

Comparison of Visual Function Tests in Intermediate Age-Related Macular Degeneration

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Purpose: Identifying the most sensitive functional measure in intermediate age-related macular degeneration (iAMD) could help select an appropriate test for monitoring disease progression and evaluating the efficacy of novel interventions for the early stages of AMD. The purpose of the study was to determine which commonly used visual function test is the most discriminatory when comparing individuals with iAMD to normal participants.

Methods: In this prospective observational study, iAMD cases and healthy controls underwent visual function testing (best corrected visual acuity (BCVA), low luminance visual acuity (LLVA), mesopic microperimetry, dark adaptation, and scotopic perimetry following photobleach), clinical eye examination, and multimodal retinal imaging in a single study visit. The data of each functional parameter were converted into z-score so that all the parameters had a common scale to allow a direct comparison between different functional parameters.

Results: Forty-eight subjects (23 normal control, 25 iAMD) participated. Although all five parameters showed a significant reduction in function in iAMD eyes compared to controls ($P \leq 0.003$), the rod intercept time (RIT) detected the greatest reduction in function followed by the scotopic sensitivity, mesopic sensitivity, BCVA, and LLVA, with the absolute mean z-score of 4.5, 2.2, 1.0, 1.0, and 1.2, respectively.

Conclusions: Among the five visual function parameters commonly used, RIT is the most discriminatory functional parameter in the early stages of AMD.

Translational Relevance: The RIT could be considered for assessing visual function and evaluating efficacy of novel interventions aimed at improving retinal function in eyes with early stages of AMD.

Introduction

There are now a number of treatments aimed at preserving vision once neovascular AMD is present and there are several promising interventions being trialed which aim to slow the growth of geographic atrophy lesions. However, other than supplements and lifestyle advice, there is still no specific treatment proven to slow conversion of the earlier stages of AMD to late stage complications.^{1,2} Designing trials that aim to intervene early to slow disease progression is difficult as traditionally they have been required to be large and long-term to ensure adequate power to detect a difference in conversion to late stage AMD. Much

work is underway to better define earlier anatomical endpoints, now that multimodal imaging has allowed for earlier signs of disease progression to be identified.^{3,4} However, it would be preferable to be able to show a benefit in a functional outcome, yet many functional tests are fairly normal or only moderately reduced in this earlier disease population. The difficulty then is to choose the most appropriate functional test that is likely to show a difference in the actively treated group compared to a placebo over a time frame of only a few years at most.

Several functional parameters, measured under different lighting conditions, have been investigated for their abilities to detect deficits in the early stages of AMD and to monitor functional changes over

time. These parameters includes best corrected visual acuity (BCVA), low luminance visual acuity (LLVA), mesopic microperimetry, scotopic microperimetry, and dark adaptation (DA).^{5–20} Reduced LLVA,^{5–7} mesopic and scotopic sensitivity,^{8–11} and increased rod intercept time (RIT)^{12–18} during dark adaptation have been reported in eyes with large drusen. In addition, prolonged RIT has been shown to be worse in eyes with large drusen if they also have the reticular pseudodrusen (RPD) phenotype when compared to AMD eyes without RPD.^{9,10,21}

Although various levels of functional changes detected by these parameters have been reported, a direct comparison of these parameters, within the same eye, at the same time, in their ability to detect functional deficits in early stages of AMD have not been investigated. Hence, the purpose of this study was to compare functional results in these commonly performed tests to determine the magnitude of functional abnormality, in a cohort with bilateral large drusen when compared to normal participants; with all participants performing all of the tests in the same visit. It was hoped that the results will provide the evidence to help the decision making around which tests to include when designing interventional trials aiming to slow progression of the earlier stages of AMD.

Methods

This prospective observational study was approved by the Human Ethics Committee of the Royal Victorian Eye and Ear Hospital (RVEEH) and conducted in the Macular Research Unit at the Centre for Eye Research Australia (CERA) in adherence with the Declaration of Helsinki. Written informed consent was obtained from all participants after the study had been explained.

