Preliminary Evaluation of Flicker Sensitivity as a Predictive Test for Exudative Age-Related Maculopathy

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Flicker contrast sensitivity was tested in the “good” eyes of 13 patients with monocular exudative age-related maculopathy (ARM). The stimulus was a foveal, long-wavelength, low spatial frequency 2.8° circle in an equiluminant (photopic) surround. Two of these ARM-risk eyes have since developed exudative ARM. Compared to healthy age-matched eyes, the two eyes that developed exudative ARM had significantly lower sensitivity at 10–40 Hz up to 9 mo before exudative symptoms appeared. The implications of these results regarding the time-course of ARM and the predictive value of foveal contrast sensitivity testing are considered. Based upon data and theoretical considerations, the authors speculate that sensitivity loss between 10 and 40 Hz is a good predictor of which eyes will develop exudative ARM. This proposal will be tested by new data from current as well as new ARM-risk subjects.


Exudative age-related maculopathy (ARM) is the leading cause of visual loss in the United States among the elderly.1,2 Once vision loss from exudative ARM begins, it tends to spread quickly. If the affected area is extra-foveal, the current practice is to limit damage by cauterizing subretinal neovascular nets using laser photocoagulation to conserve central vision. However, this requires prompt recognition by the patient that there is a problem that needs immediate attention. Unfortunately, many people miss, ignore, or deny the earliest, most treatable stages of vision loss associated with exudative ARM, unaware of the consequences of doing so.

The goal of our research is to identify those at risk for exudative ARM before any symptoms of visual change appear. A sensitive screening test could alert those at risk to more carefully monitor their vision for early visual distortion or loss so they would not delay clinical evaluation and treatment. A sensitive test also might give information about the progress and rate of development of pre-exudative stages of ARM. Also, as a continuous index of retinal health (rather than a measure reflecting visual loss resulting from the end-state of macular degeneration), such a screening test could prove useful in evaluating proposed treatments for early stages of exudative ARM.

In accompanying papers in this issue, we reported that foveal contrast sensitivity to a long-wavelength, low spatial frequency stimulus was reduced during early pre-exudative stages of ARM.3,4 We found that mid-temporal frequencies were most affected1 and that flicker sensitivity at two flicker rates—14 Hz and 10 Hz—could reliably discriminate ARM-risk eyes from healthy age-matched eyes.4 Here we report on the temporal contrast sensitivity of two ARM-risk eyes that have developed exudative ARM. For both patients, contrast sensitivity was especially low for mid-temporal frequencies before development of exudative symptoms. We speculate on the implications of these results regarding the time-course of exudative ARM and the predictive value of foveal contrast sensitivity testing.

Materials and Methods

Subjects

We tested 13 ARM-risk eyes and 19 healthy older eyes over 1 to 2 yr. An ARM-risk eye was defined as the “good” eye of a patient with monocular exudative ARM in the fellow eye. Exudative ARM usually is binocular, with a few years elapsing between appearance of symptoms in the first and second eye.5–7 Therefore, the “good” eye of a monocular exudative ARM patient is more at risk for developing exudative ARM than the general age-matched population.

The mean age for the ARM-risk group was 71.7 yr and for the healthy-eye group was 70.3 yr. All subjects consented to take part in the research after the procedures had been explained fully, and all were in rela-
tively good general health. Details of the health and history for both groups can be found in an accompanying paper in this issue.3

ARM-risk eyes and healthy eyes had Snellen acuity of 20/30 or better and intraocular pressure of less than 22 mmHg (Goldmann applanation). The fundus of all eyes and the angiogram of ARM-risk eyes were rated for exudative ARM Risk on a scale of 0–4, with a rating of 4 indicating very high risk. The healthy eyes had fundi within normal limits, as determined by indirect and direct ophthalmoscope examination (no or trace hard, yellow drusen; no disturbance of pigmentation, pigment epithelium, or vascularization.) The opacity of optical media was also rated in both groups of eyes.*

Exudative ARM developed in the second eyes of two ARM-risk patients, GW and TM. Details of their health history are shown in Table 1. Both ARM-risk maculas were classified as having atrophic ARM by the usual clinical criteria, and both patients were instructed to regularly monitor their vision in the ARM-risk eye with an Amsler grid. GW began losing acuity approximately 7 wk after we tested her foveal flicker sensitivity. Within 8 wk after our testing, her best corrected Snellen acuity had dropped to 20/200.† TM reported sudden distortion and loss of vision 9 mo after we tested her. Upon examination, her best corrected Snellen acuity had dropped to 6/400.‡ Both patients received detailed clinical examinations and angiographic checks on a regular basis between psychophysical testing and the first detection of exudative ARM. No exudative reaction with temporary remission was observed before the first diagnosis of exudative ARM, and neither patient received any form of treatment in the ARM-risk eye before that time.

