Flicker Sensitivity and Fundus Appearance in Pre-Exudative Age-Related Maculopathy

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**Purpose.** To evaluate whether foveal flicker sensitivity and fundus appearance are good predictors of exudative age-related maculopathy (ARM) when the effects of aging, retinal illumination, and criterion differences are controlled.

**Methods.** Fellow eyes of monocular exudative ARM patients were tested at baseline. Seven of these eyes have now developed exudative ARM. Therefore, at baseline they were in pre-exudative stages of ARM. The foveal flicker sensitivity and fundus appearance of the pre-exudative and nonconverted eyes were compared with healthy, age-matched eyes. The flicker stimulus was a uniform, 2.8 deg circular field at 660 nm, modulated sinusoidally at frequencies from 2.5 to 50 Hz. Fundus photographs were evaluated using the Wisconsin ARM grading system.

**Results.** Flicker modulation sensitivity at two frequencies discriminated pre-exudative from healthy older eyes with 100% accuracy. Using the same criterion, pre-exudative eyes also were discriminated from nonconverted eyes with 100% accuracy. Whereas an overall fundus ARM risk score discriminated pre-exudative from healthy older eyes with 100% accuracy, it did not discriminate pre-exudative from nonconverted eyes at better than chance levels.

**Conclusions.** There were functional changes in the retina preceding development of exudative ARM. Foveal flicker sensitivity at low- to mid-temporal frequencies seemed highly sensitive to these pre-exudative changes in this relatively small group of subjects. The authors hypothesize that foveal flicker sensitivity is a good predictor of exudative ARM and a sensitive monitor of retinal function in pre-exudative ARM. These predictions are being tested on a larger, independent sample.

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Age-related maculopathy (ARM) is the leading cause of visual loss in the United States among the elderly. The exudative form (also referred to as neovascular, disciform, or "wet" macular degeneration) is one of two varieties of ARM and generally is the more debilitating. The other type is nonexudative (also called geographic, dry, or atrophic) ARM. In this paper, we investigate some changes in visual function and retinal appearance that precede development of exudative ARM.

Exudative ARM is distinguished by subretinal neovascularization in the macula. Its clinical signs are: neurosensory detachment of the macula; macular lipid deposits; a gray subretinal membrane involving the macula; retinal pigment epithelial detachment; cystoid macular edema; submacular choroidal folds; and/or submacular hemorrhage. Some people with exudative ARM may notice blurred or distorted vision, but many are unaware of a problem until one eye is inadvertently covered. They then detect a scotoma near or at fixation in the other eye. Once macular function is lost, return of good vision is infrequent.

The etiology of exudative ARM is not known. It is thought that histopathologic changes take place in the macula long before the clinical symptoms and signs that define exudative ARM are manifest. Efforts to identify these changes have taken two main approaches—the anatomic and the functional. Included in the anatomic approaches are studies of retinal and
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Characteristics of the fundus appearance as documented by fundus photography include subretinal histopathology and changes in various functional approaches which may reflect compromised physiology such as foveal temporal modulation sensitivity, dark-adapted absolute threshold, dark adaptation rate, color matching, blue-cone-mediated sensitivity, the electro-oculogram, the electroretinogram, and spatial contrast sensitivity.

In a preliminary analysis, we reported on the temporal modulation sensitivity of two pre-exudative ARM (PE-ARM) eyes. We define eyes as PE-ARM if they do not manifest the clinical criteria for exudative ARM at baseline testing but later develop exudative ARM. For both patients who previously had PE-ARM, temporal frequencies at baseline were especially low for mid-temporal frequencies at baseline. We now have five additional patients with exudative ARM who were tested in the pre-exudative stage. In this paper, we report on the temporal modulation sensitivity and fundus appearance of all seven patients with PE-ARM.

MATERIALS AND METHODS

Subjects

We have tested 16 fellow eyes of patients with monocular neovascular exudative ARM for a period of 1.5 to 4 years. The fellow nonaffected eye of a patient with monocular exudative ARM is at higher risk than the general age-matched population for developing exudative ARM. We have referred to these fellow eyes as "ARM-risk" eyes. The mean age of the patients at baseline testing was 71.9 years. Nine were women. The mean age of the seven patients in whom exudative ARM developed in their second eye was 71.3 years at baseline. We refer to these seven patients as "converted" or as having "PE-ARM" eyes at the time of baseline testing.

We have also tested 20 older adults with no evidence of either exudative or atrophic ARM in either eye. Their mean age was 70.2 years. Ten were female.

This research followed the tenets of the Declaration of Helsinki. Subjects consented to take part after they were informed of the nature and possible consequences of the study. The procedures were approved by the UCSC Human Subjects Activities Review Committee.

