Scanning Laser Entoptic Perimetry for the Screening of Macular and Peripheral Retinal Disease

Daniel J. Plummer, PhD; Stanley P. Azen, PhD; William R. Freeman, MD

Objective: To determine the effectiveness of scanning laser entoptic perimetry as a noninvasive platform for screening for retinal damage in visually asymptomatic patients within the central 120° (diameter) of vision.

Design: A masked study comparing entoptic perimetry with fundus photographs.

Setting: The Shiley Eye Center and the AIDS Ocular Research Unit at the University of California, San Diego.

Patients: Fifty-eight patients recruited during ophthalmologic visits for treatment or follow-up of ocular disease.

Measurements: For each testing session, we compared the presence of a disturbance in the entoptic stimulus with the presence of retinal disease within the central 120° of vision, centered on the fovea.

Results: Scanning laser entoptic perimetry has a sensitivity and specificity of more than 90%, a positive predictive value of 100%, and a negative predictive value of 89% for screening retinal lesions within the central 120° diameter of vision.

Conclusion: Scanning laser entoptic perimetry may be an effective and inexpensive screening test for diagnosing retinal disease in hospitals and community clinics.

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One of the most challenging problems in ophthalmology is the development of effective retinal screening tests for peripheral retinal disease. Visual dysfunction is unique in that patients experiencing peripheral retinal damage often remain visually asymptomatic. Patients generally do not notice any disturbance of the visual field until retinal damage occurs close to the fovea. Repression of peripheral scotomas is related to the Troxler phenomenon. In the Troxler phenomenon, a fixed spot of light above threshold presented to the peripheral visual field will begin to slowly disappear from view. This phenomenon applies primarily outside 12° from fixation. This is likely due to neural mechanisms in the brain, and has the adaptive value in human vision of allowing structures in a constant position in the visual field (e.g., blood vessels) to be repressed and not interfere with visual function. Scotomas due to retinal damage are also repressed by the Troxler phenomenon, and therefore are not perceived by patients, especially if they are outside the fovea.

Early detection of potentially treatable infectious retinopathies, ocular melanomas, and other retinal diseases is essential for the prevention of severe vision loss and potentially fatal systemic diseases. Damage due to many of these diseases (e.g., cytomegalovirus [CMV] retinitis) may be insidious, particularly because it often affects the peripheral retina first and patients are often asymptomatic until irreversible destruction of central retina (macula) and loss of visual acuity occurs. A procedure that can measure the extent and locations of retinal scotomata would therefore be expected to give a relatively precise determination of the retinal damage.

Until now, there have been no rapid, noninvasive screening techniques for peripheral visual dysfunction. The Amsler grid is a perimetric tool administered to the patient for central and paracentral scotomas. It is commonly used by ophthalmologists as a diagnostic technique for measuring changes in visual function. Observation of a grid of lines on a paper that subtend a 10° radius from fixation will detect central retinal scotomas. How-
PATIENTS AND METHODS

PATIENTS

We recruited 38 patients from the Shiley Eye Center and from the AIDS Ocular Research Unit at the University of California, San Diego. Patients were selected from the general retina clinic of one of us (W.R.F.). There was no minimum requirement for visual acuity. A total of 110 eyes were tested using scanning laser entoptic perimetry. (Six patients had only 1 eye tested due to disease causing complete blindness in the fellow eye.) All patients were recruited during ophthalmologic visits for treatment or follow-up of ocular disease. Participation was voluntary and we received informed consent.

STIMULUS

Scanning laser entoptic perimetry consisted of a monocular presentation on a VRD of monochromatic random particle motion. Each “pixel value” could be either on at 635 nm or off. The VRD delivered the entoptic stimulus through a narrow exit pupil (1 mm), which was then viewed by the patient.

The stimulus presented to the patient through the VRD was also “mirrored” by virtue of a video signal splitter that displayed the identical stimulus on a computer monitor. This allowed the experimenter to view the identical stimulus as the patient and control the entoptic perimetry program without interfering with the view of the patient in the VRD.