Methods

The flicker stimulus was a uniform, 2.8° circular field formed from an array of 25 high-luminance 660 nm light-emitting diodes set behind a circular diffusing screen. The long-wavelength light was used to minimize scatter and absorption from aging optical media or macular pigment.9 The stimulus, which was on continuously, was mounted in the center of the surface of an equiluminant, white, concave hemisphere with a radius of 61 cm. Average luminance of stimulus and surround was 120 cd/m².

The observer viewed the stimulus monocularly from a forehead and chin rest placed at the center of the hemisphere (distance 61 cm). A mirror reflected an image of the observer’s eyes to a video camera and recorder for measuring pupil size. Contrast thresholds for flicker fusion were collected with a two-interval forced-choice, three-up-one-down staircase procedure. Each 0.5 sec display interval was a cosine bell, or Hanning window,10 whose beginning and end were designated by short beeps. The rate of sinusoidal flicker and its amplitude were controlled by a computer (Apple II+ with custom interface). Staircases for temporal frequencies between 1.8 and 50 Hz were interleaved as the program swept repeatedly from low to high frequencies. Two complete de Lange11 or contrast sensitivity functions (CSFs) were measured for each subject and averaged.

To remove effects of retinal illuminance differences between subjects resulting from pupil size differences and spectacle absorption, we measured these for each subject. Then we compared actual performance for that subject with what would be expected for his or her retinal illuminance based upon norms derived

* The media opacity and fundus and angiogram rating scales were devised for these studies.3
† GW had no loss of Snellen acuity 1 wk after our flicker sensitivity testing. However, at her next clinical examination, 7 wk after flicker testing, acuity had dropped to 20/200.† TM reported sudden distortion and loss of vision 9 mo after we tested her. Upon examination, her best corrected Snellen acuity had dropped to 6/400.‡ Both patients received detailed clinical examinations and angiographic checks on a regular basis between psychophysical testing and the first detection of exudative ARM. No exudative reaction with temporary remission was observed before the first diagnosis of exudative ARM, and neither patient received any form of treatment in the ARM-risk eye before that time.

Table 1. Health and vision data on patients whose tested eye developed exudative ARM

<table>
<thead>
<tr>
<th>Patient</th>
<th>TM</th>
<th>GW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>70.0</td>
<td>72.3</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Acuity (20/)</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>IOP (mmHg)</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Media opacity (0–4)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Retina</td>
<td>Fairly extensive dry involutional degenerative stigmata</td>
<td>Dry, patchy atrophic pigment deficits, more confluent centrally</td>
</tr>
<tr>
<td>Risk rating: Fundus</td>
<td>2.5</td>
<td>2</td>
</tr>
<tr>
<td>Risk rating: Angio</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Time since 1st eye (wk)</td>
<td>116</td>
<td>approx. 104</td>
</tr>
<tr>
<td>Iris color</td>
<td>Hazel green</td>
<td>Green</td>
</tr>
<tr>
<td>General health</td>
<td>Good (no medications)</td>
<td>Systemic hypertension (Dyazide)</td>
</tr>
<tr>
<td>Cigarettes (yr X cig/day)</td>
<td>120</td>
<td>2280 (quit 9 mo)</td>
</tr>
</tbody>
</table>

IOP, intraocular pressure.
from the performance of 30 younger subjects (18–24 yr) with healthy eyes who were tested by the same methods used in the present study.\textsuperscript{12}

**Results**

Mean contrast sensitivity as a function of flicker rate for the healthy older and ARM-risk groups is shown with large solid circles and squares, respectively, in Figure 1. (These data are similar to that shown in accompanying papers\textsuperscript{3,4} except here the ARM-risk means do not include the data of patients GW and TM.) Contrast sensitivity for the two ARM-risk eyes that developed exudative ARM are shown with smaller symbols and broken lines in Figure 1. We refer to these as the “converted” eyes.

For both converted eyes, sensitivity was especially reduced for mid-temporal frequencies. The error bars on the group means indicate 1.96 standard errors. The frequencies that are outside the error bars of both groups for GW and TM are 28, 34, and 40 Hz. In addition, 10, 14, and 20 Hz are outside the error bars of the healthy older group for GW and TM. The function for GW, who was within 7 wk of converting, is more depressed than the curve for TM, who was within 9 mo of converting.