Participants

Participants were invited to participate in the study if they met the inclusion criteria of being at least 50 years of age and having a best-corrected visual acuity of 0.48 logMAR (20/60 Snellen equivalent) or better. Control participants were required to have no drusen nor pigmentary abnormalities, nor reticular pseudodrusen (RPD) in either eye. AMD participants were required to have drusen >125 µm with or without any AMD pigmentary abnormalities in both eyes, satisfying the classification of intermediate AMD (iAMD) based upon the Beckman classi-

fication.²² Cases with any late-stage AMD, including nascent GA were excluded.

Other exclusion criteria included a myopic refractive error of greater than –6 diopters (D), a hyperopic refractive error greater than +4D, a cataract grade >2 (WHO grading system)²³ or any significant ocular media opacity that could obscure the fundus examination or multimodal imaging examination, diabetic retinopathy, glaucoma, severe neck and spinal problems preventing the performance of the perimetry tests, and taking medications that might affect the retinal function.

Procedures

All participants underwent an interview for systemic and eye history followed by all the functional testing, including BCVA, LLVA, dark-adapted chromatic perimetry, and mesopic microperimetry within a single visit. A comprehensive eye examination and multimodal retinal imaging were then performed to determine the AMD status. Only one eye, which was the eye with better BCVA, was selected as the study eye to undertake the mesopic and dark-adapted chromatic perimetry. If both eyes had the same BCVA, the right eye was selected as the study eye. The fellow nonstudy eye was patched during perimetric testing. Details about each of these functional tests have been described previously and briefly described as follows.

Visual Acuity

BCVA was measured after subjective refraction using the Early Treatment Diabetic Retinopathy Study protocol under a standard photopic condition. LLVA was then measured after placing a 2.0 log unit neutral density filter in front of the refractive correction.²⁴ Both BCVA and LLVA were recorded as the number of letters read.

Scotopic Perimetry and Dark Adaptation

Scotopic perimetry and dark adaptation were performed in a completely dark room, using a dark-adapted chromatic perimeter (DACP; Medmont Pty Ltd, Nunawading, Victoria, Australia).⁹ The DACP has fixed Goldmann V (1.73°) stimuli distributed on a black bowl. Our test grid consisted of 14 test points located at 4°, 5.7°, 8°, and 11.3° radius from the fovea. Pupils were dilated to at least of 6 mm prior to testing. The study eye was then bleached, approximately 20%, with a customized Ganzfeld flash²⁵ while the fellow eye was patched. Retinal sensitivity was assessed regularly for 30 minutes after photobleaching using the 505 nm stimuli. The changes in retinal sensitivity

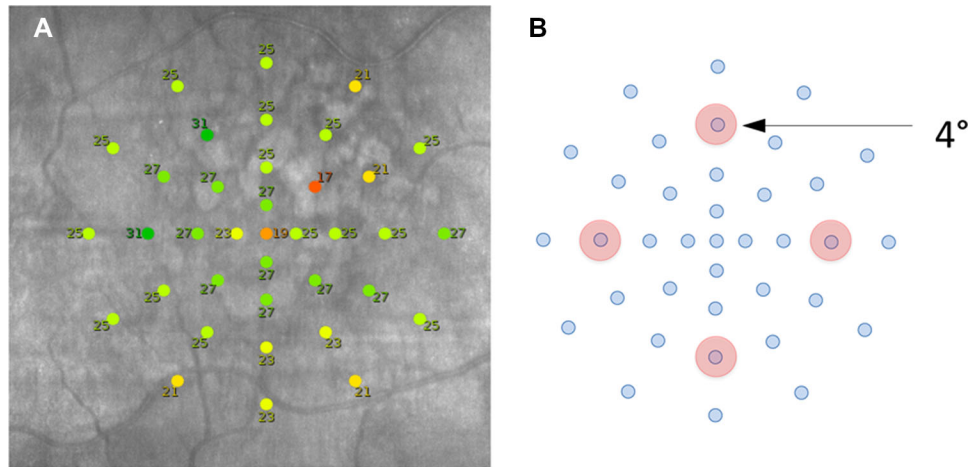


Figure 1. Stimulus grid of the MAIA (A). While DACP and MAIA tested multiple points only four test points located at the 4° ring in the inferior, nasal, superior, and temporal retina were identical points (red and blue overlapping locations seen in panel B). Only data from these test points were used for the comparison between tests.

