Severity Staging by Early Features of Age-Related Maculopathy Exhibits Weak Relationships with Functional Deficits on SWS Grating Acuity

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Purpose. To examine the relationship between short-wavelength–sensitive (SWS) resolution acuity and epidemiologically defined stages of early age-related maculopathy (ARM).

Methods. Subjects consisted of 88 adults aged 51 to 87 years. Psychophysical testing was undertaken in only one eye of each subject (the study eye). All study eyes had a LogMAR acuity of 0.30 (20/40 Snellen) or better. SWS and achromatic grating resolution acuity were measured at 6° eccentricity from the fovea. Stereoscopic color fundus photographs centered on the macula were taken on both eyes of each subject and were graded using the Wisconsin Age-Related Maculopathy Grading System (WARMGS). After grading, features of ARM were combined to assign a severity stage from 0 to 5 using the methods described by the Rotterdam Eye Study. Relationships between visual function, study eye ARM stage, and fellow eye status were examined with the use of standard statistical analysis.

Results. Although SWS resolution acuity was significantly reduced in eyes classified as having any ARM compared with eyes classified as having no ARM ($P = 0.002$), there was no relationship between the severity of functional deficits and the morphologic severity from stage 1 to stage 4. On reassigning subject eyes to a revised severity staging (stage 0, stages 1 to 4 combined, and stage 5), SWS acuity was significantly different among these three groups ($P < 0.001$). No significant relationship was found between achromatic resolution acuity and ARM staging. The status of the fellow eye (advanced macular degeneration present or absent) was not significantly related to visual function in the study eye.

Conclusions. Significant functional deficits in SWS resolution acuity were found in eyes with ARM features, but the severity of functional loss did not correlate well with the currently accepted method of assigning a morphologic severity stage. Longitudinal studies may reveal further information on the relationships between functional deficits, ARM status, disease progression, and outcome. (*Invest Ophthalmol Vis Sci.* 2006; 47:4624–4631) DOI:10.1167/iovs.05-1227

Age-related macular degeneration (AMD) occurs as two main phenotypes, nonexudative and exudative, and is the leading cause of irreversible new vision loss among older adults in the Western world.[1–3] Nonexudative AMD is most commonly represented by geographic atrophy (GA) and exudative AMD by choroidal neovascularization (CNV), pigment epithelial detachment (PED), or both. Epidemiologic study suggests that soft confluent drusen and pigmentary irregularities, which represent some of the clinical features of macular aging or age-related maculopathy (ARM), are risk factors for the development of the late stages of the condition.[4–7] Recent longitudinal epidemiologic study, using morphologic features of disease progression, has suggested that there are stable patterns in the progression of early ARM and that several different severity stages of the disease exist.[5] However, longitudinal epidemiologic study has also shown that only a proportion of patients (10%–15%) with drusen and pigmentary irregularities acquire late AMD over a 5- to 10-year period.[6,7] Indeed an exudative outcome can develop in eyes without these early manifestations.[5] It is also known that the risk for exudative outcome vastly increases to between 23% and 38% over a similar time period in the fellow eye of patients who have already experienced an exudative outcome in one eye.[7–9] Based on fundus characteristics alone, the relationships between clinical features of early age-related maculopathy and later development of AMD are weak. Thus, there is a need to identify separate markers of disease status that would increase and complement our present understanding of the disease.

One promising avenue in the pursuit of such goals is the investigation of the usefulness of functional measures of vision in early ARM. Traditionally, visual function is assessed with high-contrast achromatic acuity (e.g., Snellen chart) and, more recently, letter charts with improved standardization.[10,11] However, many people who show retinal signs of ARM are classified as having normal visual function according to this measure. This has led to the investigation of other measures of function that are capable of detecting subtle levels of visual dysfunction before conventional visual acuity is lost.[12–19]

As is often the case in other retinal diseases,[20–22] short-wavelength–sensitive (SWS) cone function is compromised in early ARM eyes compared with non-ARM eyes.[15,18,23–29] SWS cone function has been suggested as a method of assessing the progression of ARM before the manifestation of atrophic or exudative macular lesions,[27] and lower sensitivities may be associated with impending visual loss[24] or a future exudative outcome.[30] In addition, reports indicate that high SWS cone increment thresholds may be associated with high-risk fundus characteristics.[26,31] Previous studies of SWS cone function in early ARM are limited by their small sample size and variable

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classification of disease status, often only comparing eyes with normal function with early ARM eyes. Because of recent epidemiologic findings,[5] we wanted to examine the relationships between SWS cone acuity and morphologic features of early ARM according to standardized grading criteria and these recognized severity stages. If measures of SWS cone resolution acuity were to exhibit relationships with the epidemiologically identified risk factors,[5] they would strengthen the hypothesis that ARM features are manifestations of pathogenetic pathways for disease progression.