All subjects were in relatively good general health and underwent careful ophthalmologic evaluation before baseline flicker testing. All were tested monocularly, and the tested eye had no pigment epithelial detachment, no subretinal neovascularization or hemorrhage or scarring, and no macular geographic atrophy at baseline. Best corrected Snellen acuity was 20/30 or better, and intraocular pressure was less than 22 mm Hg (Goldmann applanation). Ocular media were clear enough so that fundus details could be seen and graded. We excluded subjects with diabetes, myopia greater than 5 D, a history of strabismus, intraocular surgery (other than for cataract), or retinal, choroidal, or optic nerve vasculopathy. Characteristics of the subjects in the three outcome groups are listed in Table 1.

The healthy older eyes were examined with both indirect and direct ophthalmoscopy and had no or a few small, hard, yellow retinal drusen and no disturbance of retinal pigmentation, pigment epithelium, or subretinal neovascularization. For the ARM-risk eyes, both color fundus photography and fluorescein angiography were used to confirm the absence of exudative ARM in the ARM-risk eyes at baseline. The ARM-risk eyes have been evaluated clinically at approximately 1-year intervals since entering the study.

Although we have tested the flicker sensitivity of several of our subjects more than once, this paper considers only data at baseline. For the seven converted eyes, baseline sensitivity measurements preceded development of exudative ARM by 1485 (patient 32) to 55 (patient 34) days.

Flicker

The flicker stimulus was a 2.8°-diameter circle formed from an array of 25 light-emitting diodes (IDI 4310H1) set behind a diffuser. The LED peak output was 650 nm, with width at half-height of 20 nm. Long-wavelength light was used to minimize scatter and absorption from aging optical media or macular pigment. The stimulus, which was on continuously, was mounted in the center of the surface of an equiluminant, white, concave hemisphere (radius = 61 cm). Average luminance of stimulus and surround was 120 cd/m².

The subject viewed the stimulus monocularly from a forehead and chin rest placed at the center of the hemisphere. A mirror reflected an image of the subject's eyes to a video camera and recorder for measuring pupil size. Michelson contrast modulation thresholds were collected for most subjects with a two-interval forced-choice (2IFC), modified three-up-one-down staircase procedure. For a few subjects, yes-no procedures were used. We have shown that the yes-no thresholds are typically higher (less sensitive) than the 2IFC. But the yes-no data are equated with the 2IFC results when modulation sensitivity relative to retinal illuminance matched controls is calculated (see below).

Each 0.5 second display interval was a cosine bell, or Hanning window, whose beginning and end were designated by short beeps. The rate and amplitude of the sinusoidal flicker were controlled by a computer.
TABLE 1. Subject Characteristics and ARM Grade