over 30 minutes of dark adaptation were used to determine the rod intercept time (RIT) as we have described previously.^{9,26} RIT was defined as the time, in minutes, for the stimuli to recover to a criterion level at -3.0 log units of stimulus intensity after an exposure to the photobleach derived from a modeling exponential decay function.^{25,27–29} The scotopic perimetry data (scotopic sensitivity) were also used for assessing the visual function. In this study, we referred the scotopic sensitivity (in decibels, dB) as the sensitivity of the last perimetric test at 30 minutes after photobleach. Both the RIT and the scotopic sensitivity were included in the analysis. However, we chose to only analyze the four locations in the 4° radius where the locations were identical between the DACP and mesopic microperimetry (see Fig. 1)

Mesopic Microperimetry

Mesopic microperimetric testing was performed using a macular integrity assessment device (MAIA; CenterVue; Padova, Italy), and using a customized stimulus grid consisting of 37 test points located at 0°, 1°, 2.33°, 4°, and 6° radius from the fovea (Fig. 1).⁶ The MAIA system presented Goldman III stimulus size (0.43°) on a background of 1.27 cd/m². All tests were required to have a false-positive rate of 25% or less. The mesopic sensitivity in decibels (dB) was used for the analysis.

Multimodal Imaging

Multimodal imaging was performed after perimetric tests were completed to avoid additional bleaching of the retina. All participants underwent near-infrared reflectance (NIR), short-wavelength fundus autofluorescence (SW-FAF), optical coherence tomog-

raphy (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany), and color fundus photography (Canon CR6-45NM; Canon, Saitama, Japan). We obtained 49 B-scans within the central 20° × 20° of the retina and averaged 25 frames for every single OCT scan. All multimodal images were graded to confirm AMD classification and phenotypes by two graders, masked to the visual function data. The control and AMD grading was based on the Beckman Classification and Grading System.²² We included individuals with no apparent aging changes (no drusen and no AMD pigmentary abnormalities), and no RPD in the control group. Cases with intermediate AMD (drusen > 125 μm with or without any AMD pigmentary abnormalities) were subgrouped into those with and without RPD, where only those graded with definite RPD being included in this RPD cohort and only definitely absent in the no RPD group. We excluded anyone who did not have either definitely present or definitely absent RPD in both eyes. The diagnosis of RPD on SD-OCT has been described in our previous study.¹⁰ Briefly, definitely present RPD required the presence of at least five clear round or cone-shaped subretinal deposits between external limiting membrane (ELM) or outer plexiform layers and retinal pigment epithelium (RPE) on SD-OCT in more than one B-scan and in at least one en face modality (CFP, FAF, NIR) or RPD present on two en face modalities in the absence of SD-OCT findings (including outside the SD-OCT grid).

Analysis

To make a direct comparison on the performance of different perimetric and DA parameters in detecting a visual dysfunction, only data at the four test points corresponding to identical locations in both the MAIA

and DACP were included in the analysis. These test points were located at the 4° ring in the inferior, nasal, superior, and temporal retina (Fig. 1B). The data of each test point were used to compare the performance between perimetric and DA parameters using a point-wise approach (four data points per eye). The comparison was performed using multilevel mixed-effects linear regression models with the study groups were considered fixed effects, test points nested within the participants were random effects, and age was a covariate. To compare the perimetric and DA parameters with visual acuity, we calculated the average sensitivity and RIT of the four data points for each subject (one data point per eye). Linear mixed models were used for the comparison in the performance between perimetric and DA parameters and visual acuity with age as a covariate. The fitness of the models was assessed by visual inspection of the distribution of the residuals. In a simple term, the linear regression model for each functional parameter can be described as the following equation:

$$\begin{aligned} & \text{Functional parameter} \\ & = \beta_0 + \beta_1 \times \text{Group} + \beta_2 \times \text{Age} + \zeta_0 + \varepsilon \end{aligned}$$

Where β_0 through β_2 represent the fixed effects associated with the intercept, the study groups (control, no RPD, and RPD) and age, ζ_0 represents the random test locations nested within participant effect (only applicable to the perimetric and DA parameters), and ε represents the residual.