We also wanted to ascertain whether the status of the fellow eye (exudative or nonexudative) is related to function in the better eye. Longitudinal observational study has shown this to be a significant factor for disease progression,[8,9] but it has not been considered in many of the previous studies investigating visual function in early ARM.

To examine SWS cone function in this study, sinusoidal grating resolution acuity (the ability to identify grating orientation) under conditions of SWS cone isolation was measured. Such methods have a useful clinical advantage over SWS increment sensitivity thresholds because measurements are not significantly reduced by optical blur[32] or by small amounts of simulated and age-related lens yellowing.[32,33] Given that achromatic and SWS resolution acuity have previously been shown to slowly decline in parallel with increasing age,[33] any apparent selective loss of SWS acuity relative to achromatic acuity in ocular disease is most likely to be pathologic in origin and not simply reflect an artifact of aging. Therefore, by comparing SWS and achromatic acuity, we sought to determine whether the severity of early ARM features exhibit relationships with the degree of selective loss in SWS resolution acuity.

METHODS

Subjects

Subjects with known diagnoses of early or late ARM were recruited from the macular retinal clinics of a specialist (UC). Control subjects were relatives of those attending the macular clinic or were recruited by means of poster and leaflet advertisements. In total, 88 subjects (32 men, 56 women; age range, 51–87 years; mean age, 71.4 ± 8.2 years) were recruited between July 2002 and December 2003. The study was conducted according to the tenets of the Declaration of Helsinki, and full ethical approval for the study was obtained from the relevant review bodies. Informed written consent was obtained from all subjects before participation. Subjects were required to be older than 50 years of age and to have best-corrected visual acuity of 0.30 LogMAR (20/40 Snellen) or better in at least one eye. Intraocular pressure was less than 21 mm Hg in each eye, as determined by Goldmann applanation tonometry. Exclusion criteria included visually significant cataract, diagnosis of diabetic retinopathy, glaucoma, amblyopia, retinal vascular disease, or any other retinal abnormality. Seven (8%) subjects had previously undergone cataract extraction with intraocular lens insertion in the study eye. Refractive corrections of all the subjects in the study were between +9.50 DS and –6.00 DS, with mean cylindrical correction less than 2.50 DC.

Visual Function Tests

All visual function tests were performed during a single visit lasting approximately 3 hours. Contrast sensitivity, color vision, and achromatic and SWS resolution acuity were undertaken on the study eye, which was the better eye. Better eye status was based on best-corrected LogMAR distance visual acuity. If acuities were equal in both eyes, one eye was randomly assigned to undergo psychophysical testing.

Visual Acuity

Best-corrected LogMAR acuity was measured at 4 m using the Early Treatment of Diabetic Retinopathy Study (ETDRS) LogMAR chart (Lighthouse International, New York, NY) for each eye separately. Each letter read correctly on each line was given a score of 0.02 log units, and the final acuity was given by the formula: LogMAR acuity = 1.10 – (total number of letters read correct at 4 m × 0.02).

Contrast Sensitivity

Contrast sensitivity was measured at 1 m using the Pelli-Robson contrast sensitivity chart (Clement Clarke International Ltd., Harlow Essex, UK) in each eye separately. This corresponded to a fixed spatial frequency of 1.5 cyc/deg at this testing distance. The chart was evenly illuminated to 100 cd/m^2. Log contrast sensitivity score was recorded as the faintest triplet where two of the three letters were named correctly. Credit was given for the circular letters O and C if these were named interchangeably.

Color Vision

Color vision was assessed in the study eye using the second edition of The City University Color Test (Keeler, Berkshire, UK) under the standard recommended lighting conditions with the fellow eye occluded. Error type and number of errors at each circle size were recorded.

Achromatic and SWS Resolution Acuity

Achromatic and SWS resolution acuities were measured with a custom-built resolution perimeter that has been fully described in previous studies (Fig. 1).[33–35] Stimuli were generated (Visual Stimulus Generator VSG2/3; Cambridge Research Systems, Rochester, UK) and displayed on a gamma-corrected high-resolution monitor (500PS; Sony, Tokyo, Japan). The monitor had a frame rate of 100 Hz, a pixel resolution of 1024 × 768, and a screen size of 30 × 40 cm^2.