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Iris Color</th>
<th>Acuity (20/20)</th>
<th>IOP (mm)</th>
<th>Media (0-4)</th>
<th>Retina</th>
<th>Wise ARM Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>69.7</td>
<td>M</td>
<td>Blue</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>77.4</td>
<td>F</td>
<td>Brown</td>
<td>25</td>
<td>18</td>
<td>1</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>65.9</td>
<td>F</td>
<td>Brown</td>
<td>25</td>
<td>14</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>65.3</td>
<td>F</td>
<td>Blue/grey</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>69.6</td>
<td>F</td>
<td>Blue/grey</td>
<td>25</td>
<td>21</td>
<td>1</td>
<td>Normal, trace drusen</td>
</tr>
<tr>
<td>6</td>
<td>69.7</td>
<td>F</td>
<td>Hazel</td>
<td>20</td>
<td>16</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>71.8</td>
<td>M</td>
<td>Blue</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>68.8</td>
<td>F</td>
<td>Blue/grey</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>9</td>
<td>71.3</td>
<td>M</td>
<td>Green</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>10</td>
<td>66.2</td>
<td>F</td>
<td>Green</td>
<td>20</td>
<td>17</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>11</td>
<td>70.0</td>
<td>F</td>
<td>Hazel</td>
<td>25</td>
<td>16</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>12</td>
<td>67.7</td>
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<td>Blue</td>
<td>25</td>
<td>18</td>
<td>0</td>
<td>Normal</td>
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<td>13</td>
<td>66.1</td>
<td>M</td>
<td>Brown</td>
<td>25</td>
<td>20</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>14</td>
<td>70.7</td>
<td>M</td>
<td>Brown</td>
<td>20</td>
<td>17</td>
<td>0</td>
<td>Normal, trace drusen</td>
</tr>
<tr>
<td>15</td>
<td>87.6</td>
<td>M</td>
<td>Blue</td>
<td>25</td>
<td>15</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>16</td>
<td>67.6</td>
<td>M</td>
<td>Blue</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>Normal, trace drusen</td>
</tr>
<tr>
<td>17</td>
<td>69.1</td>
<td>M</td>
<td>Blue/grey</td>
<td>15</td>
<td>19</td>
<td>0.5</td>
<td>Normal</td>
</tr>
<tr>
<td>18</td>
<td>72.0</td>
<td>F</td>
<td>Green</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>19</td>
<td>70.1</td>
<td>M</td>
<td>Green/blue</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>20</td>
<td>68.1</td>
<td>M</td>
<td>Green/grey</td>
<td>20</td>
<td>16</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>Nonconverted risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>81.8</td>
<td>F</td>
<td>Hazel</td>
<td>20</td>
<td>17</td>
<td>1.5</td>
<td>Few drusen, some RPE atrophy</td>
</tr>
<tr>
<td>22</td>
<td>76.1</td>
<td>F</td>
<td>Hazel/green</td>
<td>25</td>
<td>16</td>
<td>0.5</td>
<td>RPE atrophy throughout macula with pigment clumping in upper macula; fine drusen</td>
</tr>
<tr>
<td>23</td>
<td>68.9</td>
<td>M</td>
<td>Blue</td>
<td>20</td>
<td>15</td>
<td>0</td>
<td>RPE mottling, scattered small drusen</td>
</tr>
<tr>
<td>24</td>
<td>66.1</td>
<td>M</td>
<td>Blue</td>
<td>30</td>
<td>11</td>
<td>2.5</td>
<td>Mild RPE mottling, peripapillary chorioretinal atrophy</td>
</tr>
<tr>
<td>25</td>
<td>70.2</td>
<td>F</td>
<td>Green</td>
<td>25</td>
<td>15</td>
<td>0</td>
<td>Hypopigmentation, 1/5 disc diameter, adjacent to fovea, inferotemporal macula</td>
</tr>
<tr>
<td>26</td>
<td>68.2</td>
<td>F</td>
<td>Green/blue</td>
<td>25</td>
<td>17</td>
<td>0</td>
<td>Fine RPE mottling</td>
</tr>
<tr>
<td>27</td>
<td>60.4</td>
<td>F</td>
<td>Green/blue</td>
<td>25</td>
<td>16</td>
<td>0.5</td>
<td>Perimacular geographic pigment defects, hypofluorescent nerve head, arteriolar narrowing</td>
</tr>
<tr>
<td>28</td>
<td>87.4</td>
<td>F</td>
<td>Green</td>
<td>30</td>
<td>11</td>
<td>0</td>
<td>Multiple small RPE defects with spots and patches of atrophy inferior to fovea</td>
</tr>
<tr>
<td>29</td>
<td>78.5</td>
<td>F</td>
<td>Blue</td>
<td>30-13</td>
<td>2-3.5</td>
<td></td>
<td>Arteriolar narrowing in retinal vessels, low grade peripapillary subretinal neovascularization</td>
</tr>
<tr>
<td>Pre-exudative ARM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>73.2</td>
<td>M</td>
<td>Green/blue</td>
<td>30</td>
<td>14</td>
<td>1, 2</td>
<td>Irregular pigment mottling, asteroid hyalosis</td>
</tr>
<tr>
<td>31</td>
<td>74.4</td>
<td>M</td>
<td>Blue</td>
<td>25</td>
<td>16</td>
<td>1</td>
<td>Scattered, tiny, punctate hypopigmented spots in posterior pole</td>
</tr>
<tr>
<td>32</td>
<td>73.1</td>
<td>M</td>
<td>Blue</td>
<td>25</td>
<td>13</td>
<td>0</td>
<td>Confluent drusen, involutional macular changes</td>
</tr>
<tr>
<td>33</td>
<td>75.2</td>
<td>M</td>
<td>Blue/grey</td>
<td>30</td>
<td>17</td>
<td>1, 2</td>
<td>Confluent drusen in temporal macula</td>
</tr>
<tr>
<td>34</td>
<td>72.3</td>
<td>F</td>
<td>Green</td>
<td>25</td>
<td>14</td>
<td>1</td>
<td>Dry patchy atrophic pigment defects, more confluent centrally</td>
</tr>
<tr>
<td>35</td>
<td>61.2</td>
<td>M</td>
<td>Blue</td>
<td>25</td>
<td>15</td>
<td>2</td>
<td>Multiple spots of RPE atrophy and hyperpigmentation</td>
</tr>
<tr>
<td>36</td>
<td>70.0</td>
<td>F</td>
<td>Hazel/green</td>
<td>25</td>
<td>15</td>
<td>2</td>
<td>Fairly extensive dry involutional degenerative stigmata</td>
</tr>
</tbody>
</table>
Flicker Sensitivity and Fundus Features

(Apple [Apple Computer, Cupertino, CA] II+ with custom interface). Staircases for frequencies from 2.5 and 50 Hz were interleaved as the program swept repeatedly from low to high frequencies.

Two complete de Lange34 or modulation sensitivity functions (MSFs) were measured for each subject and averaged. These can be analyzed directly, but whereas retinal illuminance differences from optical absorption were controlled by the long-wavelength stimulus, retinal illuminance could still vary because of pupil size differences and spectacle absorption.35 To compensate for the retinal illuminance differences from these sources, we measured pupil size and estimated spectacle absorption for each subject. Then we took the ratio of that subject’s actual sensitivity to predicted sensitivity at that subject’s retinal illuminance. The predicted sensitivity was calculated from the performance of 30 younger subjects (18 to 24 years of age) with healthy eyes who had been tested by the same methods used in the present study.39 The resulting measure is referred to as relative modulation sensitivity.

