

Delays in Rod-mediated Dark Adaptation in Early Age-related Maculopathy

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Objective: To determine whether there are disturbances in the rod-mediated kinetics of dark adaptation in early age-related maculopathy (ARM).

Design: Comparative, observational case series.

Participants: Twenty older adults with early ARM as defined by one or more large ($>63\ \mu\text{m}$) drusen, focal hyperpigmentation, or both, but no choroidal neovascularization or geographic atrophy, and 16 adults in the same age range with none of these fundus features. All participants had 20/25 visual acuity or better in the tested eye.

Methods: Dark adaptation functions were measured using a modified Humphrey Field Analyzer (Zeiss Humphrey Systems, Dublin, CA) to assess the rate of rod-mediated sensitivity recovery at 12° on the vertical meridian in the inferior visual field after exposure to the equivalent of a 98% bleach. Baseline (prebleach) scotopic sensitivity, visual acuity, contrast sensitivity, and photopic sensitivity were also measured.

Main Outcome Measures: Rod-cone break; second and third components of rod-mediated dark adaptation; time to baseline sensitivity; and baseline (prebleach) scotopic sensitivity.

Results: Although their visual acuity was at least 20/25, patients with early ARM on average exhibited deficits in almost all rod-mediated parameters of dark adaptation as compared with age-similar healthy participants. For example, the rod-cone break was delayed approximately 10 minutes in early ARM patients as compared with healthy participants. Age-related maculopathy patients were more likely to fall outside the normal reference range for variables representing dark adaptation kinetics than for steady-state visual functions such as scotopic sensitivity. For example, 85% of ARM patients fell outside the normal reference range in at least one dark adaptation kinetic parameter, whereas only 25% of ARM patients fell outside the normal reference range for steady-state scotopic sensitivity.

Conclusions: Rod-mediated kinetic parameters of dark adaptation, which reflect the sensitivity recovery of the visual cycle, are disrupted early in ARM pathogenesis. *Ophthalmology* 2001;108:1196-1202 © 2001 by the American Academy of Ophthalmology.

Age-related maculopathy (ARM) is a heterogeneous group of disorders in older adults in which central retinal photoreceptors are lost, either by an atrophic process, the most common disease expression, or by a neovascular event, the most destructive form causing severe vision impairment.¹ The mechanisms underlying vision loss in ARM are incompletely understood, but they are believed to be multifactorial and complex.^{2,3} Although ARM is the

leading cause of new blindness in older adults in developed countries,⁴⁻⁶ there are no effective treatments for its early form when there is still opportunity for preventing serious progression and severe vision loss. Recent histopathologic studies on human donor retinas with ARM indicate a predilection for parafoveal loss of rod photoreceptors over cones in the early, nonexudative form of the disease.⁷ Although both rods and cones in the parafovea degenerate in ARM, rod loss precedes and is more severe than cone loss in most donor retinas evaluated, and even in the exudative form of ARM, there is greater retention of cones compared with rods.⁷ Given the loss of rods early in ARM pathogenesis, the existence of a test to probe rod function may prove useful as an assay in tracking progression in observational studies on ARM or for monitoring interventions targeted at the earliest forms of the condition.⁸

Functional studies have revealed scotopic dysfunction in the early stages of ARM,^{9,10} and are thus consistent with rod vulnerability early in the pathogenesis of this condition. In a recent study, more patients with early ARM showed deficits in scotopic (rod-mediated) sensitivity than photopic (cone-mediated) sensitivity, and in most patients the mag-

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nitude of the rod-mediated loss was greater than that of the cone-mediated loss.¹⁰ Scotopic sensitivity in this study was measured on a zero background (i.e., complete darkness) after the retina had adequate time to adapt to darkness (i.e., under steady-state conditions).