The monitor was contained in a light-tight box with a viewing aperture for the subject. Within the apparatus setup, isolation of the SWS system was achieved by selective chromatic adaptation using a broadband yellow adapting background (Commission Internationale de l'Eclairage [CIE] $x = 0.51$, $y = 0.48$, luminance 600 cd/m^2 at the eye). The bright yellow background was produced by placing a long-wavelength pass yellow filter (530 nm half-height; Schott OG530; Edmund Optics Ltd., York, UK) in front of the lens of a halogen globe. The yellow light was then projected, from a position perpendicular to the monitor, through a white diffusing screen toward a beam splitter angled at 45°. The observer viewed the monitor straight ahead through the beam splitter, allowing the adapting background to cover a greater area than the monitor at all times. The yellow background, in combination with a dilated pupil, provided adequate retinal illumination to ensure that resolution of the short-wavelength stimulus would be mediated by the SWS cone pathway.[34]

Circular patches of short-wavelength sinusoidal grating stimuli (4° diameter, 90% contrast) were generated on the color monitor positioned 0.74 m from the subject. SWS gratings generated using only the blue gun of the monitor (CIE, $x = 0.147$, $y = 0.07$) had the same mean luminance, 0.9 cd/m^2, as the blue surround of the screen. Gratings were presented within a sharp-edged disk and at all times contained at least two full cycles at the acuities measured.

For achromatic resolution acuity measurements, patches of green on green sinusoidal grating stimuli, which were contained in a two-dimensional Gaussian window to avoid any edge effect (spread parameter, $r = 2°$; 90% contrast) were generated using only the green gun of the monitor (CIE, $x = 0.294$, $y = 0.616$) and had the same mean luminance (40 cd/m^2) as the green surround. At least six grating cycles were displayed within 2 σ spatial spread.

With the use of such mean stimulus luminance, we attempted to measure SWS and achromatic acuity under comparable adaptation

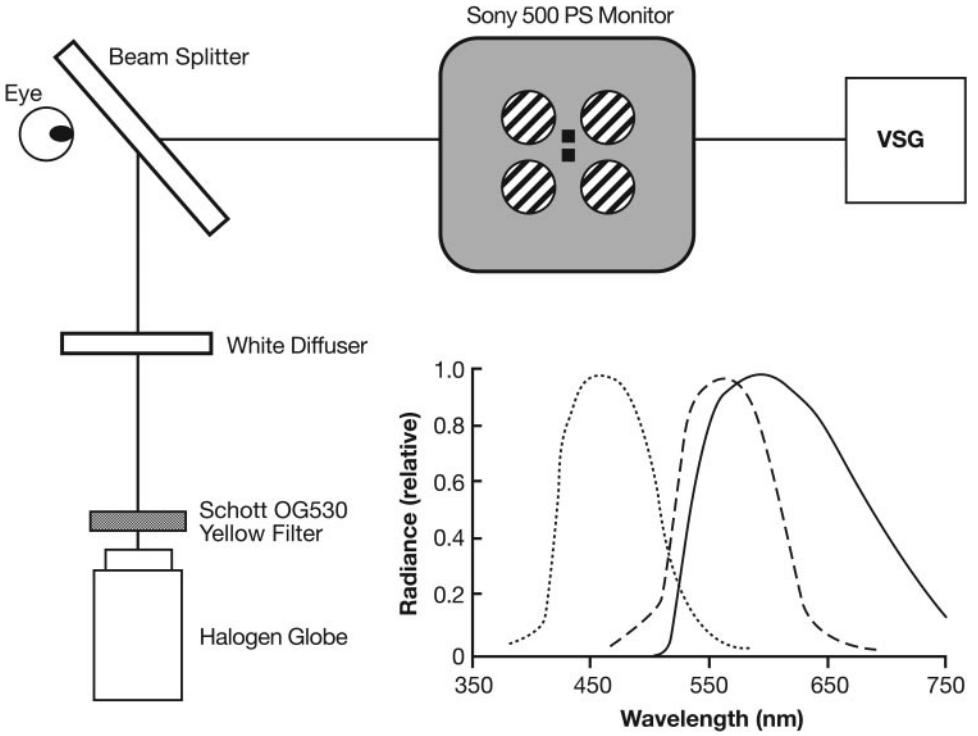

FIGURE 1. Schematic figure representing experimental setup used for measuring SWS and achromatic resolution acuity. Apparatus was contained in a light-tight box with a viewing aperture for the subject. The *solid black line* shows the spectrum of the background yellow light used for measuring SWS acuity. The *dashed line* shows the spectrum of the output of the green gun. The *fine dashed line* represents the spectrum of the output of the blue gun. Spectrum curves are expressed in units relative to the maximum.

conditions. Although acuity initially increased with increasing mean luminance of the grating (for SWS and achromatic acuity), a plateau was reached at which resolution acuity did not change with luminance for either the achromatic[36] or the SWS pathway.[20,32,37] For SWS resolution acuity, this finding was independent of the subject's SWS acuity.[20,37] In the present study, retinal illuminance resulting from the blue or green background alone was sufficiently high so that all eyes tested should have been in this range, thus ensuring that neither SWS nor achromatic acuity would be affected by potential changes in adaptation conditions, at least for normal eyes.

