



Published in final edited form as:

Arch Ophthalmol. 2004 November ; 122(11): 1647–1651.

Scanning Laser Entoptic Perimetry for the Detection of Age-Related Macular Degeneration

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Abstract

Objective—To determine the sensitivity and specificity of scanning laser entoptic perimetry for detecting visual function damage due to age-related macular degeneration (ARMD).

Methods—We measured the presence or absence of visual field disturbances by entoptic perimetry and determined the severity of ARMD based on masked readings of fundus photographs. A prospective masked study comparing the findings of entoptic perimetry with fundus photographs was performed. We recruited 91 patients with ARMD and 24 patients without ARMD during ophthalmologic visits. An appropriate institutional review board approval was obtained for the project. The main outcome measure was the detection of visual scotomata.

Results—Scanning laser entoptic perimetry had an overall sensitivity of 82% and a specificity of 100% for the detection of ARMD. The sensitivity for early stages of the disease is greater than 70%, and increases to above 90% for moderate to late stages.

Conclusion—Scanning laser entoptic perimetry is a specific and sensitive test for detecting ARMD, even at the earliest stages when patients are typically asymptomatic.

Age-related macular degeneration (ARMD) is the leading cause of severe irreversible visual loss in elderly Americans.¹ The number of cases of ARMD in the United States has been predicted to increase from 2.7 million in 1970 to 7.5 million by 2030.² The prevalence of ARMD also increases dramatically with advancing age. The over-all prevalence of any type of ARMD is approximately 20% in the 65- to 74-year-old age group and up to 35% in the 75- to 84-year-old population.^{3,4} Exudative ARMD has a 3-year incidence of approximately 1% in Americans after the age of 65 years.^{4,3} High-risk drusen are present in 13% of the elderly population.⁶

Ophthalmoscopic findings of patients with ARMD include 1 or more of the following: the presence of drusen (yellow deposits below the retinal pigment epithelium [RPE]), hyperpigmentary and hypopigmentary changes of the RPE, atrophic macular degeneration (a well-defined area of atrophy, called geographic atrophy, or another atrophy of the RPE and choriocapillaris), and neovascular macular degeneration (choroidal neovascularization [CNV], serous or hemorrhagic detachment of the RPE, and subsequent scarring of the macular area).³ Most ARMD patients have the dry type (including drusen, RPE changes, or RPE atrophy). Of the patients, 10% develop the wet type of ARMD (including CNV, RPE detachment, RPE tears, fibrovascular disciform scarring, and vitreous hemorrhaging).^{3,7}

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Financial Disclosure: None.

Funding/Support: This study was supported by grants E407366 (Dr Freeman) and EY11961 (Dr Plummer) from the National Eye Institute, Bethesda, Md; and by Research to Prevent Blindness, New York, NY.

The identification of patients at risk for developing the exudative form of ARMD allows for them to be monitored for early symptoms of CNV. Furthermore, in these at-risk patients, prophylactic treatment, such as vitamins⁸ or laser photocoagulation of soft drusen, may be feasible.⁹ Patients with only drusen in the early form of ARMD may be asymptomatic but are at higher risk of developing CNV than the healthy population.^{4–6}

Our goal was to determine if entoptic perimetry could detect such central disturbances in vision despite good Snellen visual acuity in patients with early ARMD. We developed a scanning laser device to stimulate the retina, and used it as an entoptic perimeter to test for visual disturbances. The technique of entoptic perimetry was first described in 1989 using random visual noise patterns.^{10–13} Repression of extrafoveal scotomata is due to the Troxler effect.¹² In brief, a fixed spot of light provided to the peripheral visual field will disappear from view if saccades are suppressed or if the light remains on the same area of the retina. We, therefore, used a novel scanning laser—based entoptic perimeter, which screened the central 60° of vision (30° radius) in patients with and without ARMD.

The Amsler grid is a perimetric tool by which patients look at a 10° × 10° grid of line spaces at 1° intervals, and is designed to measure central visual function. While easy to administer and interpret, the Amsler grid is relatively insensitive to relative scotomata that indicate early stages of disease. Other techniques to detect ARMD include frequency-doubling perimetry, but the researchers conclude that commercial units would require modification to detect the small relative scotomata present in patients with early ARMD.¹⁴ Loewenstein and associates studied the use of a hyperactivity computerized visual field test, and found better sensitivity than that of the Amsler grid in detecting ARMD; however, the test is not widely used.¹³

Indeed, the Amsler grid is not widely used by non-ophthalmologists. Other psychophysical tests to screen for ARMD have been evaluated, including noise field perimetry¹⁶ and multifocal electroretinography.^{17,18} Test results of shape discrimination¹⁹ and contrast sensitivity²⁰ are also abnormal in ARMD patients and may have a role in screening as well.