Hallmarks of ARM include thickening of Bruch's membrane and formation of deposits that contain high levels of neutral lipids, causing Bruch's membrane to become hydrophobic.^{11–15} Thus, it would not be surprising if these structural changes served as barriers that limit the pool of vitamin A available to the retinal pigment epithelium (RPE), or slow the transport of 11-*cis*-retinal to the rod outer segment from the RPE. This situation could delay rhodopsin regeneration in early ARM. It is also important to make note of recent advances in the molecular basis of human dark adaptation that are relevant to the health of the Bruch's membrane–RPE complex.^{16,17} This complex supplies the rod outer segment with 11-*cis*-retinal, which is necessary for rhodopsin regeneration. Diseases such as vitamin A deficiency¹⁸ and Sorsby's fundus dystrophy¹⁹ that affect the pool of 11-*cis*-retinal in the Bruch's membrane–RPE complex cause a slowing of rhodopsin regeneration. This effect manifests itself as a decreased rate of sensitivity recovery during the second component of dark adaptation. We propose that ARM-related changes in the Bruch's membrane–RPE complex may have a similar effect on the regeneration of rhodopsin in the rods in early ARM.⁸ Specifically, ARM-related changes in the Bruch's membrane–RPE complex may cause an insufficient supply of 11-*cis*-retinal to the rod outer segment. This condition would slow rhodopsin regeneration and decrease the rate of sensitivity recovery during the second component of dark adaptation. Dark adaptometry techniques allow one to examine this issue.

Prior studies are consistent with rod-mediated dark adaptation delays in early ARM,^{9,20–22} but as a group these studies are difficult to interpret for a number of reasons. For example, in some studies the presence of disease was not defined on the basis of standard fundus grading systems,^{20–22} so it is uncertain as to what specific level of disease subtype or severity was being evaluated. Subjective techniques were typically used for characterizing dark adaptation functions.^{9,22} Only a small number of ARM patients were studied in some papers.^{20,21} Other studies have focused primarily on cone-mediated adaptation problems.^{23–27}

The purpose of this study was to examine whether disturbances in kinetics of rod-mediated dark adaptation occur in the early stages of ARM as compared with a normal, age-similar reference group, using techniques that overcome the methodologic limitations of the earlier work. Specifically, a standard grading scale of macular health was used to define the presence of ARM,^{28,29} stimulus parameters were selected to probe rod function and minimize cone intrusion, and an objective statistical technique was used to estimate dark adaptation parameters.³⁰ If present, the extent of these rod-mediated deficits in the kinetics was compared with any deficits observed in steady-state visual function such as scotopic sensitivity, photopic sensitivity, and contrast sensitivity.

Table 1. Description of the Macula Grading System

Grade	Description
0	≤5 small (≤63 μm) drusen
1	>5 small (≤63 μm) drusen
2	≥1 large (>63 μm) drusen, focal hyperpigmentation, or both
3	Drusen and choroidal neovascularization
4	Drusen and geographic atrophy
5	Drusen and choroidal neovascularization and geographical atrophy

Patients and Methods

Patients with ARM were recruited based on consecutive chart review of patients seen over a 6-month period in the Retina and Vitreous Service of the Department of Ophthalmology, University of Alabama at Birmingham. Inclusion criteria were as follows: (1) at least 60 years of age; (2) 20/25 visual acuity or better (best-corrected distance) in the eye to be tested psychophysically, as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart³¹; and (3) a diagnosis of ARM in the test eye based on fundus photography. Fundus photographs taken on the day of testing were evaluated by a trained grader using a standardized scale of macular health (Table 1), based on the international classification system^{32,33} and as described in our previous work.^{28,29,34} To be classified as having early ARM, the test eye had to have one or more large (>63 μm) drusen, focal hyperpigmentation (grade 2 in Table 1), or both, but no choroidal neovascularization or geographic atrophy. The fellow eye could have any grade. The grader was unaware of the participant's visual functional status, prior ocular diagnoses, and age. Exclusion criteria were as follows: (1) glaucoma, ocular hypertension, diabetes, or any other ocular, neurologic, or systemic disease that would compromise vision in either eye, as indicated by a comprehensive eye examination within 6 months of enrollment; and (2) use of medications that would complicate interpretation of the data (e.g., retinotoxic drugs). The final sample of ARM patients consisted of 20 persons (mean age, 75 years; standard deviation, 6 years; range, 66–88 years), consisting of 14 men and 6 women, all of whom were white.

Older adult healthy volunteers (n = 16; 6 women and 10 men, all of whom were white) were recruited from the Primary Care Clinic of the School of Optometry. Mean age of the healthy reference group was 72 years (standard deviation, 5 years; range, 62–79 years). With respect to funduscopy appearance, the test eyes of healthy participants were either graded as having five or fewer small (≤63 μm) drusen or more than five small (≤63 μm) drusen (grades 0 or 1 in Table 1), but no large drusen, focal hyperpigmentation, choroidal neovascularization, or geographic atrophy. Other inclusion and exclusion criteria were as described above.

