

## SCIENTIFIC REPORT

# Scanning laser entoptic perimetry for the detection of visual defects associated with diabetic retinopathy

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**Aim:** To determine the sensitivity and specificity of entoptic perimetry for diagnosing diabetic retinopathy at all levels of severity.

**Methods:** A prospective clinical study at the Shiley Eye Center, University of California, and San Diego. 30 patients with photographically documented diabetic retinopathy and 24 controls with a similar age distribution. Sensitivity and specificity of entoptic perimetry were computed for detecting clinically significant macular oedema within the central 120 degree radius of the fovea compared to fundus photographs.

**Results:** Entoptic perimetry can detect clinically significant diabetic retinopathy with a sensitivity of 0.88 and specificity of 1.00. Entoptic perimetry can detect the earliest stages of diabetic retinopathy with a sensitivity of 0.86.

**Conclusion:** Scanning laser entoptic perimetry is an effective tool for detecting visual function loss caused by diabetic retinopathy.

The prevalence of diabetic retinopathy varies from 17% to 98%<sup>1,2</sup> depending on duration of diabetes.<sup>3</sup> Macular oedema, ischaemia,<sup>4</sup> and the consequences of proliferative diabetic retinopathy<sup>5</sup> may cause vision loss. The optimal time for treating diabetic macular oedema is when it has reached a clinically significant state and preferably before visual acuity is significantly affected.<sup>6</sup> The detection of retinal ischaemia would help detect patients at risk for proliferative retinopathy.<sup>7</sup> We have developed a scanning laser device based on the principle of the Troxler phenomenon<sup>8–11</sup> to stimulate the central 60 degrees at the retina and used it as an entoptic perimeter to test for visual disturbances. Testing time is relatively rapid (usually less than 1 minute). We found that patients were able to detect visual field abnormalities for a variety of retinal diseases (for example, cytomegalovirus (CMV) retinitis, diabetic retinopathy, macular degeneration) as well as damage caused by glaucoma within the central 120 degrees of the visual field.<sup>12–13</sup>

During entoptic perimetry, a patient is presented with a monochromatic field of random particle motion. While looking at the central fixation spot, patients with dense scotomas (that is, caused by CMV retinitis) reported that in some areas of the visual field the random particle motion disappears and is replaced with grey. If a patient has relative scotoma he typically reports that there is some residual particle motion in the affected areas.<sup>12–14</sup> Other groups using different types of entoptic perimetry have also validated its ability to detect retinal disease and glaucoma.<sup>15–16</sup>

## PATIENTS AND METHODS

### Patients

At the University of California, San Diego, Shiley Eye Center, we recruited patients who were diagnosed with diabetic

retinopathy, in one or both eyes. We also recruited a control group of volunteers who were classified as normal in the same clinic. There was no minimum requirement for visual acuity. We received informed consent from each patient and normal controls before testing.

### Stimulus

The stimulus was delivered through a virtual retinal display (VRD) developed by Microvision, Inc (Bothell, WA, USA). The VRD delivered a monochromatic image. Each pixel could have one of two values: off (black) or on (635 nm, a deep red).<sup>12</sup> The overall effect was that the visual field was filled with random particle motion.

Our previous studies<sup>12–13</sup> proved that minimising head movement increased the sensitivity of the test.

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 dilated fundoscopic examination using an indirect ophthalmoscope and slit lamp biomicroscopy followed by fundus photography.

A digital pen allowed the user to draw virtual lines on the computer and to control the stimulus. This test was performed on both eyes unless there was a confounding variable such as no light perception in the fellow eye. Each patient was instructed to outline, as best as they could, the edge of the extent of any area of the stimulus differing qualitatively from the monochromatic particle motion.

During the testing phase one eye was patched. The patient was aligned on the VRD until he reported that he was able to see the entire screen filled with particle motion. The narrow aperture proved to be a benefit because it forced the patient to focus on the stimulus at all times. The field of view of the VRD was 60 degrees in diameter, with the patient looking at the centre of the screen. We also tested for defects by having the patient look at each corner of the screen, thus testing a field with a radius of 60 degrees. Thus by having the patient view the corners of the image, we effectively tested a 120 degree diameter visual field.

### Scoring ophthalmological findings

We determined the presence of diabetic retinopathy clinically, and by slit confirmed it by masked reading of fundus photographs and angiogram. Scoring of the photographs was performed by two ophthalmologists and reviewed by an expert in retinal disease (WRF). The ophthalmologists classified each eye into one of eight categories by grading stereoscopic colour photographs and angiograms. The following photographic categories were used: mild background retinopathy, moderate background retinopathy, pre-proliferative retinopathy, proliferative retinopathy, non-clinically

**Abbreviations:** CMV, cytomegalovirus; VRD, virtual retinal display

**Table 1** Sensitivities and specificities (SD) for eyes diagnosed with diabetic retinopathy, and normal controls stratified or grouped by severity of disease

Diagnosis	No	Sensitivity	Specificity
Background (mild)	10	0.90 (0.1)	
Background (moderate)	7	1.00 (0.0)	
Pre-proliferative (no neovascularisation)	4	0.50 (0.3)	
Proliferative retinopathy	13	0.85 (0.1)	
Non-clinically significant macular oedema	1	1.00 (0.0)	
Clinically significant macular oedema, mild	8	1.00 (0.0)	
Clinically significant macular oedema, moderate	9	0.89 (0.1)	
Special cases	4	0.75 (0.3)	
Groups 1–3	21	0.86 (0.1)	
Groups 4–8	31	0.89 (0.0)	
All groups together	52	0.88 (0.1)	1.0 (0.0)
Normal control eyes	43		1.0 (0.0)

significant macular oedema, mild or moderate clinically significant macular oedema, or special cases such as traction detachment or preretinal haemorrhage.

