Articles

Entoptic Evaluation of Diabetic Retinopathy

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Purpose. Studies using optimized entoptic viewing of the parafoveal retinal vasculature have shown that normal subjects see their own capillaries with greater detail in the fovea than seen typically in fluorescein angiography. The authors have extended these investigations to persons with diabetes to evaluate the sensitivity, specificity, and accuracy with which they can detect and locate their own parafoveal retinal defects untrained.

Methods. A vascular entoptoscope using Maxwellian view optics creates a high-contrast entoptic view of retinal vasculature abnormalities in the parafoveal area. Using a double-masked protocol, 70 patients with diabetes and 29 control subjects described, drew, and quantified their entoptic image. These entoptic records were compared to angiograms and color photographs obtained immediately after the entoptic evaluation.

Results. Angiograms or color photographs or both showed that 61 of 70 patients with diabetes had retinal defects (e.g., microaneurysms or exudates or both) within the field of view of the Vascular Entoptoscope (8.1° or 11.6° circular field depending on the Vascular Entoptoscope used: parafoveal area subtends ≈9.7°). Of these 61 patients with diabetes, 51% (31) observed dark "spots" or "blobs" in the entoptic field corresponding to retinal defects in the angiograms or photographs or both. Seven (18%) of the 38 patients (9 patients with diabetes and 29 control subjects without defects in the entoptic field) said they saw something when angiograms or photographs or both showed nothing (false-positive). Thus, the sensitivity and specificity (using angiograms or photographs or both as the gold standard) with which untrained patients with diabetes detect their own parafoveal area defects are 51% and 82%, respectively. Superimposition of the entoptic image (as drawn by the patient) and the angiograms or color photography or both often showed excellent correspondence. Most (22 of 29) of the control subjects and more than half (40 of 70) the patients with diabetes were able to quantify the size of their foveal avascular zone (FAZ) from the entoptic view, whereas only 22 of 70 of the capillary loops defining the FAZ were visible in the optimal frame of the capillary phase of the fluorescein angiogram. As reported previously in a smaller sample, large FAZs often were associated with poor visual acuity.

Conclusions. More than half the untrained patients with diabetes were able to visualize their own parafoveal retinopathy entoptically, and most untrained patients with diabetes and control subjects where able to quantify the size of their FAZ. Patients and control subjects without parafoveal defects rarely report defects not visible photographically. Patients can be trained to detect their defects. Clinical entoptic monitoring will require verification that patients can detect changes in their retinopathy. Entoptic testing is low cost, noninvasive, and can be performed as often as needed at no risk to the patient. It is, therefore, a promising research technique for subjective monitoring of the early natural history of parafoveal area disease processes. Invest Ophthalmol Vis Sci. 1997;38:783–791.

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Each year, diabetes causes 65,000 new cases of proliferative eye disease and 8000 new cases of blindness, making diabetic retinopathy the major cause of blindness in the working age population.[1–3] It is estimated that there are 500,000 cases of macular edema with 75,000 new cases annually.[4] Studies have shown that laser treatment of diabetic retinopathy and, in particular, of clinically significant macular edema can reduce significantly the loss of vision from diabetic eye disease.[4] Because laser treatment is destructive, it is not

initiated until the disease has reached a point where vision loss is believed to be imminent. Unfortunately, diabetic retinopathy often is asymptomatic during its most treatable stages[4] and, as a consequence, sight-threatening changes in diabetic retinopathy that occur between regular eye examinations can go unnoticed. Given the recent advances in laser treatment and its demonstrated effectiveness, early detection and monitoring of eye pathology in diabetes has been identified as an area where "if the Federal Government does not pay the cost of preventing blindness (*i.e., the cost of detection and monitoring*), it will surely pay the price of the disability," which is seven times higher.[5]

Entoptic visualization of the retinal vasculature is achieved by producing a moving high-contrast shadow image (Fig. 1)[6] of the vessels in the plane of the photoreceptors. It is important that the shadows move (stabilized retinal images are not visible or disappear or both[7]), which can be achieved by moving the entry point of the light source.

Several techniques have been developed to allow entoptic visualization of the retinal vessels, but as early as the nineteenth century, Helmholtz[8] observed striking foveal vascular detail when illuminating the retina directly through the natural pupil with a small point source (the exit pupil of a microscope) moving around in the eye's pupil plane. In our research, we have capitalized on the observations by Helmholtz[8] and designed a Maxwellian-view instrument: the Vascular Entoptoscope. Details of the theory and operation of this device have been presented earlier.[9] Studies of normal subjects show that foveal capillary detail invisible with standard fundus photography and often invisible with fluorescein angiography can be seen using entoptic testing.