PROCEDURES

Patients’ eyes were initially dilated, an ophthalmologic examination was performed, and fundus photographs taken. Fundus photographs were taken to include all areas of retinal disease as previously described. A diagram of lesion locations was made by a qualified ophthalmologist (W.R.F.). Presence and locations of these lesions was confirmed by fundus photography, thereby effectively providing documentation of true location of any lesions on the retina within 1 hour of testing. In all cases, lesions observed by indirect ophthalmoscopy were in complete concordance with fundus photographs.

Next, patients were shown the computer monitor that mirrored the stimulus inside the VRD, and were shown an example of the entoptic stimulus. Patients were given instructions on how to use the virtual pen. Patients were explained that they would view the identical stimulus (but for the red color) within the VRD.

The entoptic program has 2 modes of display. The stimulus mode displays the entoptic stimulus. As the virtual pen was brought into close proximity to a touch-sensitive pad, the stimulus mode ended and the program entered the “recording” mode, where patients were presented with a blank workspace for drawing. The recording mode had several options. Placing the pen on the pad and moving it (keeping a firm, light pressure on the stylus) produced a black line against the background. Removing the pen from the pad but keeping it in close proximity to the pad (ie, close than 1 cm) allowed the patients to move the cursor on the screen without drawing. Pulling the pen away from the pad further than 1 cm returned the viewer to the stimulus mode. Placing the pen close to the pad would again return the patient to the drawing screen, and previously drawn scotomas would remain. In this way, participants were able to turn the stimulus on and off under their own control. All actions were monitored by the technician who viewed the computer monitor during testing. This instructional phase rarely took longer than 2 minutes.

After instructions, patients were seated in front of the VRD and asked to view the VRD with 1 eye (an eyepatch was provided). They were asked to fixate in specific locations within the visual field, and while remaining fixated, to report any perceptual changes.

Unlike computer monitors that can be viewed from a wide variety of angles, by virtue of the narrow exit pupil, patients had to concentrate on fixing within the VRD to see the entoptic stimulus. If their gaze wandered, the stimulus disappeared from view and they saw a black field. Thus, unless the patient was fixated centrally within the VRD, patients were unable to see the stimulus.

However, the Amsler grid may be ineffective for detecting disturbances in vision even within the central 10° radius of vision, and certainly cannot detect defects peripheral to this. As a result, there currently exist no noninvasive techniques for detecting peripheral disturbances in vision that can be administered to the patient without specialized equipment. Teich and Saltzman have increased the effectiveness of the Amsler grid with a new stimulus out to a 22.5° radius (45° field), but they reported only a 65% sensitivity, which is insufficient for large-scale screening of patient populations. Visual field perimetry is an alternative that accurately measures the location and extent of peripheral visual field scotomata, but is impractical to primary care physicians as a screening test because of cost, testing time, and need for trained technicians.

Entoptic, or snow-field perimetry, is based on the work of Aulhorn and Köst and later work by Ramachandran. A simple computer monitor filled with random particle motion, when viewed by someone with a normal visual system, will appear as “visual noise.” Aulhorn and Köst noted that patients with peripheral retinal lesions were able to outline their scotomas. Areas corresponding to the damaged retina appeared to have no random motion, and were “gray” or “motionless” in appearance. Areas where patients reported no random particle motion corresponded to retinal lesions.

Based on these results, our group first developed and then enhanced a clinically useful screening test for retinal damage in patients with the acquired immunodeficiency syndrome caused by CMV retinitis with the use of a computer monitor. We found that with this test, patients with CMV retinitis can see scotomas in the eye(s) with the infection. We demonstrated that entoptic perimetry had a high sensitivity and specificity to detect lesions due to CMV retinitis within a 30° radius from the fovea (60° field).
The VRD we used had a capability for screening out to 30° radius when the patient was fixated centrally on a fixation crosshair. However, as there was no peripheral image distortion by having the patient fixate on the corners of the virtual screen, we placed crosshairs at the 4 corners of the screen as well as halfway along the vertical and horizontal edges of the screens. By having patients fixate on a corner of the virtual image (eg, lower left), we were effectively able to screen out 60° from fixation for a given quadrant. This procedure was repeated for the 3 other corners in a random order, therefore screening the entire central 120° of the retina.