Written informed consent was obtained from all participants before the protocol began, and approval for the study was obtained from the Institutional Review Board for Human Use at the University of Alabama at Birmingham. Dark adaptation functions were measured using a modified Humphrey Field Analyzer (HFA; Zeiss Humphrey Systems, Dublin, CA), a computer-automated perimeter for measurement of light sensitivity that was modified for dark adaptometry as described in detail previously.²⁹ An infrared CCD camera and light source to monitor fixation in the dark and an additional filter wheel to control target wavelength were installed in the HFA. The participant's head was positioned on a chin and forehead rest. The test eye was aligned to the fixation light using the camera built into the HFA. Participants viewed the test target from a distance of 30 cm with their best optical correc-

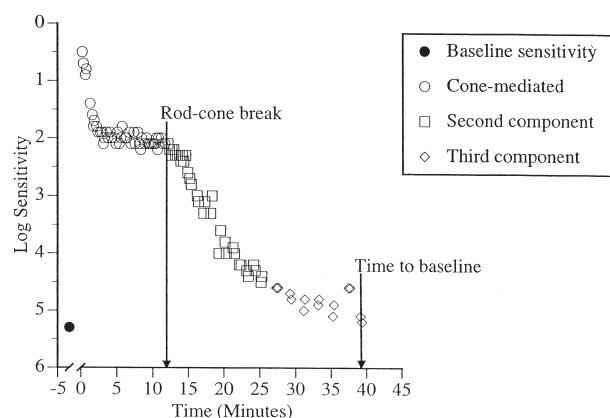


Figure 1. An example of a dark adaptation function showing the parameters of dark adaptation that are provided by the nonlinear regression analysis. This study focuses on rod-cone break, the second and third components of rod-mediated dark adaptation, time to baseline sensitivity, and the baseline (prebleach) sensitivity.

tion for the test distance. The fellow eye was patched. Before the bleach and measurement of the dark adaptation function, each participant's baseline sensitivity was measured after 30 minutes of adjustment to darkness. A three-down-one-up modified staircase threshold procedure was used to estimate threshold. An external computer controlled the threshold measurement procedure and recorded responses. The test target consisted of a 500-nm (Ealing #35-3508; FWHM 7.4, peak 50%) circular test spot (1.7° diameter), located 12° in the inferior visual field along the vertical meridian.

After baseline sensitivity was measured, the test eye underwent a bleach (0.25 milliseconds) using an electronic flash of white light (7.65 log scotopic Trolands-second); this flash produced an equivalent approximately 98% bleach in the area of the retina to be tested.³⁵ Threshold measurements began 5 minutes after flash offset. Target intensity started at 4.85 cd/m². Targets were presented for a duration 200 milliseconds every 2 to 3 seconds. The participant was asked to press a response button when the target was visible and had 750 milliseconds to make a response after target onset. If the participant did not respond to the target, its intensity remained at 4.85 cd/m² until the participant responded. If the participant indicated the target was visible, the target intensity was decreased by 0.3 log unit steps on successive trials until the participant stopped responding that the target was present. After the participant responded that the stimulus was invisible, target intensity was increased by 0.1 log units until the participant responded that the target was once again visible. This target intensity was defined as threshold. Successive threshold measurements started with a target intensity 0.3 log units brighter than the previous threshold estimate. Threshold estimates were made twice every minute for the first 25 minutes and twice every 2 minutes thereafter. This process stopped when the participant's sensitivity was within 0.3 log units of the previously measured baseline (prebleach) sensitivity.