We have developed the technique of entoptic perimetry, initially based on the work of Aulhorn and Kost,¹³ Ramachandran,¹⁰ and Ramachandran and Gregory.¹¹ This noninvasive test requires a brief instructional period. Testing time is relatively rapid (usually < 1 minute), and the test can be potentially self-administered. Our early versions of the test used a television screen or a computer monitor to screen for cytomegalovirus retinitis. In subsequent studies, patients observed the stimulus in a scanning laser device. We found that patients were able to detect visual field abnormalities due to various retinal diseases (cytomegalovirus retinitis, diabetic retinopathy, and macular degeneration) and damage due to glaucoma within the central 120° of the visual field.^{21,22}

During entoptic perimetry, a patient is shown a monochromatic field of random particle motion. While looking at the central fixation spot, patients with dense scotomata (due to cytomegalovirus retinitis) reported that in some areas of the visual field the random particle motion disappears and is replaced with gray. If a patient has relative scotoma (due to early glaucoma, cotton-wool spots, or another retinal injury), the patient typically reports that there is some residual particle motion in the affected areas; these areas are qualitatively different from the remainder of the visual field. The particle motion of entoptic perimetry seems to circumvent the Troxler effect.^{21–23}

METHODS

PATIENTS

We recruited patients who were diagnosed as having ARMD in 1 or both eyes. We also recruited a control group of volunteers who were classified as healthy in the same clinic. Patients were recruited by one of us (W.R.F.) during ophthalmologic visits for the treatment of ARMD from the retina clinics at the Shiley Eye Center, University of California, San Diego. There was no minimum requirement for visual acuity. Participation of all subjects was voluntary. We received informed consent from each patient and healthy control before testing.

STIMULUS

The stimulus was delivered through a virtual retinal display (VRD) developed by Microvision, Inc, Bothell, Wash. The VRD delivered a monochromatic image via a scanning laser beam projected onto the retina from the standard videographics array output signal generated by a portable computer (Macintosh G3 Powerbook). Each pixel in the image could have 1 of 2 values: off (black) or on (deep red [635 nm]). The stimulus was previously described in detail.²¹ In brief, at a given time, each pixel was randomly assigned either the on or off value. These values changed over time. The overall effect was that the visual field was filled with random particle motion. There were no discernible patterns within the image over time.

The appearance of the VRD is similar to a telephotographic camera lens. Patients viewed the image through a 1-mm aperture at one end of the VRD. The opposite end was connected to the video input from a computer. The VRD was secured to the table to reduce vibrations. Patients minimized head movements by placing their chin and forehead against an adapted slitlamp headrest that was also secured to the table. Previous studies^{21,22} proved that minimizing head movement increased the sensitivity of the test. This also allowed people to fixate more readily on the narrow exit aperture.

The computer generating the stimulus passed the video signal through a splitter. One cable from the splitter was attached to the VRD, while the second was attached to a separate computer monitor that displayed the image in black and white. The monitor allowed the technician to control the stimulus and view the program without requiring the patient to move from the VRD.

PROCEDURES

Before testing, each patient underwent a dilated ophthalmoscopic examination using an indirect ophthalmoscope and slit-lamp biomicroscopy followed by fundus photography.

The technician briefed each patient on the purpose of entoptic perimetry and the testing requirements. Patients who agreed to the testing procedure received a brief overview of the procedure, including potential risks, and then were given a consent form. Following informed consent, patients received a tutorial on entoptic testing. The instructional component rarely took more than 2 minutes. By using the computer monitor, the experimenter showed the stimulus and the fixation point to the patient. Patients were told that if there were areas where the particle motion changed or looked qualitatively different, they should use the digital pen to outline the edges of the area of disturbance. The digital pen allowed the user to draw virtual lines using a touch tablet and stylus on the desk next to the stimulus. The lines appeared on the computer and to control the stimulus (described later). When satisfied with a drawing, it would be saved in the computer. If the patient believed that the drawing was inaccurate, the patient would be allowed to redraw it. This test was performed on both eyes unless there was a confounding variable, such as no light perception in the fellow eye.

The entoptic program had 2 display modes: stimulus and drawing. When in the stimulus mode, random particle motion filled the screen, except for the central fixation cross. Patients switched from stimulus to drawing mode by bringing the digital pen close to the tablet (within approximately 1 cm). The screen then became uniformly colored (white on the computer monitor and red on the VRD). Moving the pen just above the tablet changed the location of the cursor. This allowed the patient to relocate the pen to areas of visual disturbance without drawing a line. Conversely, pressing the pen against the pad and moving it slowly with a firm but light pressure drew a line on the screen. If the patient made a mistake or was unsatisfied with any aspect of a drawing, the experimenter either used the undo function to remove the previous line or cleared the drawing pad and allowed the patient to redo the trace.