To overcome the potential problems with different dynamic ranges and scales among the functional tests, we used the data of the control group to calculate the z-score (standard deviation, SD) for each data point of each test for each subject. By using the z-score, measurements of all functional parameters were converted to a common scale, which allowed for a direct

comparison between tests. An individual z-score within ± 2 (< 2 SD) was considered as within the normal range. The average z-score and 95% confidence interval (CI) of each functional parameter and study group were calculated and compared. All analyses were conducted using Stata software version 16.0 (Stata Corp, College Station, TX).

Results

Forty-eight participants (23 normal control and 25 iAMD) were recruited for this study. Of the 25 eyes with AMD, 12 eyes had RPD (drusen + RPD, RPD⁺ group) and 13 eyes did not have RPD (drusen only, RPD⁻ group). On average, iAMD participants (72.7 ± 8.4 years) were older than control participants (65.1 ± 8.8 years, $P = 0.003$).

The comparison between control and AMD eyes on different functional parameters are shown in the Table. All the parameters demonstrated a significant reduction in function in the AMD eyes compared to the control eyes. Among the five functional parameters examined, the RIT had the largest z-score, demonstrating its ability to detect the greatest magnitude of functional deficit in eyes with AMD compared to the other parameters.

To examine the sensitivity of these parameters in assessing visual function in different AMD phenotypes, the data were further analyzed with the AMD eyes subdivided into those with RPD (RPD⁺) or without RPD (RPD⁻). The results of various functional parameters by the study groups are shown in Figure 2. The RIT, scotopic sensitivity, and mesopic sensitivity showed a significant reduction in function in eyes without RPD and eyes with RPD compared to the healthy control eyes ($P \leq 0.005$, Fig. 2A), and that eyes

Table. Comparison Between Control and iAMD Group on Various Functional Parameters

Functional Parameters	Control [$n = 23$]	iAMD [$n = 25$]	P Value*
	Mean \pm SD	Mean \pm SD (95% CI)	
Rod intercept time, minutes	7.4 \pm 2.4	18.0 \pm 8.2	<0.001
Scotopic sensitivity, decibels	50.5 \pm 3.4	43.4 \pm 8.9	<0.001
Mesopic sensitivity, decibels	27.8 \pm 2.1	25.7 \pm 3.1	<0.001
BCVA, letters	89.7 \pm 5.1	84.4 \pm 6.4	0.003
LLVA, letters	79.2 \pm 7.4	70.6 \pm 10.7	0.002
Rod intercept time, z-score	0 \pm 1	4.5 \pm 3.5 (3.8 to 5.2)	<0.001
Scotopic sensitivity, z-score	0 \pm 1	-2.2 \pm 2.8 (-2.8 to -1.6)	<0.001
Mesopic sensitivity, z-score	0 \pm 1	-1.0 \pm 1.6 (-1.3 to -0.7)	<0.001
BCVA, z-score	0 \pm 1	-1.0 \pm 1.3 (-1.6 to -0.5)	0.003
LLVA, z-score	0 \pm 1	-1.2 \pm 1.4 (-1.8 to -0.6)	0.002

SD = standard deviation, CI = confidence interval, * age adjusted.