Clinically, entoptic visualization has been used to help evaluate the functional status of the retina behind obstructed media.[10,11] To our knowledge, other than our own studies,[12,13] only one study has used entoptic visualization of the retinal vessels to monitor an active disease state. Kluxen and Wilden[14] trained 136 insulin-dependent patients with diabetes to observe their retinal vasculature entoptically using a transscleral illumination technique. They found that in patients with one to five microaneurysms as shown by fluorescein angiography, 55% entoptically could detect their own pathology. In patients with 6 to 20 microaneurysms, the percentage increased to 77%. In patients with more than 20 microaneurysms with severe background and proliferative retinopathy, 90% reliably could detect their own pathology, and many could document the appearance of new and the disappearance of old microaneurysms over time.

Combining the observation of Kluxen and Wilden[14] with the report by Klein et al,[15,16] showing that the number of microaneurysms in the diabetic eye is correlated directly with the severity of the diabetic retinal disease, along with two experimental studies[17,18] showing that the foveal avascular zone (FAZ) enlarges as the severity of the diabetic retinopathy increases, and the fact that parafoveal hard exudates are a result of macular edema, we thought that an optimized entoptic viewing technique (as opposed to the cruder transscleral penlight technique) may be an excellent noninvasive tool for monitoring the natural history of diabetic retinopathy in the macula before visual acuity loss.

Over the past several years, we systematically have investigated the entoptic visualization of the retinal vasculature and its clinical implications.[9,12,13,19,20] We have shown that large vessels over a wide area of the

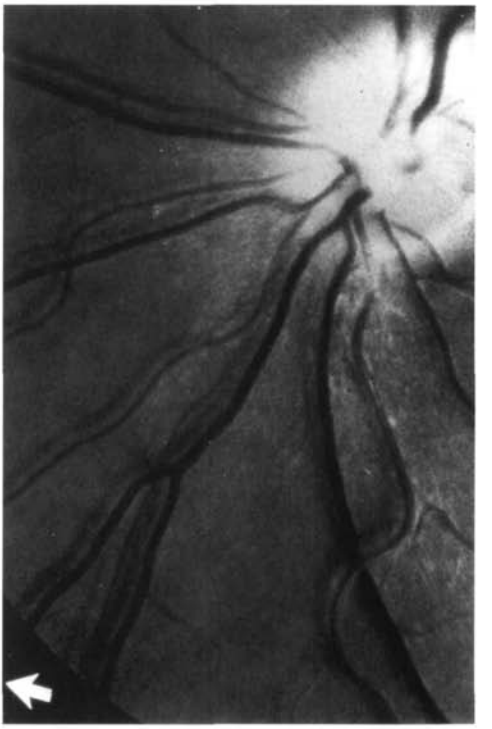

FIGURE 1. Fundus photograph using oblique illumination of the fundus. An illuminating fiber optics bundle was applied on the conjunctiva. The angle of incidence of light at the posterior pole of the eye was estimated to be 30°, and the projected direction is indicated by an arrow. The distance between the vessel and its shadow is 149 ± 10 μm (average of 16 sites). The shadow is formed on a surface located $\approx 140/\tan(30°)$ or 240 μm posterior to the vessels. (Reprinted with permission of the publisher, The Optical Society of America, and the first author, Francios Delori. *Applied Optics.* 1989;28:1069.[6])

retina, smaller vessels in the parafoveal region, and capillaries in the fovea can be observed readily using optimized entoptic viewing procedures.[20]

In applying entoptic methods to the detection and monitoring of diabetic retinopathy, we have made the strategic decision to target the parafoveal and foveal area specifically, because the impact of diabetic retinopathy on vision is most profound when the pathologic changes affect those areas. These are also the exact areas in which entoptic viewing has its highest resolution.[9,19]

In unpublished pilot work, we showed, similar to that of Kluxen and Wilden,[14] that we could train patients with diabetes to detect their own parafoveal area microaneurysms, hard exudates, and retinal hemorrhages. Encouraged by these findings and the noninvasive nature of the test, we believed that entoptic viewing of the central retinal area could provide the clinical researcher with fundamental information concerning the early natural history and pathogenesis of parafoveal area disease and offer the potential for early detection and diagnosis, a firm foundation on which to base a rationale for new preventative therapy, and a sensitive means of evaluating therapy and treatment designed to alter the natural course of the disease.[9]

Here we report results of an ongoing NIH- and NEI-supported study designed to evaluate the sensitivity and specificity with which untrained diabetics can use the optimized entoptic viewing technique to detect, describe, and quantify their own parafoveal pathology.

METHODS

Subjects

Seventy patients with diabetes ranging in age from 18 to 70 years and 29 age-matched normal control subjects visiting the Ophthalmology Clinic of the University Health Center, San Antonio, were asked to serve as subjects. Age-matched control subjects were recruited from patients with fundus photography of abnormal optic papillae or choroidal nevi and had no observable parafoveal pathology clinically or photographically. Although no subjects were excluded or selected based on race, the majority (78) were Hispanic, which reflects closely the racial makeup of our clinic.