One possible confound in the stimulus is that the perception of the visual field disturbance disappears when switching from stimulus to drawing mode. This was mitigated by allowing the patient to switch between modes simply by varying the distance of the digital pen from the tablet. Patients received instructions to use a trial-and-error method by which they would flip between stimulus and drawing mode to carefully trace out edges of all visual field disturbances. We allowed patients to practice drawing and switching between modes throughout the instructional phase of testing. Each patient was instructed to outline, as best as the patient could, the edge of the extent of any area of the stimulus that differed qualitatively from the monochromatic particle motion.

During the testing phase, one eye was patched. The patient was aligned to the VRD. The subject's head was placed in the headrest, and the VRD was moved into position by the technician until patients reported that they were able to see the entire screen, filled with particle motion, as they had observed on the computer monitor. No patient reported any problems in alignment or ability to view the stimulus within the VRD once properly aligned. The narrow aperture proved to be a benefit because it forced the patient to focus on the stimulus at all times. If the patient's gaze or attention wandered, the patient would not be able to perceive the stimulus. Patients were told to concentrate their attention on the central cross. The stimulus was started, and patients were then allowed to use the pen to switch between modes and record the locations of disturbance. The field of view was 30°.

SCORING OPHTHALMOLOGIC FINDINGS

As previously noted, fundus photographs of each patient were taken as part of the normal examination during the visit. We determined the presence of retinal damage due to ARMD by indirect ophthalmoscopy and confirmed by fundus photographs. Scoring of the photographs was performed by 2 ophthalmologists (W.R.F. and M.E.-B.), and reviewed by an expert in retinal disease (W.R.F.). The ophthalmologists classified each eye into 1 of 8 categories by grading stereoscopic color photographs and angiograms. The following categories were used: mild drusen, moderate drusen (many soft drusen), mild geographic atrophy, moderate to advanced geographic atrophy, pigment epithelial detachment, untreated CNV, inactive previously treated CNV, and untreated but regressed CNV. We resolved any conflicts in categorization by consensus.

SCORING PERIMETRIC FINDINGS

An expert psychophysicist (D.J.P.) scored all entoptic tracings for the presence or absence of a visual field disturbance. A given eye was classified as having no visual field disturbance if the patient made no marks on the screen with a digital pen (negative), while having any marks within the visual field was classified as a disturbance in visual function (positive). The psychophysicist was masked to ophthalmologic findings until completion of all scoring.

STATISTICAL ANALYSIS

For each classification, we determined the ratio of eyes that were positive by entoptic perimetry and fundus photography (true positives by entoptic perimetry) to the eyes positive by fundus photography (the gold standard). Similarly, specificity was determined as the ratio of the number of eyes scored negative by entoptic perimetry, which were also negative by fundus photography (true negatives by entoptic perimetry), to the number of eyes scored negative by fundus photography (the gold standard).

Sensitivities were calculated for each of the 8 classifications of ARMD and the combination of those 3 stages that compose early ARMD. Specificity was derived from healthy control eyes.

RESULTS

We recruited 91 patients (41 women and 50 men) with ARMD, for a total of 171 eyes (mean \pm SD age, 68.76 ± 10.29 years). We did not test 11 fellow eyes from this group because of poor central vision, resulting in the inability to perceive the stimulus. We recruited 24 healthy control patients, for a total of 43 eyes (mean \pm SD age, 64.30 ± 15.81 years). We did not test 5 fellow eyes from these patients. There were no significant differences in mean age between groups ($P > .40$).

The Table provides a summary of results, including stratification by severity of disease. Overall, we found that scanning laser entoptic perimetry has a mean \pm SD sensitivity of 0.82 ± 0.04 and a specificity of 1.00.

The sensitivity for early stages of the disease (mild and moderate drusen and mild geographic atrophy, with a visual acuity better than 20/40), when patients typically remain asymptomatic, ranges from 0.70 to 0.93 (mean \pm SD, 0.77 ± 0.06). The sensitivity of entoptic perimetry increases for later stages of the disease, averaging approximately 0.93. Patients are able to detect visual field disturbance due to CNV with a high sensitivity (treated, 0.92; and untreated, 1.00). We had 4 special cases of advanced ARMD in which diagnoses crossed more than 1 grouping boundary. For all 4 eyes, patients reported entoptic disturbances.

COMMENTS

It was previously demonstrated that scanning laser-based entoptic perimetry is an excellent screening tool for detecting retinal injury due to various diseases, including ARMD.²¹ In that study, relatively few ARMD patients were tested and many had moderate to advanced disease, potentially limiting the interpretation of the results. This study directly addresses the limitations of the previous studies. We tested many eyes (171 vs 4) and developed a method of stratification by disease stage. This provides a metric for determining how sensitive entoptic perimetry (or any screening test) is for detecting ARMD during early vs late stages of the disease.