Psychophysical Procedure

After acuity, contrast sensitivity, and color vision assessment, the subjects' pupils were dilated with 1% cyclopentolate and 2.5% phenylephrine (Chauvin Pharmaceuticals, Essex, UK). In addition to improving SWS cone isolation, pupil dilation also helped to reduce any confounding caused by differential pupil sizes in older eyes. For each task, the subject's vision was optically corrected for the distance of the screen, including an additional arbitrary compensation for defocus because of chromatic defocus (–1 DS) and the cycloplegic effects of the mydriatic. Achromatic resolution acuity was measured first, and the fellow eye was patched during the procedure. An initial practice period took place until the investigator was confident that the subject fully understood the nature of test; this was followed by a short rest period before SWS resolution acuity was to be measured. Each subject was given 2 minutes to adapt to the yellow background; this was followed by a practice period so that the subject could become familiar with the task. Adaptation was assumed to be complete when the initial adaptation time and practice period were finished. Total adaptation time of 3 minutes or greater was similar to that used in several previous studies reporting SWS psychophysical measures in ARM eyes.[15,30,31]

Each subject sat with his or her chin on a chin rest and fixated the gap between two vertically aligned squares (0.4° size, 0.6° offset, 0° meridian). For achromatic and SWS resolution acuity, gratings were randomly presented with their centers at 6° eccentricity from a central fixation target in one of four oblique meridians (35°, 145°, 215°, 325°).

The procedure involved a two-alternative forced-choice (2AFC) orientation identification task in which the grating was oriented obliquely at 135° (to the left) or at 45° (to the right). Each subject had to press one of two buttons to register his or her response. A tone was audible between each presentation, and the subject was encouraged to respond to each stimulus even if it involved guessing. Target presentation time was 1 second (0.3 rise time, 0.3 decay), and resolution threshold was estimated using a three up/one down staircase procedure by which three correct responses resulted in a 10% increase in stimulus spatial frequency and one incorrect response resulted in a 10% decrease in stimulus spatial frequency. Gratings were initially presented suprathreshold to the expected resolution acuity, as determined within the practice period. Thirty presentations were made for each location, resulting in an average of four to five reversals for each location. Resolution threshold for each location was calculated as the mean of the reversal values.

Fundus Photography

Stereoscopic color fundus photographs centered on the macula were taken for each eye with a 35° field fundus camera (TRC-50EX; Topcon Corp., Tokyo, Japan) in combination with the appropriate software (2.11 software; IMAGEnet, Melbourne, Victoria, Australia). Images were stored as uncompressed TIF files and copied to compact discs for grading.

Photograph Grading

Images were analyzed (2.11 software; IMAGEnet) by two experienced fundus photograph graders who were masked to the main purposes of the study. Images were viewed as stereo pairs with a viewer yielding a magnification of ×25 on screen. Grading definitions were based on the Wisconsin Age-Related Maculopathy grading system (WARMGS).[38] All ARM signs (drusen size and type, pigmentary irregularities, and features of late AMD [GA or CNV]) within a fixed area (diameter, 6000 μm) around the fovea were recorded. If the graders disagreed on the grading of ARM severity, arbitration was undertaken by the consultant ophthalmologist.

Subject Staging

Each eye was assigned a stage based on the presence of features or combinations of features that were mutually exclusive (Table 1).[5]

TABLE 1. Definitions of the Mutually Exclusive Stages of ARM

Stages of ARM	Definitions
0	No signs of ARM or presence of hard drusen (<63 μm) only
1	Soft distinct drusen (>63 μm but <125 μm) only
2	Pigment irregularities only; no soft drusen (>63 μm)
3	Soft, indistinct drusen (>125 μm) or reticular drusen only
4	Soft, distinct drusen with pigmentary irregularities
5	Soft, indistinct or reticular drusen with pigmentary irregularities
6	Atrophic or neovascular macular degeneration (AMD)

Stages were defined by longitudinal epidemiologic study that revealed distinct stages of early ARM based on progression rates over a 6.5-year period.[5]

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Data Analysis

Data were entered onto a spreadsheet and analyzed (Statistical Packages for Social Sciences, version 11.0; SPSS, Chicago, IL). Table 2 shows the mean SWS and achromatic acuity values for all eyes at each of the four retinal locations of 6° eccentricity. One-way ANOVA on log-transformed data, with retinal location as the factor, showed that the location at which acuity was measured did not have a significant effect on either achromatic acuity [$F(3,299) = 0.14$; $P = 0.94$] or SWS acuity [$F(3,270) = 1.64$; $P = 0.18$]. Therefore, achromatic and SWS acuity values are presented as the mean of the individual acuity values measured at the four different locations for each subject. The performance of pseudophakic eyes on functional testing was indistinguishable from that of the phakic eyes (two pseudophakic eyes were in stage 1, three in stage 2, and two in stage 5).

