Foveal Flicker Sensitivity Discriminates ARM-Risk From Healthy Eyes

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The "good" eyes of 13 patients with monocular exudative ARM were compared with age-matched healthy eyes of 19 subjects. Membership in the two study groups was based upon careful clinical evaluation of the tested eye as well as upon status of the fellow eye. We asked whether temporal contrast sensitivity for a long-wavelength, low spatial frequency stimulus can be used to identify the group in which a given eye belongs. Using step-wise discriminant analysis, we found that the ARM-risk and healthy eyes could be classified with 78% accuracy on the basis of foveal flicker sensitivity at two temporal frequencies—14 and 10 Hz (in order of estimated weight.) Invest Ophthalmol Vis Sci 33:3143-3149, 1992.

In an accompanying report in this issue,1 we reported that foveal flicker sensitivity to long-wavelength, low spatial frequency light was significantly reduced in a group of eyes at risk for exudative age-related maculopathy (ARM). An ARM-risk eye is defined as the "good" eye of a patient with monocular exudative ARM. Exudative ARM usually is binocular, with a few years elapsing between appearance of symptoms in the first and second eye.2-4 Therefore, the "good" eye of a monocular exudative ARM patient is more at risk for developing exudative ARM than an eye from the age-matched general population.

To qualify for our study, healthy and ARM-risk eyes needed to have Snellen acuity of 20/30 or better and intraocular pressure of less than 22 mmHg. Nevertheless, we found that mean thresholds for ARM-risk eyes were higher than for healthy age-matched eyes, especially at mid-temporal frequencies.1 For the present report, we evaluated which of several methods of summarizing the flicker sensitivity data are most useful for discriminating, on an eye-by-eye basis, ARM-risk eyes from healthy eyes.

We used step-wise discriminant analysis to test which variables are most effective in correctly identifying the category to which each eye belongs. Such analyses serve two purposes. First, when data from large numbers of subjects are considered, as in the present study, discriminant analysis helps objectively identify which variables should be tested, so screening for exudative ARM risk can be accomplished quickly in a clinical setting. For example, is it necessary to test the full range of the temporal contrast sensitivity function (CSF), or will testing at only a few flicker rates suffice? Two of the methods considered here, the four-parameter fit to the CSF (Method 2) and the hypothetical impulse response function (Method 3), require full CSFs. We tested how well Methods 2 and 3 discriminate compared to contrast sensitivity values at individual flicker rates and linear combinations of a few rates. Second, the eye-by-eye identification of category membership, which is characteristic of the discriminant method, is much like the task presented to a clinician interested in screening for exudative ARM risk: "Should we worry about this eye or not?" Significant group mean differences (such as those from an analysis of variance) do not necessarily imply variables that are successful in identifying individuals. So discriminant analysis can help us evaluate whether flicker sensitivity testing can provide information that, in conjunction with other clinical data, can be useful in screening individual eyes.

We found that healthy older eyes can be reliably separated from ARM-risk eyes using foveal flicker sensitivity at only two temporal frequencies—14 and 10 Hz (in order of estimated weight.)

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Materials and Methods

Subjects
We tested 13 ARM-risk eyes and 19 healthy older eyes. 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 participate in the research after the procedures had been explained fully, and all were in relatively good general health. Details of the health and history for both groups are contained in the accompanying paper in this issue.

ARM-risk 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. 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 also was rated in both groups of eyes.

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. 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, whose beginning and end were designated by short tones. The rate of sinusoidal flicker and its amplitude were controlled by a computer.

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 Lange or 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 to what would be expected for his or her retinal illuminance based upon norms derived from the performance of 30 younger subjects (18–24 yr old) with healthy eyes who were tested by the same methods used for the present study. We refer to the mean younger performance at a given retinal illuminance as the “predicted sensitivity.”

The ability to separate healthy eyes from ARM-risk eyes was evaluated for three data summary methods, described below. For each summary method, we used SPSS's step-wise discriminant analysis, minimizing Wilks' lambda with minimum F of 1.000 for inclusion and maximum F of 1.000 for exclusion.