The results for later stages of the disease are consistent with previous findings.^{21–23} In this study, we found that the overall specificity (mean \pm SD, 1.00 ± 0.00) was high, but similar to what was previously reported.^{21–23} We also found that the overall sensitivity of entoptic perimetry was 82%. However, this may be an underestimation of the true sensitivity of entoptic perimetry. Our patient cohort is biased toward patients with early forms of the disease. More than half of the eyes in this study (56.1%) were classified within the 2 mildest forms of ARMD. These forms have the shallowest scotomata and the lowest sensitivity. We recruited many of these patients because all ARMD patients pass through this stage and these are the patients who would benefit most from emerging therapies.

For early ARMD, our a priori assumption was that entoptic perimetry would have a relatively low sensitivity for detecting these types of scotomata. In contrast, the results for the sensitivity of entoptic perimetry for detecting early and moderately advanced stages of ARMD were impressive. We found that for patients classified as having drusen we could detect visual function loss with a sensitivity greater than 70%, and for those with mild geographic atrophy at a rate of 93%. The overall sensitivity for detecting any type of ARMD, capturing patients who are typically asymptomatic, was 82%. These results suggest that, given an optimized stimulus, we can detect three quarters of all early forms of ARMD. Entoptic perimetry depends on responses from every level of the visual system, from the photo receptors to the brain, and abnormalities that are detected cannot necessarily be located to one specific area. This is important for primary care physicians or optometrists serving geriatric populations. If a physician can detect ARMD early and refer to an ophthalmologist, it is possible that future therapies will reduce the total amount of vision lost. Standard screening tests like the Amsler grid and Humphrey Field Analyzer cannot always detect visual function loss due to ARMD at this early stage of the disease. We did not, however, compare scanning laser entoptic perimetry with standard automated perimetry directly. The latter is more expensive and time-consuming.

These results suggest that scanning laser entoptic perimetry is an effective screening test for ARMD. Entoptic perimetry has another advantage in that our entoptic perimetry setup is portable. This test could be easily implemented by primary care physicians and transported to outpatient clinics and underserved communities. Because ARMD is a disease primarily affecting geriatric populations, house staff could provide periodic screenings at rest homes. The support staff at any of these locations could administer this test with a minimum time expenditure. This will allow asymptomatic patients with ARMD to be referred to ophthalmologists before severe damage occurs to central vision.

The VRD has 3 distinct advantages over flat-screen technologies when implementing entoptic perimetry. It has the capability to display a stimulus out to 30° eccentric from the fovea when fixated centrally. Because ARMD is a disease primarily of the central retina, there was no reason to screen outside these areas, as done in other studies. The VRD also produces a relatively high signal-noise ratio relative to computer monitors. Images from the VRD are projected directly into the eye at virtual infinity. This is an immense benefit when testing geriatric populations that may have latent cataracts, media opacities, and high refractive errors. The VRD, therefore, displays images on the retina more independent of the visual system's optics, reducing the importance of optical aberrations of the anterior segment and eliminating the need to perform exact refractions for each patient. We did not analyze the correlation between location of retinal abnormality and entoptic defects. Prior work^{21–23} has shown that there is a close correlation between these 2 factors. In ARMD patients, however, abnormalities are diffuse and may be difficult to locate with precision.

Entoptic perimetry is not intended to replace the need for ophthalmologists or other screening tools, like visual field perimetry. This screening test will best serve primary care physicians and optometrists in detecting ARMD in its early stages.

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Table
Sensitivities for Eyes Diagnosed as Having ARMD, Grouped by Severity of Disease*

ARMD Diagnosis	No. of Eyes	Sensitivity, Mean \pm SD
Drusen [†]		
Mild or hard	40	0.70 \pm 0.10
Moderate or soft	56	0.77 \pm 0.07
Geographic atrophy		
Mild [†]	15	0.93 \pm 0.09
Moderate or advanced	16	0.94 \pm 0.08
Pigment epithelial detachment	5	0.80 \pm 0.25
Choroidal neovascularization		
Untreated	10	1.00 \pm 0.00
Inactive, previously treated	25	0.92 \pm 0.08
Mixed eyes [‡]	4	1.00 \pm 0.00
Hard drusen, soft drusen, and mild geographic atrophy groups [†]	111	0.77 \pm 0.06
All ARMD groups	171	0.82 \pm 0.04

Abbreviation: ARMD, age-related macular degeneration.

* The specificity for the 43 healthy control eyes was 1.00.

[†] These eyes had a visual acuity better than 20/40; thus, this is a mixed classification.

[‡] More than 1 group.