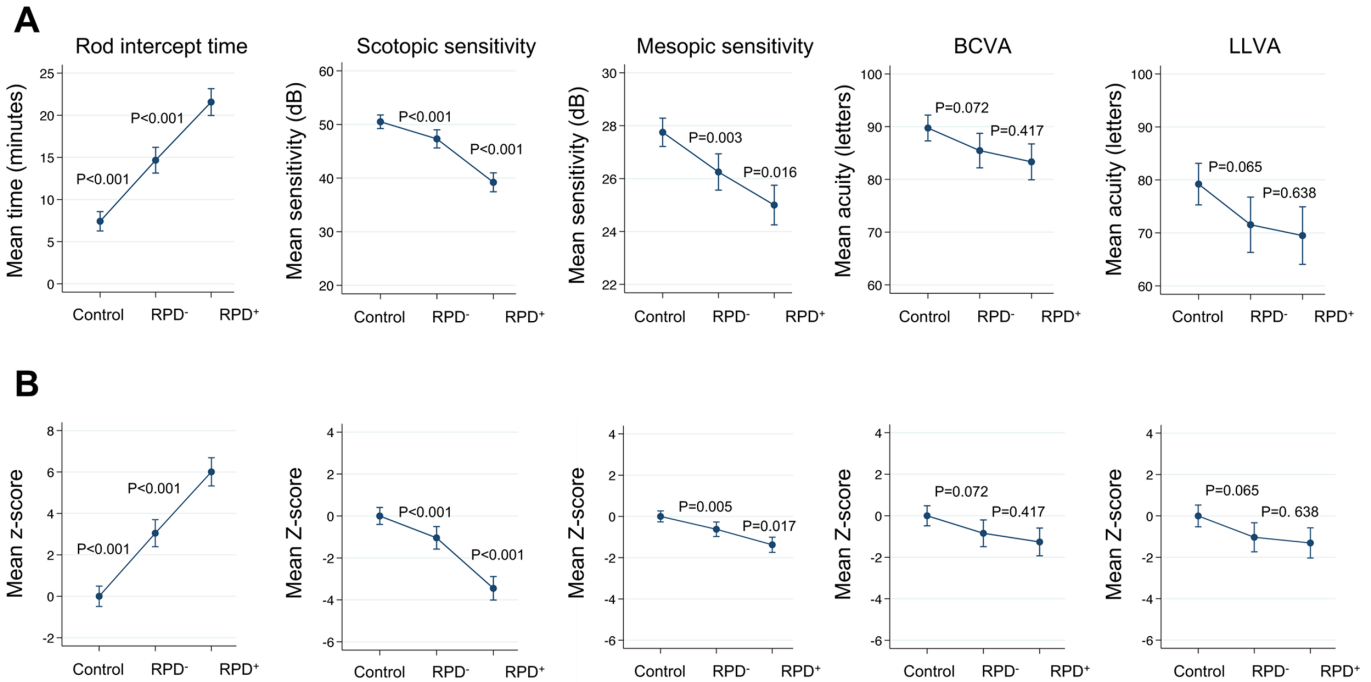


Figure 2. Mean measurements (A) and z-score (B) of various functional parameters by the study groups. RIT parameter showed the greatest functional deficit between control and no RPD (RPD⁻) group, and between RPD (RPD⁺) and no RPD group. Error bars represent 95% confidence interval.

with RPD had a greater reduction than eyes without RPD. However, the BCVA and LLVA failed to demonstrate a significant difference in function between AMD and control eyes ($P \geq 0.065$), and between RPD and no RPD eyes ($P \geq 0.417$).

The mean z-score of various functional parameters by the study groups are shown in Figure 2B. The RIT returned with the greatest z-score followed by the scotopic sensitivity. However, the mean z-score of the scotopic sensitivity for eyes without RPD