Standard statistical analysis using general linear models, analysis of variance, and post hoc tests was carried out to examine the relationship between visual function results and retinal grading stages in the study eyes. In addition, the grading of each subject's fellow eye (the nonstudy eye) was then included to allow comparison of function between eyes with and without exudative fellow eyes.

RESULTS

LogMAR acuity and contrast sensitivity were available for all 88 subjects, and color vision was recorded in 85 subjects. SWS and achromatic resolution acuity values were available for 69 and 76 subjects, respectively. Occasionally, the tests could not be performed because of poor understanding, fatigue, or time constraints, so those data were missing. Fundus images of both eyes were available for all subjects.

Subjects

Table 3 shows that there was a reasonable spread of eyes across each of the six different levels of ARM. Thirteen subjects had no ARM features in either eye, and more than half the subjects (47) had an exudative lesion in the fellow eye.

Mean ages (± SD) of subjects by ARM stage in the study eye are shown in Table 3. Significant differences in mean ages were observed among the different stages [one-way ANOVA; $F(5,82) = 5.59$; $P < 0.001$]. Post hoc comparisons (Duncan test) showed that subjects in stage 0 were significantly younger than subjects in all other stages except stage 4. Subjects in stage 4 were significantly younger than those in stage 5. No significant difference in mean age was observed between any other pairs of stages. These small but significant differences in age were accounted for in subsequent analyses with the general linear model.

LogMAR visual acuity measurements on the study eyes ranged from −0.28 to 0.30 (0.01 ± 0.11). Mean LogMAR acuity in those eyes with any ARM (stages 1 to 5; mean acuity, +0.03) was significantly lower than in eyes with no ARM (stage 0; mean acuity, −0.05; $t = 2.5$; $df = 86$; $P = 0.02$). Contrast sensitivity values ranged between 1.05 and 1.80 log units (1.51 ± 0.15). Mean contrast sensitivity value in eyes with any ARM (stages 1–5; mean CS, 1.50) was significantly lower than in eyes with no ARM (stage 0; mean CS, 1.59; $t = 2.71$; $df = 86$; $P = 0.01$).

Color Vision

Three of 32 (9.4%) male subjects had a red-green color defect on testing. Thirty-three (38.9%) subjects exhibited at least one tritan error in the study eye. Figure 2 shows the percentage of tritan errors at each stage of ARM on the City University Color Test. There was an increasing trend to make color vision errors (0, 1, or multiple errors) as ARM stage increased from stages 0 and 1 combined, to stages 2 to 4 combined, and through stage 5 (χ^2 test; linear-by-linear association, 17.7; $df = 1$; $P < 0.001$).

SWS Resolution Acuity

SWS acuity ranged from 0.56 cyc/deg to 2.53 cyc/deg (1.46 ± 0.5 cyc/deg; Fig. 3). Mean SWS acuity in eyes with any ARM (stages 1–5; mean acuity, 1.35 cyc/deg) was significantly lower

TABLE 2. Mean Achromatic and SWS Acuity Values for All Eyes at Each of the Four Retinal Locations of 6° Eccentricity

Meridian (deg)	Achromatic Resolution Acuity (cyc/deg)	SWS Resolution Acuity (cyc/deg)
35	5.99 ± 0.23	1.53 ± 0.07
145	6.06 ± 0.24	1.44 ± 0.07
215	5.90 ± 0.21	1.40 ± 0.07
325	5.91 ± 0.22	1.41 ± 0.07

Values are mean ± SEM.

TABLE 3. Numbers of Eyes and Mean Ages of Subjects in Each ARM Stage

ARM Stage	No. Eyes	Subject Age (y)
0	20	64.9 ± 7.6
1	12	71.8 ± 4.4
2	12	75.3 ± 6.8
3	9	72.9 ± 8.3
4	13	69.2 ± 9.9
5	22	75.6 ± 6.3

Ages are mean ± SD.

than in eyes with no ARM (stage 0; mean acuity, 1.80 cyc/deg; $t = 3.26$; $df = 67$; $P = 0.002$). Statistical testing according to the general linear model showed that SWS acuity was significantly different between stages [$F(5,62) = 3.60$; $P = 0.006$] but was not significantly affected by age [$F(1,62) = 1.83$; $P = 0.18$]. One-way ANOVA and post hoc comparisons (Duncan test) showed that SWS acuity was statistically significantly different between certain morphologic stages [$F(5,63) = 5.33$; $P < 0.001$], but there was considerable overlap in function between several stages (Fig. 3). Post hoc comparisons (Duncan test) showed that SWS acuity in eyes assigned to stages 0 (mean acuity, 1.80 cyc/deg), 1 (mean acuity, 1.64 cyc/deg), and 4 (mean acuity, 1.50 cyc/deg) were significantly different from that in eyes assigned to stage 5 (mean acuity, 1.03 cyc/deg). Similarly, SWS acuity in eyes assigned to stages 2 (mean acuity, 1.31 cyc/deg) and 3 (mean acuity, 1.35 cyc/deg) was also significantly different from that in eyes assigned to stage 0 (mean acuity, 1.80 cyc/deg). Significant overlap in SWS acuity was observed in all other combinations of stages, and no monotonic relationship between functional severity and morphologic severity was observed (Fig. 3).