To control for pupil size, participants' pupils were dilated with 1% tropicamide and 2.5% phenylephrine hydrochloride before testing. All participants achieved a pupil diameter of 6 mm or more, which was verified under scotopic conditions before and after dark adaptometry. Because increased lens density is associated with advanced age,^{36,37} each participant's threshold estimate was adjusted for lens density before data analysis to focus on the neural component of the threshold. Lens density was estimated in

Table 2. Comparison of Age-related Maculopathy Patients and Control Participants for Age, Acuity, Contrast Sensitivity, and Photopic and Scotopic Sensitivity

Variable	Group		P Value*
	Control	Age-related Maculopathy	
Age			
Mean	72	75	0.13
Standard deviation	5	6	
Acuity (LogMAR)			
Mean	-0.06	-0.02	0.23
Standard deviation	0.1	0.1	
Contrast sensitivity (log ₁₀)			
Mean	1.51	1.50	0.80
Standard deviation	0.07	.23	
Photopic sensitivity†			
Mean	2.02	1.80	0.006
Standard deviation	0.15	.27	
Scotopic sensitivity†			
Mean	4.56	4.16	0.02
Standard deviation	0.31	0.52	

*Based on one-way analysis of variance comparing age-related maculopathy and control groups.

†Sensitivity averaged over 27 loci in the central 18° radius field.

the test eye using a psychophysical technique described in detail in our prior work,²⁸ which is an adaptation of lens density estimation procedures described by Sample et al^{38,39} and Johnson et al.⁴⁰

Dark adaptation functions were expressed as log sensitivity as a function of time (minutes) after bleach offset. To identify rod-mediated parameters of dark adaptation, each individual's sensitivity data (lens corrected²⁹) was fit with Lamb's model of rod-mediated dark adaptation^{17,41} using a nonlinear regression

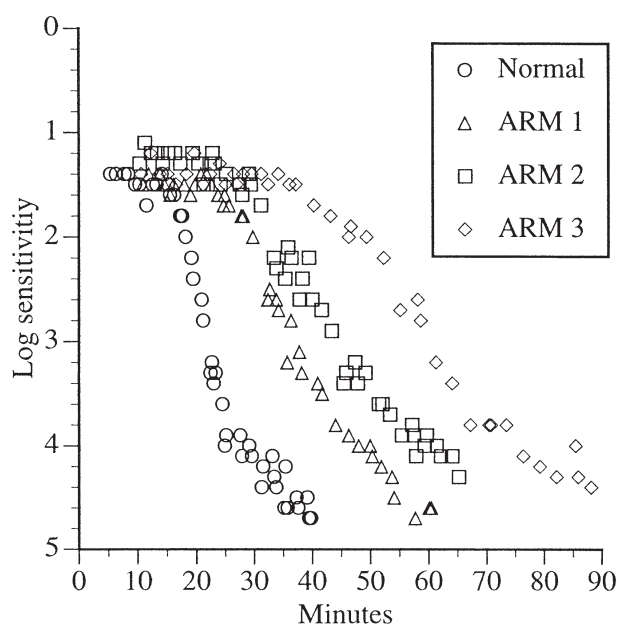


Figure 2. The dark adaptation functions for three age-related maculopathy patients and one older healthy adult. All participants had 20/25 visual acuity or better.