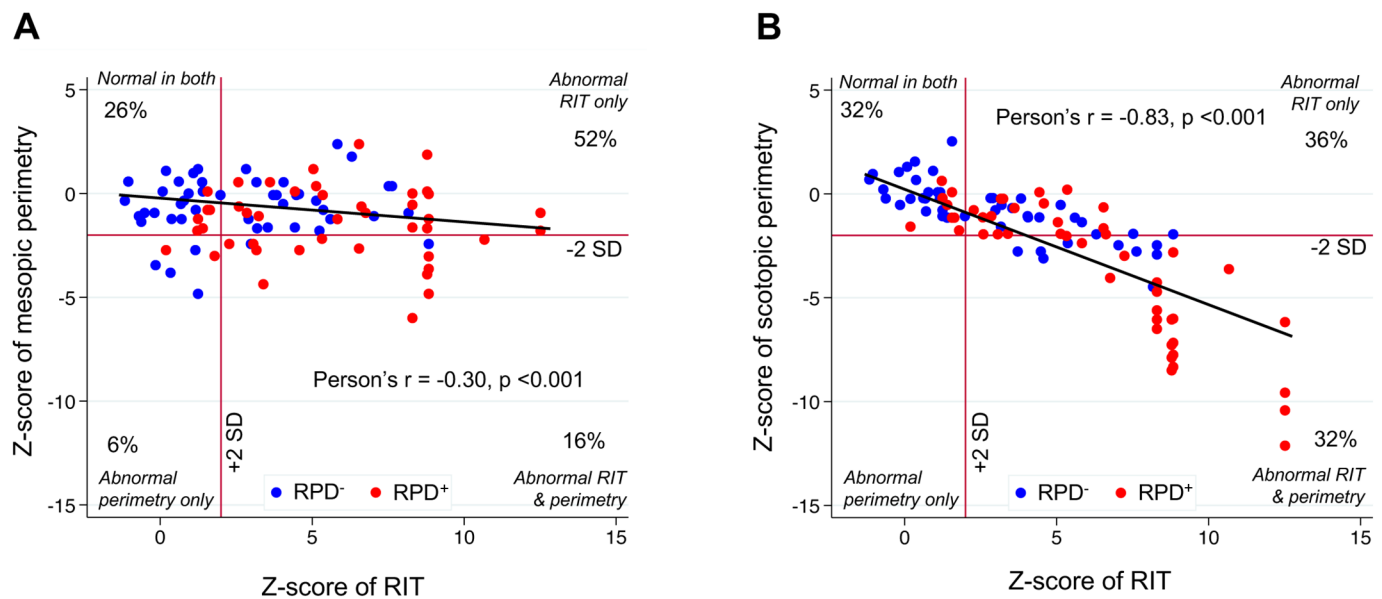


Figure 3. Relationships between the performance of RIT and mesopic perimetry (A) and RIT and scotopic perimetry (B) in detecting a functional deficit in AMD eyes. The RIT detected more test points with and a greater magnitude of abnormal function than either the mesopic or scotopic sensitivity. Note that eyes with RPD (RPD⁺, red dots) had worse function than eyes without RPD (RPD⁻, blue dots), and many but not all the abnormal test points came from eyes with RPD. The solid black lines represent the linear regression of the relationships.

was only -1.04 (95% CI, -1.58 to -0.50), thus, the scotopic sensitivity has limited sensitivity in detecting a functional deficit in eyes without RPD. BCVA and LLVA had a mean z-score of less than 2, even in eyes with RPD, indicating that only minimal functional reduction could be detected by these parameters.

To examine the relationship between the RIT and perimetric sensitivity the data were presented in scatter plots (Fig. 3). There was a weak relationship between the z-score of RIT and the z-score of mesopic sensitivity ($r = -0.30$, Fig. 3A). Abnormal function in the entire AMD cases was detected in 68% of the test points when using the RIT parameter (test points of ≥ 2 SD) compared to only 22% when using mesopic sensitivity parameters (test points of ≤ 2 SD). Only 16% of the test points were considered to be both abnormal in the RIT and mesopic sensitivity parameters.

There was, however, a strong relationship between the z-score of RIT and z-score of scotopic sensitivity ($r = -0.83$, Fig. 3B). While 68% of the test points had an abnormal RIT, only 32% of test points had an abnormal scotopic sensitivity. All test points with abnormal scotopic sensitivity had abnormal RIT.

Discussion

There are several functional parameters that are available and can be used to detect and monitor changes in function seen in the early stages of AMD. While most of these functional assessments are not routinely performed in clinical practice, they are often used in research settings to monitor AMD progression or assess the efficacy of potential interventions for early stages of AMD. However, when considering the design of an interventional study which aims to show a different trajectory in functional loss, it remains unclear as to which functional parameters are the most appropriate to use. In this study, all functional testing was performed in the same visit by the same AMD and control participants to allow a direct comparison among commonly used functional parameters to identify which of these parameters detects the greatest functional deficit in eyes with AMD. We found that the RIT parameter yielded the greatest functional deficits followed by the scotopic sensitivity. However, scotopic sensitivity had a relatively low discriminatory power between control and AMD eyes. The performance of the mesopic sensitivity, BCVA, and LLVA were similar in that they were not particularly sensitive in separating the function of AMD eyes without RPD from AMD eyes with RPD nor AMD eyes without RPD from controls.