Therefore, we reassigned subject eyes into three revised groups (group 1: stage 0, $n = 20$; group 2: stages 1–4, $n = 46$; group 3: stage, $n = 22$). The general linear model (GLM) showed that SWS acuity was significantly different in these three groups [$F(2,65) = 7.45$; $P < 0.01$] but was not significantly affected by age [$F(1,65) = 2.08$; $P = 0.15$]. One-way ANOVA and post hoc comparisons (Duncan test) showed that

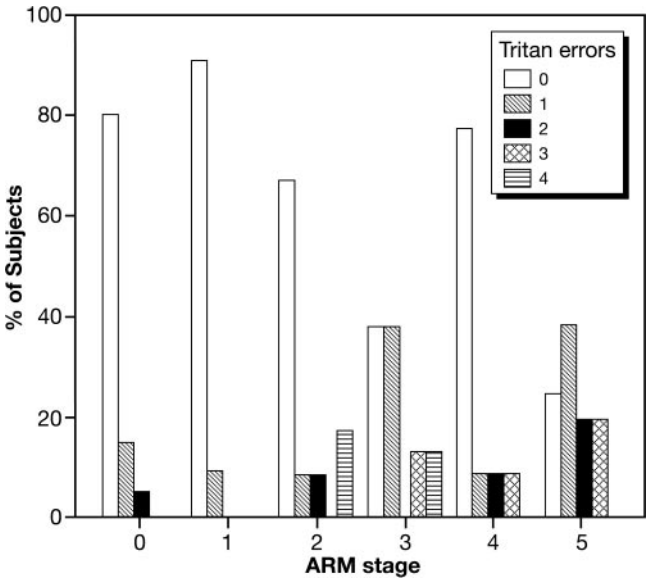

FIGURE 2. Bar chart showing the percentage of tritan errors made on City University Color Test at each stage of ARM.

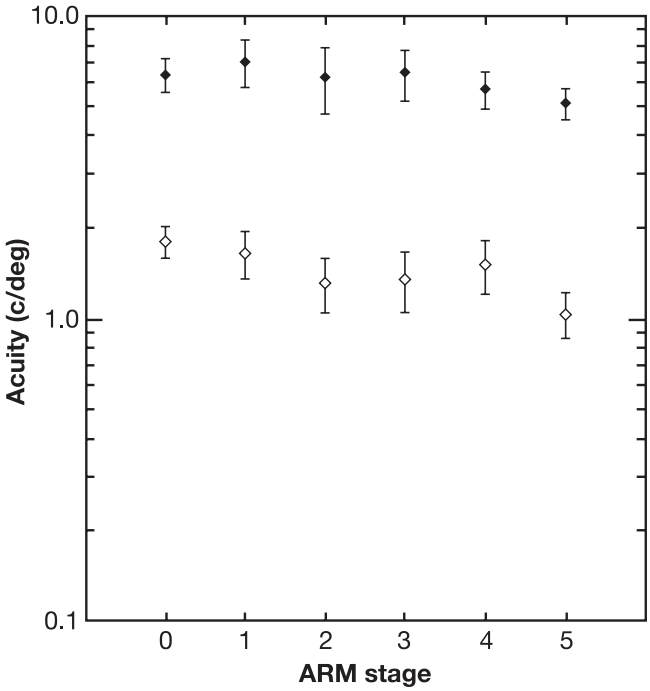

FIGURE 3. Mean achromatic resolution acuity (*closed diamonds*) and SWS resolution acuity (*open diamonds*) values with 95% confidence limits (±1.96 SEM) at the different stages of ARM.

SWS resolution acuity was significantly different in each of these 3 groups [$F(2,66) = 12.0$; $P = < 0.001$] (group 1: mean acuity, 1.80 cyc/deg; SEM, 0.11; group 2: mean acuity, 1.47 cyc/deg; SEM, 0.08; group 3: mean acuity, 1.03 cyc/deg; SEM, 0.09).