Method 1: Contrast sensitivity as a function of flicker rate: This method used the contrast sensitivity values of the de Lange function to compare ARM-risk eyes with healthy older eyes. Predicted sensitivity was subtracted from actual sensitivity for each subject at each flicker rate (where sensitivity was in decilog units), and these relative sensitivities were entered into the discriminant analysis.

Method 2: Four parameter fit to de Lange function: By assuming the de Lange function is single-peaked and smooth, the inverted U of the function can be characterized by four parameters: maximum sensitivity, flicker rate at maximum sensitivity ("peak frequency"), low-frequency slope, and high-frequency slope.
Results

Method 1: Contrast sensitivity as a function of flicker rate: Actual-minus-predicted contrast sensitivity as a function of flicker rate for each subject is illustrated in Figure 3. Figure 3A shows the 19 healthy eyes; Figure 3B shows the 13 ARM-risk eyes. Step-wise discriminant analysis of these data yielded 78% discrimination with two parameters: actual-minus-predicted sensitivity at 14 and at 10 Hz. Wilks’ lambda was 0.62, with approximate $X^2 = 13.76$, (df = 2, $P < 0.001$), and the canonical correlation of the function was 0.615.

In general, healthy older eyes and ARM-risk eyes were less sensitive than younger eyes. Typically, ARM-risk eyes had even lower sensitivity for 14 and 10 Hz. Relative sensitivity at 14 Hz had a standardized canonical discriminant function coefficient of 0.775, whereas that for 10 Hz was 0.407. Relative sensitivity at 14 Hz correlated 0.926 with the discriminant function, and 10 Hz correlated 0.694.

Classifying on the basis of 14 and 10 Hz, four ARM-risk eyes (GF, KA, ME, and PM) looked more like a healthy eye, and three healthy eyes (CT, FP, and KJ) looked more like an ARM-risk eye.* Forcing all 11 flicker rates’ sensitivities to be included increased discrimination accuracy to 88%, with two cross-classifications in each group.

Method 2: Four parameter fit to de Lange function: Step-wise discriminant analysis of actual-minus-predicted values of the four-parameter fit to each de Lange function yielded 78% discrimination with two parameters: high slope and maximum sensitivity. Wilks’ lambda was 0.79, with approximate $X^2 = 6.77$, (df = 2, $P < 0.03$), and the canonical correlation of the function was 0.456.

In general, healthy older eyes had about the same high-frequency slope as younger eyes, whereas ARM-risk eyes’ high-frequency slope was shallower. Healthy older and ARM-risk eyes tended to have lower maximum sensitivity than that predicted from younger eyes, but ARM-risk eyes were even lower than healthy older eyes. The standardized canonical discriminant function coefficients were 0.572 and -0.531 for high slope and maximum sensitivity, respectively. High-frequency slope correlated 0.914 with the discriminant function, and maximum sensitivity correlated -0.899.

Although discrimination was as good with this method as with the two-frequency discriminant function of Method 1, less variance was accounted for (canonical correlation) with the two parameters of the four-parameter fit. Method 2 cross-classified three healthy (BS, CT, and PJ) and four ARM-risk (GF,

* In signal detection terminology, the ARM-risk eyes that looked more like members of the healthy group could be termed “misses”, and the healthy eyes that looked like ARM-risk eyes could be termed “false positives.” The connotations of these terms are that such cases are undesirable. However, because of the classification issues addressed in the Discussion, we prefer the more neutral term “cross-classification” plus identification of its particular type.
KA, ME, and PM) eyes using the two significant parameters. Discrimination was not improved by including all four parameters.

Method 3: Stork and Falk/Swanson impulse response function: Step-wise discriminant analysis of actual-minus-predicted values of the Fourier transform parameters yielded 69% discrimination with one parameter—peak amplitude of the first lobe. Wilks' lambda was 0.76, with approximate $X^2 = 8.16$, (df = 1, $P \leq 0.004$), and the canonical correlation of the function was 0.492.

In general, the first lobe for healthy older eyes and ARM-risk eyes had less amplitude than predicted, but ARM-risk eyes typically had even less amplitude in the first lobe. Six healthy (BE, FR, KJ, MF, WD, and WL) and four ARM-risk (GF, KA, LM, and PM) eyes
were cross-classified by using the two parameters of the IRF method. Forcing the use of all 12 parameters of Method 3 improved discrimination accuracy to 75%.