Fundus Grading

The nonstereoscopic color fundus photographs, centered on the macula, were evaluated for presence and severity of various characteristics of drusen and other lesions typical of ARM. A single grader used the Wisconsin Age-Related Maculopathy Grading System36 while masked as to subject characteristics. For this, a scoring grid divided the fundus into nine subfields—three circles concentric with the center of the macula, with four radial lines dividing the two outer circles into upper, lower, temporal and nasal quadrants. The central field diameter was 1 mm, about 3.5 °, which was somewhat larger than the 2.8 ° diameter area tested for flicker sensitivity. The diameters of the middle and outer circles were 3 mm and 6 mm, respectively.

Details of the scoring procedure are described elsewhere.37 Briefly, presence of drusen, retinal pigment epithelium (RPE) degeneration, increased retinal pigment, retinal or choroidal degeneration, retinal edema, RPE or serous sensory retinal (SSR) detachment, and a number of other lesions were noted within each subfield. Drusen size, drusen area, and area of increased pigmentation were estimated by comparison with standard circles. The predominant drusen type was noted, based upon size, uniformity of appearance, and sharpness of edges. Where drusen were distinct, the percentage of drusen area showing confluence was estimated. The area of RPE detachment was also roughly estimated.

We examined the various scored features of the central subfield. We also evaluated an overall fundus score summarizing the status of the eyes with respect to nine features thought to be characteristic of ARM.9,11,13,14,27,28 They are drusen size, drusen area, drusen type, RPE degeneration, increased retinal pigment, geographic atrophy, RPE/SSR detachments, subretinal hemorrhage, and subretinal fibrous tissue (the latter four features being characteristic of late ARM). The resulting overall ARM score was an ordinal scale ranging from 1 to 15, where 1 to 6 was classified as no ARM, 7 to 11 was considered early ARM, and 12 to 15 represented late ARM. None of our subjects had late ARM at baseline. The overall ARM scores are listed in Table 1.

For comparison with an earlier report,31 we calculated largest drusen size, most serious drusen type, summed drusen area, and summed drusen confluence over the central plus middle (3 mm diameter) scoring areas as described in that paper. (Retinal pigment epithelial degeneration and geographic atrophy were also identified as potentially discriminating, but none of our subjects had any scores on these scales so they were not applicable.)

Fundus photographs were available for all the pre-exudative eyes and for all but one of the nonconverted ARM-risk eyes. The photographs were taken as part of regular ophthalmologic examinations that were not conducted on the day of psychophysical testing. For the converted eyes, the fundus photographs were taken 260 days before to 251 days after flicker testing, but before conversion. For the nonconverted eyes, the photographs were taken 191 days before to 120 days after flicker testing. These intervals were not ideal but were ameliorated by the fact that the subjects with longer intervals had fundus photographs bracketing the flicker testing session, and the grading of most of these was unchanged. If the ARM fundus grade did change between the bracketing photographs, we used an interpolated value. For all nonconverted and all but one converted eye, the fundus photographs (as well as fluorescein angiograms) taken after flicker testing confirmed the absence of exudative ARM. For one converted eye (TM), the bracketing fundus photograph taken 140 days after flicker testing was graded as showing RPE and/or SSR detachment within the central and inner circles. This was not the case in the preceding fundus photograph (or angiogram). That patient’s best corrected acuity was also worse at the second exam—20/30 versus 20/25 at the earlier clinical exam. However, the fundus photograph and fluorescein angiogram taken at the second clinical exam showed no evidence of subretinal neovascularization. Therefore, at the time of flicker testing, there may have been RPE or SSR detachment but probably no neovascularization in TM’s tested eye.

For the nonconverted and PE-ARM eyes, the overall Wisconsin ARM grades were based upon fundus photographs, as described above. For the healthy older eyes, we did not have fundus photographs. How-
ever, we did have clinical descriptions of their fundi, and according to the criteria for their selection, they would have received grades 1 to 2. Therefore, for each healthy older subject, we estimated an overall ARM fundus grade from the clinical records.

RESULTS

Flicker Sensitivity

All three subject groups showed the expected inverted-U shape of the deLange function. The mean modulation sensitivity functions relative to retinal-illuminance-matched healthy younger subjects are shown in the visuograms of Figure 1. The horizontal line at "0" Relative Sensitivity represents the luminance-matched younger eyes' performance. Sensitivity was greater for younger subjects than for all three groups of older subjects. But the PE-ARM eyes showed even greater losses than the healthy-eyed or nonconverted groups.

Statistical Comparisons With Healthy Older Eyes. A Group (2) by Frequency (11) MANOVA of the PE-ARM versus healthy older relative modulation sensitivities (Fig. 1) showed that the factors of Group and Frequency were highly significant \((P < .001; \text{df} = 1, 25\) and \(10, 250\), respectively), as was the Group by Frequency interaction \((P < .001, \text{df} = 10, 250\)). Multiple \(t\)-tests of the interaction means showed differences at the \(P \leq .005\) (two-tailed, \(\text{df} = 25\)) level for frequencies from 2.5 to 14 Hz, and at \(P \leq .001\) for 5, 10, and 14 Hz. (Because 11 interaction mean tests were conducted, a criterion for statistical significance more stringent than \(P \leq .05\) is appropriate.) For each of these frequencies, PE-ARM eyes were less sensitive than healthy age- and retinal-illuminance-matched eyes by 2.4 to 4.0 decilogs. We find that psychometric functions for our 2IFC flicker testing typically are complete within 3 to 4 decilogs, so threshold losses of 2.4 to 4 decilogs are behaviorally as well as statistically meaningful.

