Loss of Cone Function in Age-Related Maculopathy

Joanna A. Phipps, Robyn H. Guymer, and Algis J. Vingrys

PURPOSE. To evaluate cone visual function of subjects with age-related maculopathy (ARM).

METHODS. Cone thresholds in 16 patients with ARM and 14 age-matched control subjects were compared. All subjects had visual acuity of 6/12 or better in the studied eye. A range of contrast thresholds were measured to evaluate diverse aspects of cone visual function under steady state conditions (spatio-temporal, color and luminance, and photopic sensitivity) or after bleaching (adaptation dynamics).

RESULTS. ARM produced a diffuse loss across all cone steady state visual functions in 31% to 44% of subjects. The adaptation time constant of cone recovery was significantly prolonged in most (69%) ARM eyes. A cross-correlational analysis found adaptational kinetics to be independent of other steady state losses, with cone photopigment regeneration being the most affected visual function in ARM ($\chi^2 = 4.03, P < 0.05$).

CONCLUSIONS. The results show that cone-adaptational kinetics are affected in ARM more so than are steady state thresholds. Given that cone recovery is easy to examine in a clinical setting, this test may provide a useful index of photopic function in patients with ARM. (Invest Ophthalmol Vis Sci. 2003; 44:2277–2283) DOI:10.1167/iovs.02-0769

Age-related macular degeneration (AMD) is a disorder of the macula that causes considerable vision loss in the elderly. Deposition of extracellular material (collagen, lipid, and phospholipid) occurs early in AMD, between the retinal pigment epithelium (RPE) and Bruch’s membrane, forming basal laminar deposits. This is accompanied by degeneration and pigment clumping in RPE cells and formation of drusen. As a consequence, the photoreceptors of the outer retina can degenerate and die. The early stage of this process is known as age-related maculopathy (ARM), in contrast to the more severe forms of AMD that involve geographic atrophy or neovascular complications.

Although ARM is known to affect the RPE and photoreceptors, autopsy studies have shown that cones are relatively spared. Such a finding should not be taken to mean that cone function is unaffected in the early stages of ARM. Visual losses in both rods and cones are well documented in this disease with the suggestion that rod dysfunction may be the earliest involvement. However, many of the studies that considered visual losses were based on clinical populations not well defined in terms of modern classification systems, making a precise quantification of ARM losses difficult to obtain from their results. A recent trial on rod function concluded that the kinetic aspects of rod visual adaptation are more affected in ARM than are steady state thresholds. This latter observation can be interpreted to reflect the compromised exchange across Bruch’s membrane that accompanies ARM and that may be expected to affect cone function as well.

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changes, in one or both eyes, being classified as having ARM. The final categorization of the ARM group was performed by examination of fundus photographs and fluorescein angiograms by two masked and experienced graders according to the Wisconsin grading scale, which is known to be both reliable and repeatable.8,32 The characteristics of experienced graders according to the Wisconsin grading scale, which categorization of the ARM group was performed by examination of each) and subjects who made more than one false response 36 were negative stimuli were included (5% presentation rate for thresholds were achieved with a 20-step yes/no bestPEST34 paradigm for 1 second that included a 200-ms ON-OFF cosine ramp followed by steady state prebleaching (photopic) contrast threshold (average of three estimates) for a 0.5° spot flickering at 5 Hz and shown on a 30 cd/m² background. Pilot trials showed that flickering the target aided detection during recovery. The recovery time to various contrast multiples above photopic threshold (3.5x, 3x, 2.5x, 2x, and 1.5x) were established after a 40-second bleaching (>95% bleaching of photopigment) by a diffusing screen illuminated by a quartz-iodine

### Psychophysical Testing

Visual stimuli were generated on a gamma-corrected color TV monitor (HM-4731; Hitachi, Tokyo, Japan) using a 14-bit video board (VSG 2/5; Cambridge Research Systems, Cambridge, UK) and commercial software (Psycho for Windows, ver. 2.33; Cambridge) or special purpose software written in our laboratory (adaptation dynamics). Pupils in all subject eyes were dilated with 0.5% tropicamide 30 minutes before testing (average pupil size, 6.9 ± 0.3 mm), and all subjects wore an appropriate refractive correction for the viewing distance. Subjects were tested monocularly at a distance of 1.7 m in a room with ambient luminance of 28 cd/m². After explanation of each procedure, a 5-minute practice session was allowed on each test before data collection.