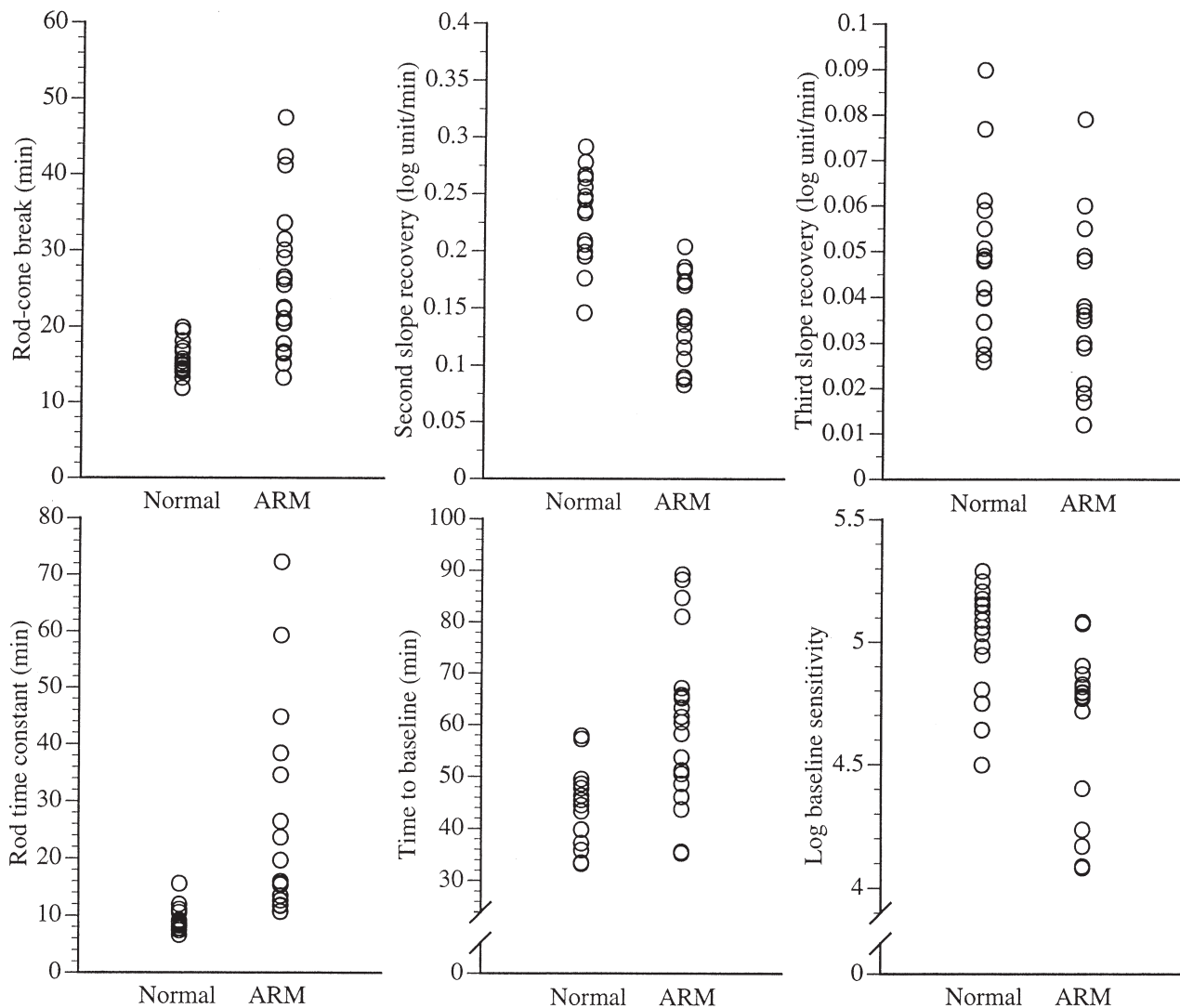


Figure 3. Scree plots of kinetic and steady state variables for all age-related maculopathy patients and age-similar healthy participants.

technique, previously described,³⁰ that minimizes experimenter bias. Figure 1 shows an example of a dark adaptation function and the relevant parameters provided by the nonlinear regression analysis. Because the cone-mediated phase of sensitivity recovery obscures the first component of rod-mediated dark adaptation, the focus in the analysis was on the second and third components of rod-mediated dark adaptation. The rates of sensitivity recovery during the second and third components are particularly germane because they are largely dictated by the rate of rhodopsin regeneration, as indicated by electrophysiologic work on animal models^{41–44} and retinal densitometry findings in humans.⁴⁵

Photopic sensitivity and scotopic sensitivity were also estimated at 27 loci in the central 18° of the visual field, using the same HFA apparatus as described above and techniques as described previously.³⁴ Briefly, the wavelength of the target was 600 nm for photopic measurements and 500 nm for scotopic testing. Target size was a Goldmann size V (1.7° of visual angle), and the circular test spot was projected for 200 milliseconds into a Ganzfeld bowl with a background luminance of 10 cd/m². Thirteen test points were located on the horizontal meridian ($\pm 2^\circ$, $\pm 4^\circ$, $\pm 8^\circ$,

$\pm 10^\circ$, -12° , $\pm 18^\circ$; $\pm 12^\circ$) and 14 on the vertical meridian ($\pm 2^\circ$, $\pm 4^\circ$, $\pm 8^\circ$, $\pm 10^\circ$, $\pm 12^\circ$, $\pm 18^\circ$; $\pm 12^\circ$). The HFA's full threshold procedure (4-2 modified staircase threshold strategy) was used to estimate sensitivity. For scotopic testing, participants adapted to the dark for 40 minutes before beginning threshold measurement. For the purpose of data analysis, scotopic and photopic sensitivity were defined as average sensitivity across all test points in the 18° radius test field. Contrast sensitivity at fixation was estimated by the Pelli-Robson chart using standard techniques⁴⁶ and the letter-by-letter scoring procedure.⁴⁷