For comparison, a group (2) by frequency (11) MANOVA of flicker sensitivity between healthy older and nonconverted ARM-risk eyes yielded no significant differences \((P = .268)\).

The MANOVA and \(t\)-tests analyze for differences between the groups. However, considering only group data can mask individual patterns. Therefore, data for the seven individual PE-ARM eyes are shown in Figure 2. The mean healthy older function is replotted for reference. Because of the steepness of the modulation sensitivity psychometric functions, the individual 1.96 SEMs (95% confidence intervals) were about ±2 decilogs. Although PE-ARM eyes had consistent losses between 2.5 and 14 Hz as a group, the individual results showed more complexity. Most individual subjects had the greatest loss between 10 to 34 Hz.

Another individual approach, discriminant analysis, asks whether PE-ARM eyes can be distinguished from healthy older eyes on an eye-by-eye basis using only the flicker sensitivity data. With discriminant analysis, each frequency between 2.5 and 28 Hz classified the eyes with better than 74% accuracy (chance discrimination = 0.62). Alternatively, the \(X^2\) probabilities were less than or equal to 0.005 for all frequencies between 2.5 and 14 Hz. The sensitivity of the discrimination (the probability of correct identification of PE-ARM eyes) ranged between 71.4% and 100%, whereas the specificity of the discrimination (the probability of correct identification of healthy older eyes) ranged between 75.0% and 90.0%.

Most impressive was sensitivity at 5 Hz. It discriminated the groups with 92.6% accuracy, correctly identifying all seven converted eyes and misclassifying two healthy older eyes. A linear combination of 5 and 10 Hz sensitivities yielded 100% correct classification of the eyes. The scatter plot for 5 and 10 Hz (Fig. 3) showed that the pre-exudative eyes tended to be less sensitive than the healthy older eyes at both 5 and 10 Hz.

PE-ARM Versus Nonconverted Eyes. A Group (2) by Frequency (11) MANOVA of the PE-ARM (converted) versus nonconverted ARM-risk relative modulation sensitivities (Fig. 1) showed that the factors of Group and Frequency were statistically significant \((P = 0.016, \text{df} = 25)\),
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FIGURE 2. Visuograms for individual pre-exudative ARM eyes compared to the mean visuogram for healthy older eyes. Numbers following patient codes indicate time from baseline testing until conversion (year:month).

df = 1, 14; and P = 0.003, df = 10, 140, respectively). The Group by Frequency interaction, however, was not significant (P = 0.096, df = 10, 140). In general, converted eyes were less sensitive than nonconverted eyes. Multiple t-tests at each frequency showed only one, 28 Hz, had a difference exceeding the P = .005 (two-tailed, df = 14) probability.

Discriminant analyses of the relative modulation sensitivity data for the pre-exudative versus nonconverted groups showed that singly, 5 Hz and each frequency from 10 to 34 Hz could classify the eyes with better than 74% accuracy (chance discrimination = 0.51). However, the X2 probabilities were less than or equal to 0.005 only for 28 Hz. The best discrimination by a single frequency was by both 5 Hz or 10 Hz, each yielding 87.5% correct, with 5 Hz having sensitivity = 85.7% and specificity = 87.5%, and with 10 Hz having sensitivity = 71.4% and specificity = 100%. When sensitivity at 5 and 10 Hz was plotted in a scatter diagram (Fig. 4), PE-ARM eyes were completely separated from nonconverted eyes with the same criterion line as for the PE-ARM versus healthy older discrimination (Fig. 3).

In summary, though the differences between the pre-exudative and nonconverted ARM-risk eyes were not so great as between pre-exudative and healthy older eyes, the pattern of differences was similar. The frequencies providing best discrimination singly were in the low- to mid-frequency range. Once again, 5 Hz provided the best discrimination as a single frequency, and a linear combination of 5 and 10 Hz yielded total separation between the groups.

Fundus Grading

Overall ARM Scores. The PE-ARM (converted) group had slightly poorer overall ARM fundus grades than the nonconverted group (mean = 7.93 and 6.5, respectively), but these differences were not statistically significant by t-test (P = 0.36, df = 13) or Mann-Whitney test (P = .28, n = 7.8). (The latter nonparametric test is more appropriate if the scale is ordinal but not interval.) The discriminant analysis using these overall grades yielded 68.7% correct classification (sensitivity = 71.4%, specificity = 66.7%) with a X2 probability of 0.2103.