The subject’s task was to fixate foveally and to respond to the presence of a stimulus by using a response box. Stimuli were presented for 1 second that included a 200-ms ON-OFF cosine ramp followed by a 1-second response interval between presentations. Steady state thresholds were achieved with a 20-step yes/no bestPEST34 paradigm (slope 65%). This paradigm has been shown to be fast (2-3 minutes per threshold) and efficient, even with an untrained population.35 False-positive and -negative stimuli were included (5% presentation rate for each) and subjects who made more than one false response 36 were asked to repeat the test. This occurred on only three occasions. In all cases, we measured contrast thresholds to minimize the effects of preretinal filtering.

### Spatial Contrast Sensitivity

Detection thresholds for targets varying in contrast were measured at four spatial frequencies (2, 4, 8, and 12 cyc/deg) that spanned the peak of the contrast sensitivity function. A Gaussian window (Gabor function) limited the sin-wave spatial profile to a fixed bandwidth (3 cyc/°, truncated at 1.5°). Figure 1 shows examples of our stimuli. These Gabor’s were presented about a mean white (1931 CIE x = 0.313, y = 0.329) background of 30 cd/m² with a maximum Michelson contrast of 0.94.

### Temporal Contrast Sensitivity

Detection thresholds were measured for 2.5° (diameter) Gaussian blobs (σ = 1.5°, Fig. 1C) at four temporal frequencies (2, 5, 10, and 25 Hz) that spanned the peak of the temporal response. Flicker was generated with a sinusoid that had a time-averaged luminance of 30 cd/m² and a maximum Michelson contrast of 0.94.

### Color Thresholds

Chromatic and achromatic thresholds were obtained with equiluminous red, green, blue, and yellow (R, G, B, and Y, respectively) blobs as well as luminous black-and-white (Bk and Wh) blobs of a common spatial and temporal extent (Fig. 1C). The subject’s task was to detect the presence of the stimulus. Stimuli were generated in MacLeod-Boynton color space 37 (R, x = 0.491, y = 0.272; G, x = 0.259, y = 0.409; B, x = 0.230, y = 0.117; Y, x = 0.410, y = 0.497; and Bk and Wh, x = 0.513, y = 0.529). The luminance of the background and equiluminous spots was 10 cd/m².

### Adaptation Dynamics

Postbleaching recovery was measured using a procedure similar to that developed by Collins and Brown.29 This begins by establishing the steady state prebleaching (photopic) contrast threshold (average of three estimates) for a 0.5° spot flickering at 5 Hz and shown on a 30 cd/m² background. Pilot trials showed that flickering the target aided detection during recovery. The recovery time to various contrast multiples above photopic threshold (3.5x, 3x, 2.5x, 2x, and 1.5x) were established after a 40-second bleaching (>95% bleaching of photopigment) by a diffusing screen illuminated by a quartz-iodine