Results

All variables were normally distributed, so parametric statistics were used. There were no missing data on any variable. Group differences between the ARM patients and healthy participants on key variables were assessed using one-way analysis of variance (two-tailed, $\alpha = 0.05$; Stat-View, SAS, Cary, NC). As indicated in Table 2, although the ARM group (mean age, 75 years) was on

Table 3. Comparison of Age-related Maculopathy Patients and Control Participants on Dark Adaptation Variables

Variables	Group		P Value*
	Control	Age-related Maculopathy	
Rod-cone break (min)			
Mean	15.78	26.01	0.0003
Standard deviation	2.17	9.48	
Second component recovery rate (log ₁₀ unit/min)			
Mean	0.23	0.15	0.0001
Standard deviation	0.04	0.04	
Third component recovery rate (log ₁₀ unit/min)			
Mean	0.05	0.04	0.065
Standard deviation	0.02	0.02	
Time to baseline (min)			
Mean	44.17	60.80	0.0006
Standard deviation	7.40	15.99	
Rod-mediated time constant (min)			
Mean	9.19	24.58	0.0013
Standard deviation	2.21	17.26	
Baseline (prebleach) sensitivity (log ₁₀)			
Mean	5.01	4.71	0.004
Standard deviation	0.23	0.33	

*Based on one-way analysis of variance comparing age-related maculopathy and control groups.

average older than the healthy reference group (mean age, 72 years), the two age distributions were not statistically different ($F(1,34) = 2.41$; $P = 0.13$). The ARM patients' acuity (range, 20/15–20/25) was comparable with that for healthy participants (range, 20/15–20/25; $F(1,34) = 1.51$; $P = 0.23$), as was their contrast sensitivity ($F(1,34) = 0.06$; $P = 0.80$). Photopic sensitivity was on average 0.2 log units lower for the ARM patients compared with healthy participants ($F(1,34) = 8.88$; $P < 0.006$), and scotopic sensitivity was on average 0.4 log units lower for ARM patients compared with healthy participants ($F(1,34) = 7.24$; $P < 0.02$).

For illustration purposes, Figure 2 displays the actual dark adaptation functions for three ARM patients, plotted next to a dark adaptation function from a healthy older adult. Figure 3 shows the distribution of kinetic and steady-state variables for all ARM patients and healthy participants, and Table 3 lists the means and standard deviations of these parameters of each group. One-way analysis of variance assessed potential group differences. The rod-cone break was significantly delayed in ARM patients compared with healthy participants ($F(1,34) = 17.79$; $P < 0.0003$), with ARM patients requiring approximately 10 minutes longer before rod-mediated sensitivity was superior to cone-mediated sensitivity. Sensitivity recovery by ARM patients during the second component of rod-mediated dark adaptation was on average 0.8 log unit/minute slower compared with the control group ($F(1,30) = 36.01$; $P < 0.0001$). The third component of rod-mediated dark adaptation was comparable between the ARM patients and healthy participants ($F(1,30) = 3.67$; $P = 0.065$). Four of the 20 ARM patients were so impaired that it was impossible to distinguish between the second and third component of rod-mediated dark adaptation, whereas this was never the case for the control group. Age-related maculopathy patients took significantly longer to return to within 0.3 log unit of their baseline (prebleach) sensitivity compared with control participants ($F(1,34) = 14.71$; $P < 0.0006$), requiring approximately 17 minutes longer than did

Table 4. Percentage of Age-related Maculopathy Patients Falling Outside the Normal Reference Range on Each Variable

Variables	Percentage
Kinetic variables	
Rod-cone break	75
Second component recovery	56
Third component recovery	0
Time to baseline	55
Rod-mediated time constant	65
Any dark adaptation kinetics	85
Steady-state variables	
Baseline (prebleach) scotopic sensitivity	25
Photopic sensitivity over 18° radius field	25
Scotopic sensitivity over 18° radius field	20
Contrast sensitivity	35

healthy participants. The time constant of the complete rod-mediated dark adaptation function was calculated based on a simple exponential fit to the rod-mediated limb of the function. On average, the time constant in ARM patients was 15 minutes longer than for healthy participants ($F(1,34) = 12.49$; $P < 0.0013$). Baseline (prebleach) scotopic sensitivity at the loci tested by dark adaptation was 0.3 of a log unit less than for healthy participants ($F(1,34) = 9.84$; $P < 0.004$).