Within the PE-ARM group, there was no apparent relation between the overall fundus grade and the particular pattern of sensitivity loss for the subject (compare Table 1 and Fig. 2).

We used ARM grades estimated from clinical records to compare the healthy older with the PE-ARM eyes. There was no overlap in the distributions of scores. A t-test confirmed that the PE-ARM eyes had overall ARM scores significantly higher (more risky) than those for the healthy older group (P ≤ 0.001, df = 25). With no overlap, discrimination between the healthy and PE-ARM eyes was 100% graphically. A t-test also showed the nonconverted eyes' overall ARM
and 10 Hz: PE-ARM vs. Healthy Older

FIGURE 3. Scatter plot of 5-Hz versus 10-Hz relative modulation sensitivity. Healthy eyes (filled circles) can be separated from pre-exudative ARM eyes (open symbols) with 100% accuracy. Original PE-ARM refers to patients reported on in a preliminary analysis.17

grades to be significantly higher than those of the healthy older eyes ($P \leq 0.001$, df = 26).

Central 1 mm Diameter Field Scores. The subscores from the fundus central field were examined for differences between the pre-exudative and nonconverted groups because the central field includes the area tested psychophysically. Eight of the subscores showed some scorable characteristic in the two groups. These were drusen size, drusen area, drusen confluence, drusen type, area of RPE degeneration, and increased pigmentation at the center circle and drusen size, and drusen type in the center point of the center circle.

Three of the nonconverted eyes had no features in the central circle to score, whereas only one of the converted eyes was without feature in the central area. Neither central point scores nor the RPE Degeneration score discriminated the groups. One of the nonconverted but three of the PE-ARM eyes had some increase in pigmentation. Both groups had some hard distinct, soft distinct, and soft indistinct drusen. For drusen size, drusen area, and drusen confluence, the distributions for nonconverted and converted eyes overlapped considerably. These latter three ordinal scales were analyzed with Mann-Whitney tests. Consistent with the visual analysis, none reached significance ($P \geq 0.09$). Pair-wise scatter plots of other scores with between-group variation also revealed no combination of central subscores associated with PE-ARM.

Central 3 mm Characteristics. Largest drusen size, maximum drusen type, total drusen area, and total drusen confluence within the central 3 mm diameter scoring area did not discriminate the PE-ARM eyes from the nonconverted eyes. We specifically checked criteria reported as effective in a previous paper.21 With a drusen size cutoff of 250 μm diameter, sensitivity was 28.6% and specificity was 66.7%, or 50% overall. With drusen type, using a soft-distinct cutoff yielded sensitivity = 28.6% and specificity = 77.8% or 56.2% overall.

Snellen Acuity

There were statistically significant differences between the healthy older group's Snellen acuity and that of the pre-exudative ($P = .004$, df = 25) and nonconverted ($P = .004$, df = 27) ARM-risk eyes. Mean acuities were 20/21.5, 20/25.7, and 20/26.7, respectively. But there was no significant difference between the PE-ARM and nonconverted eyes.

Although the PE-ARM eyes had worse acuity overall than the healthy older eyes, there was considerable overlap. As a result, discriminant analysis using Snellen acuity alone separated the PE-ARM from healthy older eyes with 70.4% accuracy (sensitivity = 85.7%, specificity = 65%; $X^2 P = 0.0038$). That is, any one of the frequencies between 2.5 and 28 Hz yielded a higher percentage correctly classified. And, although the PE-ARM eyes could be distinguished from the nonconverted eyes in terms of their flicker sensitivity, they were not distinguishable by their Snellen acuity. Discriminant analysis using Snellen acuity
alone separated the PE-ARM from nonconverted eyes with 50% accuracy, i.e., with no better than chance accuracy (sensitivity = 28.6%, specificity = 66.7%; $X^2 P = 0.9337$).

**DISCUSSION**

**Identifying Pre-Exudative ARM**

At baseline, the PE-ARM eyes looked and performed differently than the healthy older eyes of this study. There were large statistical differences ($P < 0.001$) between the two groups on both temporal modulation sensitivity and overall Wisconsin ARM-risk fundus grade.

For flicker sensitivity, the changes with PE-ARM were selective for particular frequencies. Only the frequencies from 2.5 to 14 Hz were significantly lower ($P \leq 0.005$). Furthermore, on an eye-by-eye basis, flicker sensitivity could discriminate the group to which each eye belonged with 100% accuracy using two flicker rates, 5 and 10 Hz. The overall Wisconsin ARM grade also discriminated the two groups with 100% accuracy.

It was possible that our healthy older eyes were so uncharacteristically healthy that their temporal modulation sensitivity was simply better than most older eyes. However, that was not the case. There were no statistically significant differences between the flicker sensitivity of the nonconverted eyes and the healthy older eyes, despite the fact that the fundus appearance of nonconverted eyes was graded as significantly worse than the healthy older eyes ($P \leq 0.001$). Only the PE-ARM eyes had significantly worse flicker sensitivity.