### Scoring perimetric findings

Each eye was classified in a masked manner as having no visual field disturbance, while any marks within the visual field were classified as a disturbance in visual function ("positive"). Each patient drew the area of disturbance as indicated by perceived missing particles or slower or disturbed motion of the particles. This method has been previously described in detail.<sup>13 14</sup>

### Statistical analysis

For each classification we computed the sensitivity, specificity, positive predictive value, and negative predictive value.

Sensitivity was measured as the ratio of total eyes scored positive by scanning laser entoptic perimetry to the number of eyes scored positive by fundus photography.

Specificity was measured as the ratio of the number of eyes scored negative by entoptic perimetry to the total number of eyes scored negative by fundus photography.

Sensitivities were calculated for each of the classifications of diabetic retinopathy, as well as the combination of those stages that comprise early diabetic retinopathy. Specificity was derived from normal control eyes.

### RESULTS

We recruited a total of 30 patients (14 female, 16 male) with diabetic retinopathy for a total of 56 eyes (age 66 (SD 14) years). Four eyes from this group were not tested owing to extensive damage resulting in the inability to perceive the stimulus, or for eyes classified as no light perception because of advanced stages of diabetic retinopathy. We recruited 24 normal controls for a total of 43 eyes (age 64 (SD 16) years). Five fellow eyes were not tested in these patients. There were no significant differences in mean age between groups.

Table 1 provides a summary of results including stratification by severity of disease. Overall, we found that scanning laser entoptic perimetry has a sensitivity of 0.88 (SD 0.1) and a specificity of 1.0 (SD 0.0). Sensitivity for early stages of the disease (mild and moderate background retinopathy and pre-proliferative stages), when patients typically remain asymptomatic, ranges from 0.50 to 1.00 with an average of 0.86 (SD 0.11). The sensitivity of entoptic perimetry remained high for later stages of the disease, averaging approximately 0.89. We had four special cases of advanced diabetic retinopathy where diagnoses crossed more than one grouping boundary. Three of the four patients reported entoptic disturbances.

### DISCUSSION

In this study, we found that the overall specificity (0.89) was high but similar to what we have previously reported. We also found that the overall sensitivity of entoptic perimetry was 88%. However, this may be an underestimation of the true sensitivity of entoptic perimetry. Our patient cohort is slightly biased towards patients with early forms of the disease. These forms have the shallowest scotomas and the lowest sensitivity.

We found that we could detect patients' mild or moderate background retinopathy with sensitivity greater than 90%. The overall sensitivity for these three groups, where patients are typically asymptomatic, was 86%. These results suggest that, given an optimised stimulus, we can detect four fifths of all early forms of diabetic retinopathy. We used a non-diabetic age matched control group because it may be difficult to determine if a diabetic without observable retinopathy (that is, a cotton wool spot) may have had previous retinopathy. Further studies could be performed on diabetics without ophthalmoscopically visible or angiographic evidence of retinopathy, but even this could not rule out previous retinal damage due to diabetes.

Previous work by our group and others has validated the concept that entoptic perimetry does localise pathology to diseased portions of the retina.<sup>12–17</sup> In diabetic retinopathy, defects are more diffuse and less easy to localise than in other disorders. In glaucoma, another disease with focal deficits, focal deficits are found with entoptic perimetry as well.<sup>13</sup> In neuro-ophthalmological disease, entoptic perimetry also correlates with known pathology.<sup>18</sup> The pathology of diabetic retinopathy is diffuse and includes leakage of protein into the retina, oedema, ischaemia, and retinal vascular dropout. These processes will affect both the inner as well as the outer retina, and in a diffuse way. For example, a nerve fibre layer infarction associated with a cotton wool spot will permanently destroy the ganglion cells in the area. In addition, the nerve fibre layer in that area is damaged, which is expected to produce a more diffuse and distal defect. For these reasons, it is unlikely that one can localise vision defects precisely to anatomical lesions.<sup>19</sup>

We did not directly determine specificity for diabetic retinopathy versus other types of retinopathy in this study. Thus, in known diabetics with or without retinopathy our statistical analysis of sensitivity and specificity applies. Indeed, we have previously shown that patients with non-exudative age related macular degeneration also have abnormalities in this test,<sup>20</sup> as do patients with infectious retinitis and retinal detachment. Thus, the test will show defects in patients with many types of retinal dysfunction and is not specific to a given disease.<sup>12–17</sup> Given the small numbers in each of the diabetic retinopathy subcategories, it

is difficult to comment on relative sensitivities among subgroups. For example, detection of pre-proliferative retinopathy was at a lower level than background; however, the number is small. Background retinopathy might include more cases of macular non-perfusion or oedema than pre-proliferative, for example. We recognise that we did test both eyes of each patient and that the eyes are not independent. However, there would be no substantial change in the sensitivity and specificity of our findings if we had randomly tested only one eye. The power of the study would have decreased however.

These results suggest that scanning laser entoptic perimetry is an effective screening test to detect retinal dysfunction in diabetic retinopathy. It is portable and would be easily implemented by primary healthcare providers with a minimum of expenditure in time. It might allow asymptomatic patients with diabetic retinopathy to be referred to ophthalmologists before central vision is severely impacted, but probably will not replace direct retinal examination or photography as a screening test. Further work to optimise stimulus characteristics may improve the sensitivity of this test and allow better characterisation of sensitivity and specificity for subtypes of diabetic retinopathy.

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