### SCORING PERIMETRIC FINDINGS

Presence or absence of entoptic perimetry visual field disturbance was determined by an expert psychophysicist (D.J.P.). If a patient drew an area using the computer interface that corresponded to a localized change in the entoptic stimulus, the eye was classified as having a visual field disturbance. As with the ophthalmologic findings, we classified visual field disturbances as within the central 10° (radius) of the visual field, between 10° and 30°, from 30° to 60°, or outside the central 60° radius, as measured from the fovea. The psychophysicist was masked to the outcome of the ophthalmologic findings.

### SCORING OPHTHALMOLOGIC FINDINGS

Presence or absence of retinal damage was determined by an expert ophthalmologist (W.R.F.) using indirect ophthalmoscopy and confirmed by fundus photography. For each of the diseases listed in Table 1, we determined areas of damage to the retina using the following rules:

- **Diabetic retinopathy**, branch retinal vein occlusion. Areas of nonperfusion and edema as seen with fluorescein angiography, confirmed by fundus photography. For each patient, there were also areas that had undergone panretinal laser photocoagulation.
- **CMV retinitis**. Areas of retinal destruction by fundus photography seen as “healed” retinitis.
- **Ocular melanoma**. Areas of the retina corresponding to the location of the tumor.
- **Macular hole**. Areas relating to the hole and surrounding cuff of fluid.
- **Acute posterior multifocal placoid pigment epitheliopathy**. Areas of the retinal pigment epithelium disturbed despite excellent visual acuity.
- **Age-related macular degeneration and drusen**. Areas in eyes of patients without laser surgery, both wet and dry, as confirmed by fundus photography.
- **Retinal detachment/tear**. Area of retinal detachment as confirmed by fluorescein angiography and fundus photography.
- **Toxoplasmosis**. Area of retinal scar as confirmed by fundus photography.

While early detection of retinal diseases within the central 30° radius of vision is critical to preserving macular function, a test that only screens within this area will not be useful for the majority of the peripheral retina. Practical considerations limit the amount of retina that can be screened by flat-panel technology. As one attempts to present the entoptic stimulus to more peripheral areas of the retina using a computer monitor, several problems arise. One potential solution is simply moving the patient closer to the screen. However, patients quickly reach their accommodative limit (particularly in geriatric populations who need to be frequently screened), showing that this technique has limited usefulness. Another option is having patients view a very large display (eg, a video display projected on a wall or a very large-screen television). This suffers from several problems including (1) loss of contrast and lack of lighting control, which is critical in entoptic perimetry; (2) the requirement for a large amount of space to present and store the equipment; and most important, (3) a distortion of the stimulus as one gets close to the large screen (but outside the accommodative limit) while attempting to view the image in the peripheral retina.

We have overcome the limitations of flat-screen technology presentation of entoptic perimetry by using a virtual reality device in the form of the Microvision Virtual Retinal Display™ system (VRD) (Microvision Inc, Seattle, Wash). There are several advantages to this technology over monitors. Images are projected directly into the eye, presented at virtual infinity, and can be imaged over the peripheral retina. This compensates for all but the most severe refractive errors, and also eliminates peripheral image distortion and the quality of the image allows for extremely high contrast. The scanning laser equipment is portable, easily fitting within a brief-
case, allowing mobility within a clinical setting. A narrow exit pupil in our device ensured that patients were fixated centrally, greatly reducing error rates due to inappropriate fixation.

In this study, we evaluate wide field scanning laser entoptic perimetry in assessing retinal damage from various pathological conditions, resulting in dense retinal scotomata within the central 120° diameter of the visual field.

**RESULTS**

Fifty-eight patients (41 men and 17 women) underwent funduscopic examination and scanning laser entoptic perimetry testing for a total of 110 eyes. Table 1 provides a breakdown of the numbers of patients and eyes in order of the frequency of diagnosis.

Table 2 summarizes the mean ±SD sensitivity and specificity stratified by retinal location along with both the positive and negative predictive values stratified by retinal location. Overall, we found that scanning laser entoptic perimetry had sensitivities ranging from 87% to 93% and specificities ranging from 91% to 100%, while positive predictive values ranged from 80% to 100% and negative predictive values ranged from 89% to 97%. In particular, we found that scanning laser entoptic perimetry has a sensitivity of 93% ± 6%, a specificity of 100% ± 0%, a positive predictive value of 100% ± 0%, and a negative predictive value of 89% ± 7% for detecting retinal lesions within the entire 120° visual field tested. Within the perimacular area (central 10° radius of vision), where patients are usually symptomatic, we find that scanning laser entoptic perimetry had a sensitivity of 93% ± 9%, a specificity of 91% ± 6%, a positive predictive value of 80% ± 13%, and a negative predictive value of 97% ± 5%. For areas where patients generally remain asymptomatic to retinal lesions (ie, from 10° to 60° radius from the fovea), scanning laser entoptic perimetry had a sensitivity of 92% ± 8%, a specificity of 95% ± 5%, a positive predictive value of 94% ± 7%, and a negative predictive value of 94% ± 7%.