### Table 1. Fundus Characteristics of Subjects with ARM

<table>
<thead>
<tr>
<th>Subject</th>
<th>Eye Tested</th>
<th>VA</th>
<th>Drusen Number</th>
<th>Dominant Size (μm)</th>
<th>Pigment Changes</th>
<th>Fellow Eye Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R</td>
<td>6/12</td>
<td>&gt;20</td>
<td>&gt;500</td>
<td>–</td>
<td>D</td>
</tr>
<tr>
<td>2</td>
<td>L</td>
<td>6/6</td>
<td>&gt;20</td>
<td>63-500</td>
<td>–</td>
<td>D</td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>6/6</td>
<td>&gt;20</td>
<td>63-500</td>
<td>+</td>
<td>CNV</td>
</tr>
<tr>
<td>4</td>
<td>L</td>
<td>6/6</td>
<td>&gt;20</td>
<td>63-500</td>
<td>–</td>
<td>D</td>
</tr>
<tr>
<td>5</td>
<td>R</td>
<td>6/6</td>
<td>&gt;20</td>
<td>63-500</td>
<td>–</td>
<td>D</td>
</tr>
<tr>
<td>6</td>
<td>R</td>
<td>6/12</td>
<td>&gt;20</td>
<td>63-500</td>
<td>–</td>
<td>D</td>
</tr>
<tr>
<td>7</td>
<td>L</td>
<td>6/12</td>
<td>&gt;20</td>
<td>63-500</td>
<td>+</td>
<td>D</td>
</tr>
<tr>
<td>8</td>
<td>L</td>
<td>6/12</td>
<td>&gt;20</td>
<td>63-500</td>
<td>+</td>
<td>D</td>
</tr>
<tr>
<td>9</td>
<td>L</td>
<td>6/9.5</td>
<td>&gt;20</td>
<td>63-500</td>
<td>+</td>
<td>D</td>
</tr>
<tr>
<td>10</td>
<td>R</td>
<td>6/7.5</td>
<td>10-20</td>
<td>65-500</td>
<td>–</td>
<td>CNV</td>
</tr>
<tr>
<td>11</td>
<td>R</td>
<td>6/9.5</td>
<td>10-20</td>
<td>65-500</td>
<td>–</td>
<td>D</td>
</tr>
<tr>
<td>12</td>
<td>R</td>
<td>6/6</td>
<td>&lt;10</td>
<td>63-500</td>
<td>–</td>
<td>PED</td>
</tr>
<tr>
<td>13</td>
<td>L</td>
<td>6/6</td>
<td>&gt;20</td>
<td>&gt;500</td>
<td>+</td>
<td>PED</td>
</tr>
<tr>
<td>14</td>
<td>R</td>
<td>6/6</td>
<td>&gt;20</td>
<td>&gt;500</td>
<td>+</td>
<td>CNV</td>
</tr>
<tr>
<td>15</td>
<td>R</td>
<td>6/6</td>
<td>&gt;20</td>
<td>&gt;500</td>
<td>+</td>
<td>D</td>
</tr>
<tr>
<td>16</td>
<td>R</td>
<td>6/6</td>
<td>&gt;20</td>
<td>&gt;500</td>
<td>+</td>
<td>D</td>
</tr>
</tbody>
</table>

D, drusen; CNV, choroidal neovascularization; PED, pigment epithelial detachment.
Cone Loss in ARM

After bleaching, subjects were instructed to keep their fixation steady by locating the prominent afterimage between four large lines that pointed to the center of the monitor. Targets were presented at the appropriate contrast for 400 ms (two cycles of flicker) followed by a 1-second response period. Recovery time was returned after two successive ‘seen’ responses at a given contrast level until the final (1.5×) contrast level had been detected. Recovery was complete in most control subjects within 20 to 50 seconds. The time course for recovery was modeled with a decaying exponential

\[ y = 1 + a \cdot e^{-t/t_c}, \]

where \( a \) is the \( y \)-intercept (% contrast) and \( t_c \) (seconds) is the time constant for decay. We optimized fitting of the model to our data by floating \( a \) and \( t_c \) and minimizing the sum-of-squares error term for each observer.

**Data Analysis**

Experimental results were considered in terms of between group differences and individual departures beyond age-matched limits (95%). To facilitate comparison of magnitude effects across different tests, we expressed performance in terms of the average measurement error for the control group by calculating a \( z \)-score: (control mean minus individual)/SD. Any performance beyond the 95% confidence limits was considered statistically removed (\( P < 0.05 \)) from the mean control value.

For steady state thresholds, a repeated-measures analysis of variance (RM-ANOVA, \( \alpha = 0.05 \)) considered the main effects of group (ARM, control) and variable (levels of parameter) and the group \( \times \) variable interaction. A Geiser-Greenhouse (GG) correction was applied to allow for the type I errors of repeated measures.\(^{39} \) Because the variable interaction was not significant for any parameter (i.e., the ARM group did not perform differently on any color, spatial, or temporal frequency), we used the average effect across all levels of the variable when calculating the \( z \)-score.

Estimating the confidence limits of a nonlinear relationship (adaptation) is not easy.\(^{40} \) We chose to apply a nonparametric bootstrap for this purpose, because it makes no assumptions about the underlying distribution of the data and can be used when fitting small data sets.\(^{40-42} \) Our bootstrap used 2000 replications to determine the mean and 95% confidence limits for \( a \) and \( t_c \). We applied a two-tailed criterion for group comparison by identifying significant departure from normal if the lower 97.5 percentile of the control group did not overlap the upper 2.5 percentile of the ARM group (\( P < 0.05 \)).

