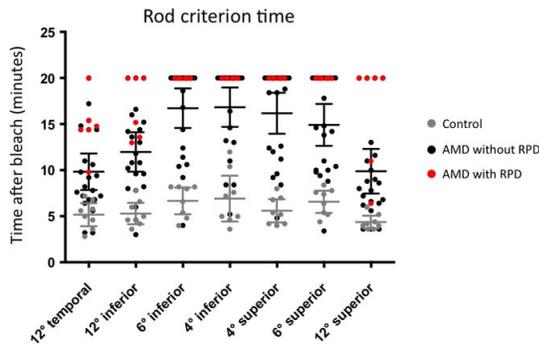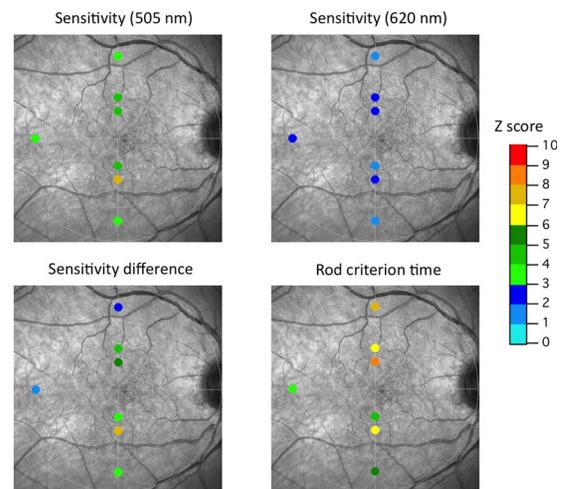

FIGURE 6. Rod criterion time of control and AMD group at various retinal loci. Group with AMD had an increased RCT compared to the control group ($P \leq 0.001$). None of the eyes with RPD recovered to the criterion level even 20 minutes after bleach (ceiling level) for retinal loci within the central 6°. *Graph* shows individual responses, and mean and 95% confidence interval for AMD (with and without RPD combined) and control groups.

FIGURE 7. Average number of standard deviation (Z-score) from static and dynamic functional parameters at different retinal loci. Of the four functional parameters examined, the RCT had the greatest number of Z-score.

AMD and RPD. This represents an important advance in the capacity for testing DAC perimetry for the purpose of monitoring disease progression at multiple locations, in a disease where it is recognized that changes are localized initially. It will be vitally important to determine if the local areas with abnormal dark-adapted rod-mediated function within an eye have any structural changes, as detected on multimodal imaging, that might correlate with these functional differences and whether worse function portends areas of atrophy. Future studies investigating the structural–function relationships and determining the predictive value of poor dark-adapted rod-mediated functional parameters are needed to answer these questions.

The main limitation of the current study is a relatively small sample size. However, the AMD cohort chosen are all of the same disease classification of intermediate AMD and with no evidence of the earliest signs of atrophy on OCT. In addition, the DAC perimeter currently does not have a large bank of control data for our population. As such, the normal data were derived from a small cohort of 8 participants of a similar age range. Furthermore, the protocol used in this study was developed with a view to creating a test with a relatively short duration. Further development of the test protocol is required to suit different clinical and research applications. An optimal protocol would require the balance of the need for a relatively fast clinical test with the need for collection of sufficient data points.

In conclusion, we have demonstrated the feasibility of using a new Medmont DAC perimeter to study static and dynamic rod function at multiple retinal locations. We showed that static and dynamic rod function are abnormal in subjects with intermediate AMD when compared to control participants, particularly in AMD participants with RPD. Regional variations in dark-adapted functional parameters also were demonstrated in subjects with AMD, highlighting the need for dark-adapted testing at multiple retinal locations. Further studies are required to establish the clinical use of the DAC perimeter for monitoring AMD progression.

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