For all variables, the normal reference range was defined as two standard deviations around the mean of the control group, and then the percentage of ARM patients falling outside the normal reference range was computed. These results are listed in Table 4. Age-related maculopathy patients were more likely to fall outside the normal reference range on the kinetic parameters of dark adaptation than on the steady-state sensitivity measurements (the only exception being the third slope of rod-mediated dark adaptation). If impairment of dark adaptation is defined as impairment in any of the kinetic parameters of dark adaptation, 85% of ARM patients exhibited an impairment.

Discussion

These results clearly indicate that the kinetics of rod-mediated dark adaptation are typically impaired in patients with early ARM, as compared with older adults who have normal-appearing maculas, and are consistent with other studies using different methodology.^{9,21} For example, the rod-cone break is delayed in early ARM patients by approximately 10 minutes, on average, as compared with healthy participants; this delay nearly doubles the time before the beginning of the rod-dominated limb of the adaptation curve. The time taken by early ARM patients to reach prebleach light sensitivity is more than 17 minutes longer than for healthy participants. The impairment in the time constant of rod-mediated dark adaptation exhibited by the ARM patients is indicative of significant impairment in the sensitivity recovery of the visual cycle. These data are consistent with the hypothesis described earlier, that ARM-related changes in the Bruch's membrane-RPE complex may cause an insufficient supply of 11-*cis*-retinal to the rod outer segment, thus slowing the visual cycle.⁸ An alternative mechanism is an abnormality in the ABCR gene product (as found in Stargardt's disease), which is a photoreceptor-based retinoid transporter,^{48–51} that could limit the

availability of 11-*cis*-retinal to the rod outer segment. However, ABCR mutations may not be a major genetic risk factor in ARM.⁵²

Unlike the other kinetic parameters, the third component of rod-mediated dark adaptation was not impaired in the early ARM patients. This is not surprising in light of our previous work²⁹ that found that during normal aging, this component exhibits substantial impairment in that the slope approaches zero. This creates a floor effect in our comparison of early ARM and healthy persons in the present study. In addition, there is greater variability in the slope of the third component in older adults as compared with young adults,²⁹ thus creating a situation where it would have been more difficult to differentiate between old, healthy participants and early ARM patients on this parameter, compared with other parameters.

Despite having good acuity, the early ARM patients exhibited significant delays in rod-mediated parameters of dark adaptation. What is striking is the demonstration that there is significant scotopic dysfunction in early ARM in the face of normal or near-normal cone-mediated vision (i.e., acuity, photopic sensitivity, contrast sensitivity). Furthermore, the kinetic aspects of scotopic dysfunction appear to be more sensitive in detecting vision impairment caused by early ARM than are the steady-state parameters in that ARM patients were more likely to fall outside the normal reference range on the kinetic parameters of dark adaptation than the steady-state scotopic measurements.

Strengths of this study include case definitions of early ARM and normality based on standard grading scales of the macula, statistical techniques for identifying dark adaptation parameters that minimize experimenter bias, and valid and reliable quantitative methodology for measuring rod-mediated dark adaptometry. A limitation is that cone-mediated parameters were not studied in the same patients for comparison purposes with rod parameters. The present study is cross-sectional; progression studies are needed to understand how dysfunction in dark adaptation parameters emerge. For example, it would be useful to examine the relative rates of rod- versus cone-mediated dysfunction early in ARM pathogenesis. Recently, we have shown that the scotopic impairment is more common than photopic impairment, and even when both exist, scotopic impairment is typically more severe.¹⁰ These findings, combined with our finding here that deficits in rod-mediated kinetic parameters coexist with good cone-mediated vision, underscore the need to understand better the factors predisposing rod vulnerability. On this basis, then, it would seem fruitful to include tests of rod function in prospective studies and in clinical interventions aimed at early ARM.

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