**RESULTS**

**Group Results**

Figure 2 shows the average (±SEM) loss of spatiotemporal and color sensitivity (20 \( \times \) log10 dB) in the ARM group at each level of the variable, compared with average control values. The lack of a significant interaction in any steady state threshold (group \( \times \) variable: \( P_{GG} > 0.05 \)), where GG represents the Geiser-Greenhouse correction) indicates a generalized loss of sensitivity across all spatial frequencies (\(-7.62 \pm 1.67 \text{ dB}; F_{1,13} = 19.86, P < 0.001 \)), temporal frequencies (\(-4.33 \pm 1.42; F_{1,13} = 6.96, P < 0.025 \)) colors (chromatic \(-4.33 \pm 1.47; F_{1,13} = 8.09, P < 0.025 \), and luminance \(-4.49 \pm 1.54; F_{1,13} = 6.85, P < 0.025 \)), as shown by the dashed horizontal lines in Figure...
Although there is a trend for high spatial frequency loss in Figure 2A, this failed to remain statistically significant after the Geiser-Greenhouse correction. The average recovery time after bleaching for the two groups is shown in Figure 3 on a semilog axis with the best-fitting relationship returned by the bootstrap given by the lines. The squares after the break in the x-axis represent the prebleaching (photopic) threshold for both groups. The ARM prebleaching thresholds were significantly different from control values (control, 2.24 ± 0.16 vs. ARM, 3.40 ± 0.27, F1,13 = 9.82, P < 0.01) consistent with the losses found in the other steady state parameters. As evident in Figure 3, the average time constant (tc) was significantly prolonged in ARM eyes (control, 18.0 ± 12.5 vs. ARM, 59.2 ± 16.7; P < 0.05), and the data show a linear relationship on a semilog axis. As a consequence, recovery times were transformed into a log scale for future comparison.

**Individual Results**

Performances are summarized as z-scores across all tests in Figure 4. Circles represent individual data, and squares represent group averages (±SEM). The dotted lines identify the 95th percentile for normal performance. This shows that just under half of all ARM subjects have significant losses in steady state thresholds (Figs. 4A–E), with the majority of subjects (69%) having a significantly prolonged time constant for recovery after bleaching (Fig. 4F).

**DISCUSSION**

The group of subjects with ARM recruited for this study comprised a well-defined subset of patients at high risk of development of AMD, who had relatively good visual acuity (Table 1), either multiple soft drusen bilaterally with or without pigmentary changes, or unilateral soft drusen and an end-stage lesion (choroidal neovascularization) in the fellow eye. These subjects were at risk for development of the later complications of AMD, and in this group, cone steady state thresholds were impaired in 31% to 44% of subjects (Table 2).

Because ARM is primarily a disease that affects the outer retina, it is not surprising that a loss in rod function has been reported, particularly in rod adaptation. This loss is thought to reflect either a barrier effect at Bruch’s membrane or dysfunction in the RPE. Both factors are likely also to produce widespread involvement of cone function. The purpose of our study was to consider whether cone adaptation was abnormal and whether it was more affected than steady state cone function, as has been reported previously for rods. Table 2 compares the percentage of the ARM group who
showed abnormal (P < 0.05) steady state and kinetic outcomes for cone function. In this table, the time constant of cone adaptational recovery was the single most affected parameter in most subjects with ARM and caused significantly more individuals (χ² = 4.03, P < 0.05) to be classified as having abnormal performance than did any of the steady state thresholds. This finding is consistent with the report of abnormalities in rods (85%), particularly the abnormal kinetics of rod adaptation (65%) noted in a similar cohort of patients with ARM.21 Although the findings for photopic and scotopic adaptational recovery were collected by using different test procedures and populations, both findings support the hypothesis that the kinetic aspects of visual function are more affected than are steady state thresholds at this stage of the disease.

The delayed kinetics of recovery in patients with ARM probably reflects a slowing in photopigment dynamics, consistent with the theory that both aging44 and disease45 cause a delay in cone photopigment regeneration. A delay in photopigment regeneration, whether it be rod or cone mediated, is a consistent finding in ARM. The molecular mechanisms underlying dark adaptation are becoming clearer in rod photoreceptors,46 and recent studies have suggested a similar process occurs for cone adaptation.47 From these studies, it is apparent that the ARM-related Bruch’s membrane and RPE changes would act to slow the recycling of visual photopigments, which could account for the increased time constant of adaptation observed in the present study.