**Discussion**

Based on analysis of variance (ANOVA), we previously reported that increased risk of exudative ARM was associated with changes in responsiveness to long-wavelength, low spatial frequency flicker.\(^\text{1,13,14}\) In the present report, we used the step-wise regression of discriminant analysis to ask whether a linear combination of flicker sensitivity variables could accurately classify individual eyes as healthy or ARM risk. We tested three methods of summarizing the flicker sensitivity data. All three methods provided reasonably good classification of individual eyes using only one or two parameters. Methods 1 and 2 were able to separate eyes with 78% accuracy using two variables, and Method 3 yielded 69% accuracy with one variable.

Whether or not 78% accuracy is impressive depends upon: (1) the probability of correct classification by chance; and (2) what weight is given to the present system for classifying eyes as healthy or ARM risk. With the present criteria for group membership, correct classification by chance has a probability of 0.52.\(^*\) Therefore, 78% accuracy is well above chance, and the chi-squared for Method 1, for example, is highly significant (\(P < 0.001\)). In this sense, the discriminant analysis results were as statistically significant as those for the ANOVA between groups reported in our accompanying paper.\(^1\) However, the limits of the current classification system must be considered. Although the ARM-risk eyes are more at risk for exudative maculopathy than would be an age-matched general population sample, not all of these eyes will develop exudative maculopathy. In addition, although the healthy eyes appeared healthy at the time, some of them eventually may develop exudative maculopathy due to subclinical pathology.\(^6\) From this perspective, it may not be desirable to select candidate classifying variables, beyond those that were statistically significant, to force discrimination to higher levels. As a result, it will be important to test the discriminating capacity of the flicker data in the long run, as well as with the present classification system.

We also emphasize that the discrimination evaluated was only that between healthy older eyes and ARM-risk eyes, as defined above. We have not assessed subjects with other retinal disorders. Other labs have shown flicker sensitivity changes with retinitis pigmentosa\(^17\) and glaucoma\(^18\) using methods similar to ours. A preliminary comparison of ARM risk and these disorders showed that the patterns of flicker sensitivity loss may be different.\(^1\) Such variation in patterns of loss suggests that flicker sensitivity also may prove useful in differential diagnosis. However, a direct test of that hypothesis was beyond the scope of the present study.

One benefit of discriminant analysis is that it is an objective method for distinguishing candidate discriminators of exudative ARM-risk from healthy older eyes. These candidate discriminators then can be tested further with longitudinal data. For example, based on our current results, our hypothesis is that 10 and 14 Hz are good discriminators and perhaps will be good predictors of who will develop exudative ARM. We can test this hypothesis as we continue to follow our subjects longitudinally during the next 5–10 yr. In an accompanying report in this issue, we reported on two patients from the ARM-risk group that have now developed exudative ARM.\(^19\) These two patients, GW and TM, were correctly classified according to their sensitivity to 10 and 14 Hz 7 wk to 9 mo before developing exudative ARM. These preliminary longitudinal results suggest that reduced flicker sensitivity at mid-temporal frequencies (although not only 10 and 14 Hz\(^2\)) is associated with early stages of exudative ARM.

**Comparison of Methods**

**Method 1: Contrast sensitivity as a function of flicker rate:** In our accompanying paper in this issue\(^1\) we tested for flicker contrast sensitivity differences between the group means for ARM-risk eyes and healthy eyes. The ARM-risk group had lower relative temporal contrast sensitivity at mid-frequencies. The loss was statistically significant at 14 Hz and approached significance for 10 Hz using a Newman-Keuls test. In the present report, the discriminant analysis showed that by using a linear combination of relative contrast sensitivity at 14 and 10 Hz, it is possible to identify which group, healthy or ARM risk, a particular tested eye belongs to with 78% accuracy. This is not a trivial consequence of the group differences found with the ANOVA.\(^1\) It is possible for the group mean differences on a variable in an ANOVA to be highly significant statistically, but because of overlap in the distributions, that same variable may have little capacity to discriminate in which group an individual belongs. The discriminant analysis suggests that contrast sensitivity at 14 and 10 Hz may provide the kind of information that is useful for identifying individual eyes at risk for developing exudative ARM.