Our findings suggest that tests performed in scotopic conditions are more sensitive and yield a greater functional deficit than tests performed in mesopic or photopic conditions. This was consistent with the literature which reports that rod dysfunction can be identified earlier than cone dysfunction in the early stages of AMD, and that eyes with RPD have worse rod dysfunction than eyes with only large drusen.^{9,10,12,21} Hence, rod-mediated function such as the RIT and scotopic sensitivity, seem to be the most appropriate parameters for assessing functional changes in early stages of AMD. While all functional tests appeared worse in AMD eyes without RPD compared to controls the difference was not sufficient to differentiate from normal variation in many of the tests.

It is important to note that scotopic perimetry may not always reflect a rod-mediated response. The cellular contribution to the scotopic sensitivity depends upon the health status of both the rods and cones.^{10,30} In the early stages of AMD when rod function is mildly reduced but cone function is normal, the scotopic sensitivity will be mediated by rods. However, when rod function is severely abnormal and potentially cone function remains relatively normal, the sensitivity under scotopic conditions could be mediated by cones. In normal eyes, rods are approximately 2.5 log units more sensitive than cones when measured with the 505 nm stimulus.³¹ Hence, if cones are normal, this is the maximum magnitude of rod abnormality that could be detected using a scotopic perimeter with a full dynamic range of stimulus luminance. However, many current scotopic perimeters have a limited dynamic range, thus, subtle rod dysfunction may be missed, and the magnitude of rod dysfunction may not be reliability determined.

It is also worth noting that the scotopic sensitivity in this study was obtained after a photobleach. This was different to many of the previous studies in which no photobleach was applied prior to scotopic perimetry testing. Photobleach was used to minimize the variation in the level and duration of ambient light exposure among the participants and to activate the dynamic aspects of rod function, which has been shown to be more affected than static function in early stages of AMD.³² We also have reported that scotopic sensitivity of AMD cases without RPD was indistinguishable from controls when tested without photobleach.¹⁰ A difference in rod function between AMD without RPD and the control group was only observed when tested with preceding photobleach. Thus, scotopic perimetry performed after bleaching provides a greater ability to detect rod dysfunction in early stages of AMD.

In our study the participants performed all the tests in the same session. This is not usually the case where different cohorts perform different tests in the previous studies. Hence, the data collected in this study are unique and allow us to comment on which parameters appear most informative when considering dysfunction in the early stages of AMD. The RIT returned with the greatest functional deficit and as such appears to be the most appropriate parameter to test when assessing the efficacy of novel interventions aiming at slowing the decline in visual function in eyes with early stages of AMD, or indeed possibly even improving function. Furthermore, it has been shown that the greatest abnormal RIT is at 4° from the fovea, and it is relatively normal beyond 12° from the fovea,¹⁰ thus measuring the RIT at multiple locations could help assessing both the safety and efficacy of novel interventions. It is recognized that dark adaptation is one of the hardest and least feasible tests to perform in a clinical trial setting, especially if needing this test to be performed at many sites on many participants. However, it does appear that the value in these results may outweigh the clinical difficulty and no number of noninformative tests, especially of photopic function will deliver the same informative data.

The strength of this study was that the mesopic and scotopic sensitivity and dark-adaptation parameters were collected at the same retinal locations, during the same session on the same patients, allowing a robust comparison among these functional parameters. There was also a large range of functional deficit which allowed a better estimation on the relationship between functional parameters. Although the number of subjects recruited for the study was relatively small, there were four data points obtained in each eye for the perimetric data and thus the total number of data points in each group were sufficient for the analysis. A potential limitation of the study was that AMD participants were older than the control subjects. However, all participants performed the same sequence of tests and thus the difference in the magnitude of dysfunction observed between tests should remain valid.

In conclusion, a direct comparison of commonly used tests for detecting a functional deficit in eyes with the early stages of AMD was performed and the RIT appears to be the most sensitive parameter in detecting the presence and magnitude of functional abnormality in eyes with AMD. Testing RIT at multiple locations in the retina is likely to deliver the best data to help show a difference in progression between arms in an intervention study in iAMD. The practicalities of conducting such tests at many sites on many participants remain a disincentive to include these tests. However, selecting an additional noninformative test will not compensate

for the missing data that can only be obtained under scotopic conditions.

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