**STIMULUS SIZE AND VISUAL ACUITY**

As previously reported, the optimal sensitivity for patients with visual acuities of 20/40 or better was obtained by using a high-frequency stimulus. However, we found that patients who have poor central visual acuity (eg, ≤20/100) often cannot perceive the fine stimulus. In this study, there were 8 eyes that required a larger stimulus size to perceive the entoptic stimulus. For each of these cases, the patients had a poor central visual acuity. We performed sensitivity and specificity analyses using the minimum pixel size that the patients could perceive.

**CASE REPORTS**

The study cohort included 1 control patient with Behcet disease but no retinal damage. Despite the opacification of the optic media, this patient was able to view the entoptic stimulus and reported no visual disturbances to the entoptic field.

The study cohort also included a patient with a new retinal detachment (3 days). The detachment involved nearly the entire hemifield from the far periphery nearly up to the fovea. Upon viewing the stimulus, the patient clearly saw entoptic visual field disturbance extending into the far periphery. The following day, the detachment was successfully repaired surgically. The patient underwent a vitrectomy without scleral buckle, had a long-acting gas injection and laser application anterior to the equator to the retinal breaks. No procedures that would

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**Table 1. Frequency Distribution and Diagnostic Description of Study Eyes**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients With Diagnosis (n = 58)</th>
<th>No. of Eyes With Diagnosis (n = 80)</th>
<th>No. of Companion Eyes Normal (n = 30)</th>
<th>No. of Companion Eyes Not Tested (n = 6)</th>
<th>Sensitivity Central 120°</th>
<th>Specificity Central 120°</th>
<th>Mean No. of Lesions in Eyes With Diagnosis</th>
<th>Mean No. of Entoptic Disturbances</th>
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</thead>
<tbody>
<tr>
<td>CMV retinitis</td>
<td>19</td>
<td>29</td>
<td>8</td>
<td>1</td>
<td>0.96</td>
<td>1.00</td>
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<tr>
<td>Age-related macular degeneration</td>
<td>9</td>
<td>14</td>
<td>3</td>
<td>1</td>
<td>0.86</td>
<td>1.00</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Retinal detachment or tear</td>
<td>11</td>
<td>13</td>
<td>7</td>
<td>2</td>
<td>1.00</td>
<td>1.00</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Diabetic retinopathy†</td>
<td>4</td>
<td>7 (1 with RD)</td>
<td>0</td>
<td>1</td>
<td>0.71</td>
<td>…</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>Macular hole</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Branch retinal vein occlusion</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>1.00</td>
<td>…</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Ocular melanoma</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>1.00</td>
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<td>1.0</td>
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<tr>
<td>AMPPE</td>
<td>1</td>
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<td>1.00</td>
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<td>1.0</td>
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<tr>
<td>Viritis</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Drusen alone</td>
<td>2</td>
<td>2</td>
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<td>1.00</td>
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<tr>
<td>Non-HIV–related toxoplasmosis</td>
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<td>1.00</td>
<td>1.00</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* CMV indicates cytomegalovirus; AMPPE, acute posterior multifocal placoid pigment epitheliopathy; HIV, human immunodeficiency virus; RD, retinal detachment; and ellipses, measures cannot be calculated.
† As determined by areas of nonperfusion.
have caused retinal destruction occurred within the visual field. We tested the patient 1 day postoperatively (2 days after the initial testing session) and despite the high refractive error introduced by the surgical procedure (due to the gas), the patient was able to view the entoptic stimulus (using a pixel stimulus size of 10) and found that the entoptic disturbance had disappeared. We followed up this patient at biweekly intervals for a period of 2 months and found no further visual field disturbances, and the stimulus size required to perceive entoptic perimetry decreased with the reduction of the refractive error due to the decrease in size of the gas bubble. These follow-up visits were not included in the sensitivity and specificity analyses presented above.