This pattern of results between fundus appearance and flicker modulation sensitivity is consistent with the notion that though pigment epithelial abnormalities are assumed to be a more "severe" stage of early ARM than soft indistinct drusen only, it is possible that exudative changes arise in the absence of pigmentary abnormalities. This would weaken the prognostic relationship between exudative ARM and the presumed severity of maculopathy as defined by the fundus photograph grades. On the other hand, the foveal flicker sensitivity changes found here, which are presumably due to functional changes in the retina, are predictive of exudative ARM ($P \leq 0.001$). Only the PE-ARM eyes had significantly worse flicker sensitivity.

**Is the Fellow Eye of Monocular Exudative ARM a Good Model of Exudative ARM?**

The fellow eye of a patient with monocular exudative ARM is important for research because the fellow eye has a higher probability of developing ARM than does the general age-matched population. However, it may be that someone who has exudative ARM in one eye is already different systemically from the general population. Therefore, the progression to exudative ARM in our ARM-risk eyes may not be representative of the pre-exudative progression in people who have no history of exudative ARM.

The most direct way to test whether fellow eyes of patients with monocular exudative ARM (ARM-risk eyes) are a good model of PE-ARM in general is to compare performance and appearance of fellow eyes that convert with conversions from eyes where there was no evidence of exudative ARM in either eye at baseline. Because none of our older subjects with healthy eyes developed exudative ARM, we could not make the direct comparison.

However, our flicker sensitivity results indirectly suggest that ARM-risk fellow eyes may be a good model of exudative ARM in general. If the course of PE-ARM is the same, regardless of the other eye's status, then nonconverted eyes should perform much like healthy older eyes, whereas PE-ARM eyes should differ from either of these groups in similar ways.

The flicker sensitivity results were consistent with these patterns. First, the nonconverted eyes did not differ significantly in flicker sensitivity from the healthy older eyes. They did, however, differ from PE-ARM eyes, and the general pattern of the group differences were similar. Second, the individual patterns of sensitivity losses across temporal frequencies for the PE-ARM eyes were coherently different than healthy older eyes (Fig. 2). By coherently different, we mean the losses or gains were shown by more than one frequency in a given region of the temporal spectrum so that it is less likely they are attributable to measurement error. The individual patterns shown by the nonconverted group, on the other hand, seemed to be a bimodal distribution. Most nonconverted eyes had MSFs that looked like those of the healthy older eyes. But two nonconverted subjects had patterns of sensitivity changes resembling those of converted subjects. Taken together, these results suggest that the original ARM-risk group was a bimodal one. One part consisted of those who were in pre-exudative stages of ARM and who subsequently developed or will develop exudative ARM. The flicker sensitivities of this PE-ARM portion were noticeably different from those of healthy older eyes. The second part of the group consisted of those who have not developed exudative ARM as rapidly as the first part. The flicker sensitivities of this second subgroup were not noticeably different from those of healthy older eyes, even though their fundi had features that were classified as early ARM.

The hypothesis that pre-exudative modulation sensitivity will show patterns of change similar to these when neither eye has exudative ARM bears testing directly.
Comparison With Previous Reports and Predictions

In earlier papers we concluded that the flicker sensitivity changes with PE-ARM were selective, and we characterized the changes as losses in the mid temporal frequencies. In the present studies again we found that the losses were selective for the PE-ARM group. But now both low and mid temporal frequencies were shown to be affected (Fig. 1). Group mean sensitivities for frequencies from 2.5 to 14 Hz were significantly lower for the converted than the healthy older eyes. Furthermore, just two low to mid frequencies—5 and 10 Hz—could distinguish the pre-exudative eyes from the healthy older eyes with 100% accuracy.

In a previous paper, we noted differences in the temporal modulation sensitivity losses between two PE-ARM eyes. We speculated that the differences may have been due to differences in time between the baseline measures and conversion. With the larger number of conversions in the present study, we can say something more now about the individual differences between PE-ARM eyes. We found different patterns of modulation sensitivity change in the PE-ARM eyes (Fig. 2). However, neither the amount of change nor the pattern seemed to be associated with time until conversion. (And within-subject data, not reported here, also do not necessarily show a progressive loss of sensitivity as the exudative stage develops.)

Also, the individual patterns of loss suggest that group changes (Fig. 1) may not be the best way to view the flicker sensitivity results. Some individuals fit the general, group-wide description of loss at 2.5 to 14 Hz, but there were also large losses (4 to 7 decilogs, or 2.5 to 5 times less sensitive than healthy older eyes) at frequencies up to 28 Hz. In future studies with more subjects, it will be important to examine the individual data to determine whether different patterns of sensitivity loss are clinically informative.

On the basis of our earlier analyses showing sensitivity losses between 10 and 40 Hz, we predicted that six of 12 ARM-risk subjects would develop exudative ARM. (Predictions actually concerned 13 subjects, but one has been lost to follow-up.) Considering those 12 subjects in our current data set, five conversions have been correctly predicted. One patient (#24) who was expected to develop exudative ARM has not done so after 4 years, and one (#31) whom we thought would remain nonexudative did develop exudative ARM about 1.5 years after baseline testing. In the current analyses, patient 24 continues to be an nonconverted subject whom we predict will develop exudative ARM. Patient 31 is now correctly selected as a conversion on the basis of his flicker sensitivities compared with healthy older eyes and nonconverted eyes. So whereas the present analyses support our previous observations of the importance of mid-temporal frequencies, patient 31’s results (and those of one other new subject, patient 35) caution that other frequencies, both higher and lower, also may be important to consider.