**Discussion**

ARM-risk eyes that develop exudative maculopathy are very informative for evaluating the usefulness of candidate predictors of exudative ARM. The data of the converted eyes of TM and GW confirmed trends of the group data but added new dimensions as well. For example, group means for ARM-risk eyes in our studies had lower sensitivity for mid-temporal frequencies, especially at 14 and 10 Hz.\textsuperscript{3} Using these two frequencies, individual ARM-risk eyes could be discriminated from healthy older eyes with 78% accuracy.\textsuperscript{6} Both GW and TM were correctly classified by the discriminant analysis, giving support to the notion that 10 and 14 Hz are possible distinguishing frequencies.

In addition, if we focus on frequencies for which both converted eyes had sensitivities outside the group, 1.96 standard errors (Fig. 1), again the mid frequencies were prominent. However, the converted eyes’ sensitivities were most distinctively different from both group means at 28, 34, and 40 Hz. In addition, they were outside the healthy group’s error bars at 10, 14, and 20 Hz. Thus, the converted eyes suggest that it may be important to monitor a broad band of mid-temporal frequencies from 10–40 Hz.

The converted eyes were expected to give a somewhat different perspective than the group data because each of the original groups was heterogeneous. Defining fellow eyes of monocular exudative ARM patients as “ARM-risk” was based upon probabilities. Not every ARM-risk eye will develop the exudative form of the disease. Therefore, mean data of the ARM-risk group represented a mixture of eyes that would remain free of exudates and neovascularization, along with eyes that were in early stages of exudative ARM. So any losses in flicker sensitivity truly associated with early stages of exudative ARM were diluted by the relatively healthy eyes. Similar arguments can be made for the healthy older group, in which the probability of an eye developing exudative ARM was less than in the ARM-risk group, but not vanishingly so. Because of this mixed nature of the study groups, if our samples had been large enough, we would have expected to see a bimodal distribution on any parameter that was truly discriminating—one mode for the eyes that would remain relatively healthy, another for those that would have converted. Based on our accompanying reports\textsuperscript{3,4} as well as our knowledge of what has happened for GW and TM, we would expect the distributions of relative contrast sensitivity at 10, 14, 20, 28, 34, and 40 Hz to have such a bimodal look. However, the samples were simply too small to do such an analysis.

**Mechanisms and a Prediction**

If, as proposed in our accompanying paper,\textsuperscript{3} early stages of exudative ARM affect primarily a “high temporal frequency” mechanism, we would not expect decreased sensitivity at only one mid-temporal frequency. The “high frequency” mechanism domi-
nates frequencies between 10 and about 40 Hz, so we would expect losses across this whole frequency range. Therefore, it is interesting that a similar range appeared to be affected in the converted eyes (Fig. 1). Thus, theory suggests that a screening criterion involving sensitivity loss across a band of mid-temporal frequencies may be useful for detecting early stages of exudative ARM.

For practical reasons, testing flicker sensitivity over a band of frequencies has advantages. Testing only one or two frequencies is appealing because they could be measured quickly. However, such a screening criterion also may be more susceptible to measurement errors. A screening criterion that looks at the relationship between frequencies over a two octave range may be more robust.

Based upon the losses shown by the two converted eyes and supported by the mechanistic and practical considerations noted above, we propose the following approximation to a screening rule: Any eye with relative sensitivity loss between 10 and 40 Hz that exceeds some criterion value is considered most at risk to develop exudative ARM. Several operational definitions of this rule are possible and testable. For example, a simple version might sum a subject's relative sensitivity from 10-40 Hz and set the cumulative loss cut-off at some value that eliminates those subjects with losses at only one or two frequencies. For the present study, we might have chosen a criterion of 20 decilog cumulative sensitivity loss for the six tested frequencies between and including 10 and 40 Hz. With this criterion, seven of our original 13 ARM-risk patients, including GW and TM, would exceed the criterion and would be expected to develop exudative ARM. In the healthy older group of 19 subjects, two would meet this criterion and therefore would be expected to develop exudative ARM. We have been monitoring our subjects to test this and other versions of our proposal.