SCANNING LASER ENTOPTIC PERIMETRY AS A GENERAL SCREENING DEVICE

We previously demonstrated that entoptic perimetry was effective in screening for full-depth scotomas from peripheral human immunodeficiency virus–related CMV retinitis. This study shows that scanning laser entoptic perimetry is sensitive and specific for screening for complete scotomas that are the result of retinal diseases. These results demonstrate that scanning laser entoptic perimetry is a viable possibility for a screening test to be administered by physicians, particularly primary care providers, and in underserved communities, where rapid, noninvasive screening procedures can be administered by support staff inexpensively. As entoptic perimetry screening takes less than 1 minute per eye, patients could potentially be routinely screened during annual physical checkups. This would not only allow asymptomatic patients with potentially sight-threatening diseases to be referred to ophthalmologists before central vision is impacted, early detection of diseases such as ocular melanoma will allow early treatment before other organs are affected.

ANALYSIS BY LOCATION WITHIN THE RETINA

In our previous studies of CMV retinitis, we specifically did not include patients with central or optic nerve damage. One of the reasons for performing subgroup analyses within different regions based on distance from the fovea is that only the central portion of vision (within 10° radius from the fovea) is affected in patients with diseases such as macular holes, acute posterior multifocal placoid pigment epitheliopathy, and age-related macular degeneration, and these patients, usually symptomatic, are artificially increasing our sensitivity. We maintained a sensitivity and specificity over 90% in our subgroup analyses, which included only those areas where retinal damage would cause patients to generally remain asymptomatic (from 10° to 60° radius from the fovea).

This study also presents the first data using scanning laser entoptic perimetry to screen for lesions due to retinal disease outside the central 30° of vision. These results show that scanning laser entoptic perimetry is as sensitive and specific for the peripheral retina (from 30° to 60°) as we previously demonstrated for the retina out to 30°. Furthermore, this method requires no more time for screening, unlike current standard perimetric methods such as threshold perimetry.

ADVANTAGES OF THE VRD

Our previous studies demonstrated that, using a large computer monitor, we could screen the central 30° radius of vision rapidly and inexpensively. With the VRD as a hardware platform, we have now demonstrated that scanning laser entoptic perimetry can screen for retinal disease with a high sensitivity and specificity within the central 120° diameter field of vision. This is a significant improvement over previous rapid screening methods such as the Amsler grid, presenting the image over 75% more retinal area. Goldmann and Humphrey visual field perimetry can be used as screening tools for mapping of retinal scotomas out to 180° from the fovea, but requires not only a significant investment in technicians and overhead for the provider, but also requires considerable time from the patient. As a result, the standard perimetric tests currently available are not good candidates for large-scale, community-based screening programs.

Entoptic perimetry is not intended to replace the current uses of visual field perimetry, but instead can provide a valuable tool for the primary care provider in...
detecting retinal disease early. Furthermore, the VRD is portable, and with optimization, could become part of school-based or other screening programs.

The case reports we present also suggest that entoptic perimetry can be used by ophthalmologists to rapidly assess visual function in patients with opacities of the optic media that might prevent clear views of the retina, especially in patients with cataracts or vitritis. Furthermore, we were able to evaluate the success of retinal detachment repair in a patient who was tested both preoperatively and postoperatively. Despite the fact that the visual acuity was assessed as hand motion, the patient was able to see the entoptic stimulus and report that the previous visual disturbance had disappeared. The fact that we had a diabetic patient who was able to view laser burns suggests that in screening tests, patients will be able to detect very small lesions throughout the visual field. These results warrant further detailed investigation.

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Corresponding author: Daniel J. Plummer, PhD, Shiley Eye Center, Department of Ophthalmology, School of Medicine, University of California, San Diego, La Jolla, CA 92093-0946 (e-mail: dplummer@ucsd.edu).

REFERENCES


From the Archives of the ARCHIVES

A look at the past . . .

Hirschberg presented five glass-blowers, over forty years of age, who had acquired opacities of the lens. He attributes the formation of the cataract to the continued heat. The opacity appears in the posterior layers of the lens, and progresses slowly.