Achromatic Resolution Acuity

Achromatic resolution acuity values ranged from 2.88 cyc/deg to 10.04 cyc/deg (6.04 ± 1.82 cyc/deg; Fig. 3). No statistically significant differences were observed in the mean achromatic acuity values between eyes with any ARM (stages 1–5; mean acuity, 5.92 cyc/deg) and those with no ARM (stage 0; mean acuity, 6.38 cyc/deg; $t = 0.94$; $df = 74$; $P = 0.35$). The GLM showed that there were no significant differences among the six stages [$F(5,69) = 1.76$; $P = 0.13$] and that age did not have a significant effect [$F(1,69) = 1.02$; $P = 0.32$]. An independent t test with dichotomization of the six groups showed that achromatic acuity was significantly higher in eyes assigned to stages 0 to 3 (mean acuity, 6.50 cyc/deg) compared with eyes assigned to stages 4 and 5 (mean acuity, 5.30 cyc/deg; $t = 2.6$; $df = 74$; $P = 0.01$). On reassignment of study eyes to three severity groups, as with SWS, achromatic resolution acuity did not separate the categories [$F(2,72) = 2.44$; $P = 0.10$].

Achromatic versus SWS Resolution Acuity

Figure 4 shows the individual log achromatic resolution acuity values plotted against individual log SWS resolution acuity values for the different stages of ARM. SWS resolution acuity performance correlated significantly with achromatic resolution performance ($r = 0.73$; $P < 0.01$), signifying that achromatic and SWS acuity changed similarly for the whole group of patients. To further examine this relationship, a regression line of slope 1 was plotted (Figure 4) through the mean of the stage 0 acuity values. This line fit the data moderately well ($R = 0.70$), indicating similar changes in achromatic and SWS acuity

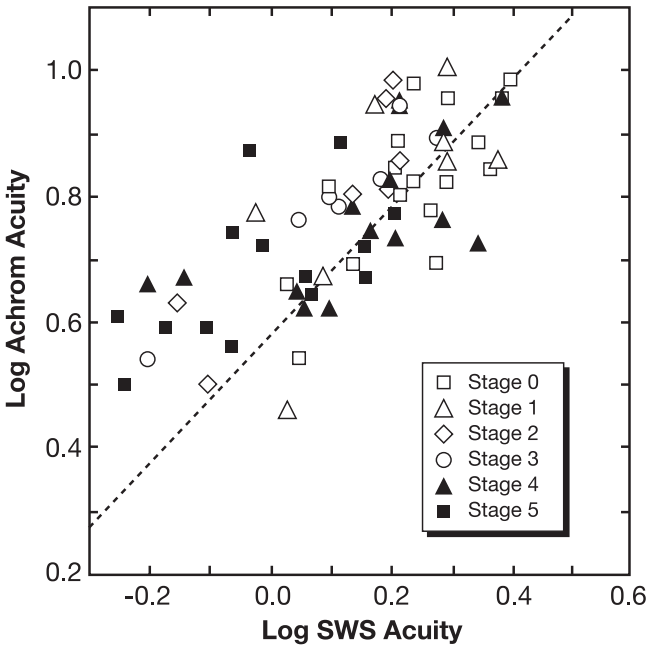

FIGURE 4. Individual log achromatic resolution acuity values plotted versus individual log SWS resolution acuity values for the different stages of ARM. The *dashed line* represents a regression line of slope 1, fitted through the SWS and achromatic acuity values from eyes in stage 0 only. This line fit the data moderately well ($R = 0.70$), indicating similar changes in achromatic and SWS acuity for eyes with no ARM. However, it can be seen that a number of data points (particularly from eyes in stage 5) lie above the line, indicating that SWS acuity was more affected than achromatic acuity in these eyes.

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Effects of Status of the Second Eye

With the GLM, we examined how the differences in SWS acuity, seen in the six-stage morphologic severity classification, were related to fellow eye status (a binary variable indicating presence or absence of an exudative fellow eye). No statistically significant interactions were seen, indicating that any differences in functional parameters between stages were the same regardless of whether advanced disease was present or absent in the fellow eye. Repeat analysis with study eyes assigned to the three-severity stage classification did not change the findings.

DISCUSSION

In this study, we investigated the relationship between SWS cone function based on grating resolution acuity and a recently proposed method of assigning disease severity stage based on the morphologic features of ARM.[5] This recent longitudinal epidemiologic study using morphologic features of disease progression suggests that there are stable patterns in the progression of early ARM and that several stages of disease severity exist.[5] It was our contention that if the staging system does indeed represent different severity levels of disease, a relationship between visual function and disease stage based on morphologic appearance should exist. Furthermore, if morphologic appearance and functional measures were found to be strongly related, it would permit a better understanding of the pathogenesis of disease progression from early-stage age-related maculopathy to choroidal neovascularization.