**Time Course of Exudative ARM**

We tested flicker sensitivity for GW's "good" eye about 7 wk before onset of exudative symptoms. For TM, our flicker testing occurred 9 months before visual loss with exudative ARM. In Figure 1, we note that TM's de Lange function was not as depressed as that of GW, except at 28, 34, and 40 Hz. In fact, for 7 Hz and below and for 45 Hz and above, TM's sensitivities were within the healthy older range. This suggests that 28, 34, and 40 Hz in particular and mid-temporal frequencies in general may be especially sensitive early-warning frequencies for exudative ARM.

For GW, the de Lange function was generally depressed, outside healthy older error bars for all frequencies. This suggests there may have been graded, successively more extensive sensitivity losses over at least a 9 mo period. According to a three-mechanism model of flicker sensitivity, up to 9 mo before onset of exudative symptoms, the main effect of early pre-exudative stages of ARM seems to be on the "high frequency" (possibly magnocellular) mechanism. But as the exudative crisis approaches, the other two flicker mechanisms are affected as well.

Appearance of exudative maculopathy in GW's second eye followed exudative ARM onset in her first eye by about 2 yr. For TM, the interval was similar (116 wk; Table 1). A conversion rate of two out of 13 fellow eyes (15%) from monocular exudative ARM patients over 2 yr is within estimates by other labs.

**Other Predictors Besides Flicker?**

We have data for our subjects on a number of other possibly relevant variables besides flicker contrast sensitivity. These include Snellen acuity, Pelli-Robson spatial contrast sensitivity, D-15 color test, and fundus and angiogram evaluation, as well as health history and medications. As with our flicker sensitivity results, any conclusions about the predictive value of other characteristics are tentative. The number of conversions and the sample sizes of the healthy and ARM-risk groups were small, so we will be monitoring these characteristics as our data sets increase. Furthermore, evaluating the predictive strength of some concomitant measurements may be even more difficult than for flicker sensitivity because the other characteristics have been restricted by selection criteria (Snellen acuity), are not available for all subjects (Pelli-Robson contrast sensitivity), or are confounded by uncontrolled variables (D-15 color test).

**Snellen acuity:** We are interested in identifying longer-range predictors of exudative ARM. Obviously, there is considerable acuity loss at the onset of foveal exudative symptoms, but what about before that time? The present study did not address this question because we were interested in evaluating flicker contrast sensitivity testing's predictive value before any significant acuity loss. As a result, all eyes in our study had Snellen acuity of at least 20/30. Because the

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* The model presented in Figure 2 of our accompanying paper shows the high frequency mechanism dominating between 11 and 36 Hz. These data were obtained at a considerably higher illuminance than for our test conditions. We expect that lower retinal illuminance would shift the contrast sensitivity curves to lower frequencies, and thus the range of each mechanism's response spectrum would be shifted to lower frequencies as well. We estimated the upper limit of the high frequency mechanism's dominance then to be about 40 Hz for our conditions.

† In Table 1 of our accompanying paper, the eyes that are predicted to develop exudative ARM are MF and FP in the healthy older group and KA, CA, BA, DC, and SM in addition to TM and GW in the ARM-risk group.
range of Snellen acuities was restricted by our selection criteria, correlations of this measure with flicker sensitivity or development of exudative ARM in the longer term are hard to evaluate. Accordingly, correlations between Snellen acuity and contrast sensitivity at each flicker rate were not statistically significant (using single test probabilities with df = 12), ranging between −0.49 (the direction that would be expected if poorer acuity was associated with flicker loss) and +0.303. The Snellen acuities for TM and GW were 20/25 and 20/30, respectively. That is, TM was not among the worst acuities, and there are several ARM-risk patients with 20/30 acuity, like GW, who have not developed exudative ARM. Therefore, the relationship between (restricted) Snellen acuity and long-term prediction of exudative ARM is not obvious. Given the remarkable tolerance of acuity tests to receptor loss, this perhaps is not surprising. On the other hand, simply because Snellen acuity may be somewhat independent of temporal contrast sensitivity loss, it is possible that acuity, with flicker losses and other clinical measures, may in the long run contribute to our ability to discriminate exudative ARM-risk eyes. We will continue to evaluate this possibility in our longitudinal studies.

**Static spatial contrast sensitivity:** In our accompanying paper, we compared subsets of the ARM-risk group and healthy older group for which we had spatial contrast sensitivity measurements using the Pelli-Robson chart. We found that the ARM-risk subset had significantly lower spatial contrast sensitivity. This fit with the hypothesis that there was a general receptor loss in early stages of exudative ARM (along with a more specific high-temporal-frequency-mechanism loss).