That only two frequencies may be needed to discriminate healthy eyes from ARM-risk eyes is appeal-

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\* The probability of correct classification using only prior probabilities is \(p = q^2\), where \(p = \text{probability that eye is healthy} = 19/32 = .59\), and \(q = \text{probability that eye is ARM risk} = 13/32 = .41\).\(^1\) Therefore, chance correct classification is 52%.
ing from a practical perspective. One could easily and quickly test contrast sensitivity for two frequencies in a clinical screening program. However, we may find we also want to discriminate ARM risk from other retinal dysfunctions (such as glaucoma, retinitis pigmentosa, etc.) on the basis of flicker testing. In this case, more than two frequencies may be required.

Method 2: Four parameter fit to de Lange function: Two of the four parameters used to fit the de Lange function (or temporal CSF) yielded 78% discrimination of the ARM-risk eyes and healthy eyes. These were actual-minus-predicted high-frequency slope and maximum sensitivity. We reported previously that maximum sensitivity, peak location, and high-frequency slope were significantly different between the ARM-risk eyes and healthy eyes. These earlier reports were based on fewer subjects, most of whom are included here. Thus, the current analysis gives us more confidence that the differences between the healthy older and ARM-risk groups can be characterized as a change in the shape of the temporal CSF (height of the curve) as well as an overall loss of sensitivity.

Methods of analysis 1 and 2 both yielded 78% discrimination with two parameters. Given equal discriminating capacity, Method 1, using contrast sensitivity directly, is preferred for practical and theoretical reasons. First, although the two methods resulted in equivalent discrimination, the four-parameter method accounted for less variance than Method 1. Second, the four-parameter method assumes that the temporal CSF is single-peaked and a smooth inverted U. However, the de Lange function probably is an envelope for two or three underlying functions. As a result, it has meaningful bumps and dips and possibly more than one peak. As our accompanying report suggests, one of these underlying mechanisms may be selectively affected by early stages of ARM. Therefore, it is better to use an analysis that does not restrict the shape, and thereby obscure differences, between healthy eyes and ARM-risk eyes. Third, in practice, Method 2 requires measurement of the entire de Lange function, followed by derivation of the two discriminating parameters. It is more efficient, for data collection as well as analysis, to simply measure two flicker rates to accomplish the same discriminability. Therefore, whereas Method 2 highlights changes in the shape of the temporal CSF, for discriminating healthy eyes from ARM-risk eyes Method 1 is preferred over Method 2.

Method 3: Stork and Falk/Swanson impulse response function: In a step-wise discriminant analysis, one parameter from the Fourier transform of the de Lange function was extracted. Actual-minus-predicted peak amplitude of the first lobe gave 69% discrimination. An advantage to carrying out analyses in the time domain of the IRF, rather than the frequency domain of the de Lange function, is the potential for identifying the temporal aspect of the response to flicker that may be affected by early stages of exudative ARM. The three-lobed IRF shown in Figure 2 can be considered to represent first an excitatory phase, followed by an inhibitory phase, then a dishibitory phase over time. Lower peak amplitude in the first lobe for the ARM-risk eyes suggests that it is primarily the excitatory phase that is affected by early stages of exudative ARM.

From a practical perspective, given the additional assumptions that are required to perform the Fourier transform analysis (some of which may not be valid), the additional time required to carry it out, and the fact that there is no gain in discrimination with it, Method 1 is preferred over Method 3 for discriminating ARM-risk eyes from healthy older eyes.

Summary

Flicker sensitivity is a good discriminator of ARM-risk eyes from healthy eyes of age-matched controls. The analyses presented here suggest that early stages of exudative ARM particularly affect sensitivity to mid-temporal frequencies, that the losses are in temporal processing as well as in overall sensitivity, and that the losses can be characterized as primarily in excitatory processes rather than in inhibitory processes. Whether flicker sensitivity losses prove to be good early warning signs of exudative maculopathy can be evaluated only through longitudinal testing of large numbers of ARM-risk eyes and healthy older eyes. However, preliminary results suggest that they may indicate early stages of exudative ARM. As a result, we are continuing to increase our longitudinal database, which includes flicker sensitivity testing as well as careful clinical evaluation and medical history for each subject.

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

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