It is important to determine whether steady state and kinetic thresholds identify the same or different aspects of ARM-related dysfunction. This was obtained by establishing correlations across test outcomes (Spearman rank-order coefficient), with the results given in Table 3, and a subset shown in Figure 5. Table 3 shows that most of the losses in all steady state thresholds (photopic, spatiotemporal and color) were either significantly correlated or gave a trend (P < 0.10) toward correlation. Visual acuity (results not shown) correlated signif-

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**TABLE 2.** Percentage of Patients with ARM Falling Outside the 95% Confidence Limits for Normal Performance on the Cone Functions Tested

<table>
<thead>
<tr>
<th>Cone Function</th>
<th>% Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinetic variable</td>
<td></td>
</tr>
<tr>
<td>Time constant (log sec)</td>
<td>69</td>
</tr>
<tr>
<td>Steady-state variables</td>
<td></td>
</tr>
<tr>
<td>Contrast sensitivity</td>
<td>44</td>
</tr>
<tr>
<td>Temporal sensitivity</td>
<td>38</td>
</tr>
<tr>
<td>Color sensitivity</td>
<td>31</td>
</tr>
<tr>
<td>Luminance sensitivity</td>
<td>38</td>
</tr>
<tr>
<td>Photopic threshold</td>
<td>44</td>
</tr>
</tbody>
</table>

All steady state tests had significantly fewer (χ² = 4.03, P < 0.05) failures compared with the time constant of adaptation.
significantly ($P < 0.05$) with spatial ($r = 0.449$) and temporal contrast sensitivity ($r = 0.594$), but not with the other functions tested. It is interesting to note that the time constant of cone adaptation did not correlate significantly with any steady state function. This demonstrates that recovery time identifies a unique aspect of ARM not available to the other tests. As it is likely that the abnormality in recovery dynamics arises from a dysfunction in pigment regenerative capacity, the other functional losses probably reflect another receptor-mediated malfunction. It is possible that this arises from the lower optical density and reduced quantal catch of the photopigment.13,48

Our findings do not exclude postreceptorial involvement, although we believe that this is less likely, given the nature of the disease, and the high correlations among the visual processes, implying a common deficit early in the visual pathway.

Our analysis shows that a combination of kinetic and steady state testing will be needed to identify visual deficits in early ARM, because these tests assay different aspects of visual function. The capacity of various combinations of steady state and kinetic tests to identify ARM is shown in Table 4. From this table, it is apparent that 12 of the 16 ARM eyes (75%) could be correctly classified with just two tests, providing that one of these tests includes a test of adaptation dynamics, whereas at least three tests are needed to identify all ARM eyes (88%) that have functional losses. If the same criteria were to be applied to the control subjects, all would be classified as having normal visual performance, using the test combinations given in Table 4.

To this extent, Figure 5 plots the relative loss of color sensitivity, compared with the time constant for adaptation. This figure illustrates the poor correlation between these two functions, reported in Table 3. Poor correlations were also evident for the other steady state parameters tested when compared with the time constant for adaptation (data not shown). Although some subjects were abnormal in both color sensitivity and adaptation (four subjects, 25%), most had prolonged recovery time (11 subjects, 69%). Very few had only color loss (one subject, 6%), whereas almost half (7 subjects, 44%) had only a delayed recovery from bleaching. Figure 5 emphasizes that adaptation dynamics identified the greatest number of subjects with ARM (69%), and the high $z$-scores for adaptation mean that subjects with ARM were easy to identify by using this test, particularly when using a linear scale. Finally, that control subjects recovered within 1 minute after bleaching makes this a simple and fast test for clinical application.

Previous reports suggest that subjects who have both abnormal color sensitivity and adaptational dynamics have a high likelihood of development of neovascularization.13,48 and, consistent with this theory, we find a delayed cone recovery in our subjects with ARM, who are all considered to be at high-risk for the development of neovascular complications. Because such persons often report difficulties recovering from bright lights and moving from light to dim situations,29 a test of cone adaptation may be a useful objective measurement in determining the extent of cone visual compromise in patients with ARM.

![Figure 5](image.png)

**Figure 5.** The relationship between the loss in color sensitivity (average across all colors) and the recovery time constant (log $t_1$) in 16 eyes with ARM. Values have been shown as standardized departures ($z$-scores) from the control value. The horizontal and vertical dotted lines: 95% confidence limits for normal performance, with the shaded region indicating normal adaptation and color vision.

<table>
<thead>
<tr>
<th>Test</th>
<th>% Detected</th>
</tr>
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<tbody>
<tr>
<td>All tests</td>
<td>88</td>
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