The converted eye of GW was one of seven from the ARM-risk group for which we had a Pelli-Robson measurement. At 1.55, GW's spatial contrast sensitivity was at the mean of the ARM-risk group. The two ARM-risk eyes that had lower sensitivity at 1.35 have not yet developed exudative ARM. And, based on flicker sensitivity testing, only one of these would be predicted to convert using the cumulative loss between 10 and 40 Hz criterion discussed above. The Pelli-Robson measurements seem to be somewhat independent of the flicker testing measurements, and in concert they may provide a firmer basis for predictions.

**D-15 color vision:** Although there are reasons why early stages of exudative ARM might affect color vision, our current data do not speak to the issue. Unlike our flicker sensitivity test, the D-15 score is influenced by absorption of the optical media and retinal illuminance differences. Therefore, although we previously reported differences between the healthy older and ARM-risk groups on the D-15 test, we do not believe these differences are interpretable.

**Fundus appearance:** All of our ARM-risk subjects had their fundi rated by one of the authors (BW), who is an ophthalmologist specializing in retinal diagnosis and surgery. On our subjective five-point rating scale, 0 corresponded to little or no risk and 4 equaled very high risk for exudative ARM. The rating was done before the time at which the outcome for the ARM-risk eye was known. Of course, as the treating physician, the author did know that the fellow eyes of these subjects already had exudative ARM.

For TM's converted eye, the rating was 2.5, and for GW the rating was 2.0. These values were assigned for the following reasons. For TM, the color slide showed speckled and mottled hyper- and hypopigmentation with fine granular changes under and around the foveal region. Localized linear deposits of hyperpigmentation were noted in the temporal part of the macula. No significant drusen were seen. For GW, there were multiple small- to medium-sized irregular areas of pigment epithelial atrophy or fine drusenoid hypopigmentation. There was irregular fine pigment mottling of the central macula, and small areas of spotty hyperpigmentation were seen at the retinal pigment epithelial (RPE) level.

These fundus ratings represent retinas that are more risky looking than any of our healthy older eyes (see Table 1 of accompanying paper). However, there are other retinas in the ARM-risk group whose fundi looked as risky or worse and have not converted (yet). We will continue to monitor the predictive value of this measure. We also are in the process of evaluating the relationship of our scale to the fundus rating scheme developed at the University of Wisconsin. We have noted that for the seven ARM-risk eyes predicted to convert on the basis of cumulative flicker sensitivity loss between 10 and 40 Hz, our fundus ratings range between 0.5 and 3.5. Thus, future data will be informative.

**Angiogram:** Nearly all of our ARM-risk subjects had fluorescein angiograms of their tested eyes as a result of the treatment regime for their exudative fellow eye. The angiograms were rated for exudative ARM risk by BW on a subjective five-point scale, where 0 represented little or no risk and 4 equaled very high risk for exudative ARM.

For both converted eyes, the angiogram rating was 3.0 (ie, they both appeared to have a high risk for developing exudative ARM, but no exudates or neovascularization were found). For TM, this rating was based upon the appearance of fine punctate hyperfluorescent spots dusting the entire macular region. They were concentrated as a geographic window defect occupying the temporal part of the macula, su-
perimposed upon curved lines of hypofluorescence. For GW, the fluorescein angiogram presented an obviously more risky appearance than did the fundus photo. At the same time, features more evident on the color picture were barely noticeable on the angiogram. The rating of 3.0 for GW was based upon far more extensive and larger lacy circular window defects, which were large to medium in size, satelliting the subfoveal region. Shallow RPE separations also may have been present in the lower macula with “fan blade” lines of blockage. No neovascularization was present.

We note that for the seven ARM-risk eyes predicted to convert on the basis of cumulative flicker sensitivity loss between 10 and 40 Hz, our angiogram ratings ranged between 1.5 and 3.0. So further monitoring of these eyes could prove valuable for evaluating the relative contributions that flicker testing and angiogram information could make to predicting the onset of exudative ARM.

Summary

We believe that older eyes that show significant losses in mid-temporal frequency contrast sensitivity are the most likely to develop exudative ARM. As pre-exudative maculopathy progresses, we expect to see losses over a wider frequency range, including the higher and lower temporal frequencies. We will be testing these predictions and evaluating the potential contributions of other variables to screening criteria for exudative ARM with additional data on healthy older and ARM-risk eyes.

Key words: age-related maculopathy, flicker, flicker mechanisms, prediction, temporal contrast sensitivity

References