Mechanisms

What mechanisms are responsible for temporal modulation sensitivity under our test conditions? Which of these are affected by PE-ARM to produce the observed selective losses?

Flicker rates of less than 25 Hz are detectable by both rod and cone systems, and our 2.8° diameter foveally viewed stimulus is large enough to exceed the average 1.25° diameter of the human rod-free zone. Therefore, our testing is at retinal illuminances where rods saturate and is well above levels where rod-cone interaction has been shown to drop out. Therefore, the mechanisms underlying sensitivity from 2.5 through 50 Hz in our test conditions probably reside in the cone systems. Because PE-ARM is most likely to affect photoreceptor rather than post-receptor functions, the loss in sensitivity with PE-ARM is probably at the level of the cones themselves.

Our flicker stimulus is large enough to stimulate foveal regions where all three cone types are present. But because short-wavelength (S) cones are several orders of magnitude less sensitive than medium- (M) or long-wavelength (L) cones at 650 nm, S cones are not likely to contribute to the flicker sensitivities measured here. Although L cones are about a factor of 20 more sensitive than M cones at 650 nm, with adaptation over time their sensitivities are probably more similar. Therefore, both L and M cones are potential contributors to the sensitivities measured here. They may make their contributions via opponent or nonopponent channels. The L-M opponent channel is about .8 log unit more sensitive than the L-M nonopponent channel under our test conditions when detecting 50 ms impulses. However, the sensitivity relationship between the opponent and nonopponent systems would be expected to change with temporal modulation, with higher flicker rates favoring the nonopponent, luminance channel. Therefore, on the basis of the stimulus and surround parameters—foveal, 2.8° diameter, 650 nm stimulus in a white, luminance-matched surround at 120 cd/m², flicker rates from 2.5 to 50 Hz—the flicker sensitivities measured here are most likely attributed to processing in both L- and M-cones and to both chromatic (opponent) and luminance (nonopponent) systems.

The different patterns of selective loss as a function of frequency in the PE-ARM subjects are consistent with more than one cone mechanism underlying the de Lange function as measured here,
more than one of these mechanisms is compromised by PE-ARM. We are testing various models of the characteristics of these underlying mechanisms.58

Sensitivity loss at low temporal frequencies but gain at high frequencies is like the sensitivity change found with more eccentric viewing of the same size stimulus. For healthy younger subjects under our test conditions, changes equal in magnitude to that shown by some of the PE-ARM subjects is accomplished with a 5\(^\circ\) to 6\(^\circ\) eccentric fixation. Our older and ARM-risk subjects sometimes do report fixing somewhere within the stimulus other than the exact center. They do not report more eccentric viewing, and, given the difficulties of maintaining eccentric fixation (e.g., Troxler fading), it seems implausible that they would adopt such a strategy. What does seem more plausible is that changes going on within the fovea result in morphologic changes that are similar to more peripheral retina—cones that are less densely packed, have larger receptive fields, and/or have shorter outer segments.

The latter possibility is consistent with color-matching data showing lower photopigment density for PE-ARM eyes and with diminished foveal absolute sensitivity.19

Limits of This Study

The above discussion rests on the assumption that the flicker sensitivity differences between groups reflect primarily retinal function. The responsiveness of flicker sensitivity to retinal inhomogeneities and other retinal diseases suggest that this is a reasonable assumption. However, the fact that this study is not an experiment (subjects cannot be assigned to the groups randomly) means that other unassessed variables besides retinal factors may be responsible for the flicker sensitivity differences. Though we have controlled for some of the most plausible of these other variables (e.g., by screening for general health, controlling for retinal illumination, using criterion-free measures), they can never be totally eliminated as underlying causes in nonexperiments.

These analyses are based upon a relatively small number of subjects. Accordingly, we consider these results preliminary. They suggest that flicker sensitivity is useful in evaluating risk for exudative ARM (when other variables that may affect flicker sensitivity have been controlled.) We are planning to test the generalizability of these findings with a larger sample of similarly screened ARM-risk eyes. We are also planning to test subjects with no exudative ARM in either eye but with more signs of dry ARM than present in the healthy older group in this study. We will also evaluate whether stereoscopic fundus photographs of the macula increase the predictive power of the fundus grading for the fellow eyes.

CONCLUSION

Both flicker sensitivity and fundus appearance differentiate the PE-ARM eyes from the healthy older eyes of this study with 100% accuracy. But only flicker sensitivity accurately discriminates the PE-ARM eyes from the ARM-risk eyes that have not developed exudative ARM.

Key Words

age-related maculopathy, temporal modulation sensitivity, fundus grading

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