Parafoveal SWS and achromatic resolution acuity have not previously been used in the assessment of eyes with ARM. However, there is a strong theoretical basis that, under the appropriate testing conditions, they measure responses from distinctly different cellular pathways in the visual system[34] and may therefore reveal the identity of the dysfunctional cells in early ARM. We found that, with the exception of achromatic resolution acuity, all measures of visual function (LogMAR acuity, Pelli-Robson contrast sensitivity, City University Color Test, and SWS resolution acuity) were significantly reduced in eyes with any ARM features, regardless of severity or extent, compared with eyes without ARM features.

The present study has shown that achromatic resolution acuity does not correlate well with ARM severity status; functional deficits were detected only in eyes with marked ARM features. Similarly, though SWS resolution acuity distinguished between some severity levels of ARM, implying that altered RPE/photoreceptor integrity has a more marked effect on certain aspects of retinal function than others, SWS acuity did not show a monotonic relationship with morphologic severity stage. Figure 4 shows that in some individual eyes, SWS acuity was more affected than achromatic acuity. This was most evident for some eyes categorized as at stage 5. However, there was no evidence of selective loss of SWS cone function with increasing severity of ARM stage for the group as a whole. These findings suggest that, though the stages of disease may represent weak risk factors for progression, not all eyes at a particular stage have associated visual defects. Future longitudinal studies should be designed to determine whether functional measures within a stage are better markers for eyes at greater risk for progression than morphologic features alone.

Although other studies have examined the relationship between ARM features and SWS cone function,[15,18,23–29] important differences have been observed in study design and findings compared with those of the present study. Sunness et al.[26] compared SWS cone increment thresholds in a small group of subjects ($n = 31$) with high-risk drusen characteristics (classified as soft drusen, confluence of drusen, and focal hyperpigmentation) with those in a group with low-risk characteristics (none of the aforementioned present). They found that there was a tendency for the high-risk group to have higher thresholds, but this was not statistically significant, and a large amount of variation within each group and significant overlap between the two groups was evident. Eisner et al.[31] studied the fellow eye of 41 subjects with exudative AMD. They classified their sample as high risk (presence of focal hyperpigmentation or more than minimal drusen confluence or large drusen size) in 32 eyes and low risk (none of the aforementioned present) in nine eyes. Eyes in the high-risk group had lower SWS cone sensitivity. However, they were unable to determine with certainty whether the difference resulted from a normal aging change in threshold rather than a difference attributed to disease status. Eisner et al.[31] also noted that SWS cone functional loss was associated with all types of funduscopic change, not with one change in particular.

In contrast to the use of increment thresholds in the aforementioned studies, achromatic and SWS resolution acuity are not significantly affected by lens yellowing or optical blur.[32,33] This is because the resolution acuity for these stimuli is not limited by lack of stimulus contrast but by the sampling density of the coarsest array in the retinal pathway, the retinal ganglion cells.[34] In a previous study, we showed that in patients with glaucoma, in whom retinal ganglion cells are lost, there is a corresponding significant reduction in SWS and achromatic resolution acuity,[35] but it is known that ganglion cells are not

significantly affected early in the ARM disease process.[39] However, ganglion cells, whether midget or small bistratified, must still receive their input from the cones. In addition, though detection and resolution acuity display different thresholds in normal eyes, the increasing loss of cone sensitivity in diseased eyes eventually begins to affect resolution acuity, especially for the SWS system, in which the difference between detection and resolution acuity is already lower.[34]

It is recognized that one of the principal risk factors for progression of early ARM to advanced AMD is the presence of an exudative lesion in the fellow eye.[8,9] Therefore, it is intuitive to think that visual function should be worse in a study eye if the fellow eye has experienced an exudative lesion in the macula. However, we did not detect such a relationship, possibly because the sample size was relatively small. Similarly, Midena et al.[14] concluded that the presence of an exudative lesion in one eye did not significantly affect macular function in the fellow eye. However, Sunness et al.[26] found that the presence of an exudative lesion in one eye resulted in increased SWS cone thresholds in fellow eyes. However, this conclusion was based on data from only three subjects. None of the other studies that examined visual function in early ARM took this factor into consideration.

Figure 3 shows variability in SWS resolution acuity among eyes assigned to the same morphologic severity stage. However, it is reasonable to expect that a large component of the acuity variability in any group represents the interindividual variability resulting from real differences in retinal cell density (which exist even in a population with normal vision)[35,40] rather than variability in the measurement. Therefore, though functional measures may have some limitations for the purposes of initial classification, they may at a later stage prove useful in following the progression of the condition. Longitudinal follow-up of ARM eyes with measurements of SWS increment thresholds have been reported,[41] and follow-up of the current cohort of subjects using SWS cone resolution acuity may reveal further information on the relationships between functional deficits, ARM status, disease progression, and outcome.

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