Classification of disease severity was determined by the Wisconsin Fundus Photographic Reading Center using the Modified Airlie House Classification of Diabetic Retinopathy as adapted for the Early Treatment of Diabetic Retinopathy Study.[21,22] The distribution of disease severity as classified by the reading center is displayed in Figure 2.

Entoptic Instrumentation

A Vascular Entoptoscope identical in principle to that described by Applegate et al[9] modified for the clinical

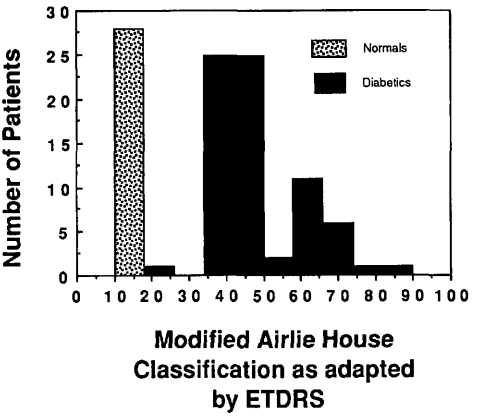

FIGURE 2. Frequency distribution of patients as a function of the Modified Airlie House Classification as adapted by the Early Treatment of Diabetic Retinopathy Study.

environment[13] was used to collect the entoptic data. The Vascular Entoptoscope uses Maxwellian-view optics to image a small (1-mm diameter) short-wavelength (blue peak wavelength λ = 430 nm) point source in the subject's pupil plane, where it travels in a circular path (diameter, 4 mm) at 3 to 5 Hz and images an 8.1° or 11.6° (depending on the particular instrument) diameter blue field onto retina. To measure FAZ size, the circular field size is adjustable (Fig. 3) down to ≈0.3° using either an electronically controlled aperture or a manual control knob (depending on clinical instrument used). A small dim fixation light was located in the field center to aid in subject fixation and locating parafoveal defects with respect to the retinal locus of fixation.

Experimental Procedures

Tenets of the Declaration of Helsinki were followed, Institutional Review Board approval was obtained, and signed informed consent was obtained from each patient. Subjects viewed a video showing how the device worked and what they were going to be asked to do. Neither the subject nor the research assistant testing knew if the patient in fact had foveal or parafoveal area defects. Therefore, unlike previous work, patients were not trained to see their own defects using feedback from angiograms or color photography.

After viewing the video, patients observed their foveal and parafoveal area entoptically using the Vascular Entoptoscope and drew their FAZ and any irregularities in the vessel pattern, such as spots and blobs.

If spots or blobs were seen, the size of each defect was recorded using an eight-level scale provided on the patient drawing sheet, and the location of the defect was drawn within the field of view with respect

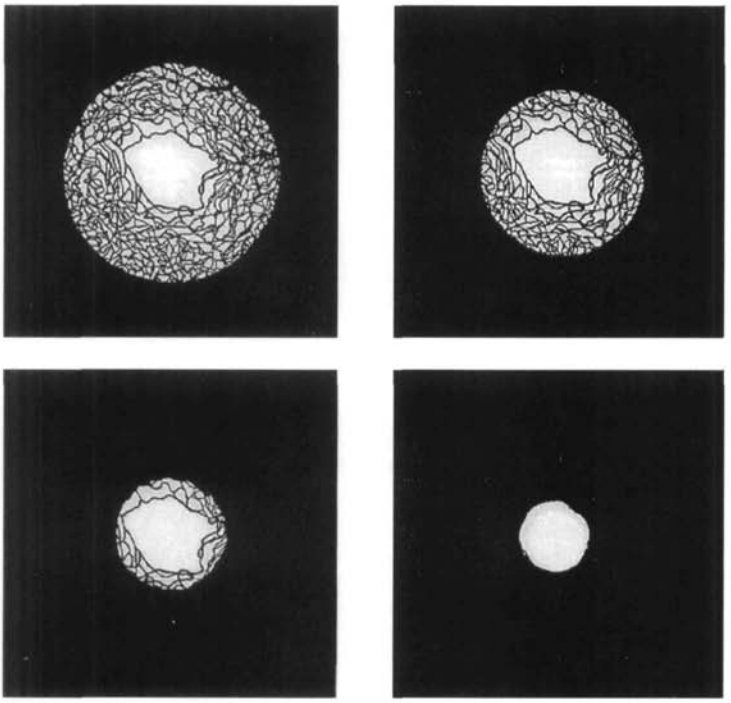

FIGURE 3. A high-contrast drawing made from an histologic preparation illustrating a normal foveal avascular zone (FAZ) and the instrument aperture stop as it appeared to our subjects. The detailed vascular pattern is similar to that observed by subjects. The FAZ diameter was measured by having each subject decrease the size of the field stop until it matches the FAZ border. The subject's view during this procedure is shown schematically in this series of pictures as the field stop is decreased in size. (Reprinted with permission of the publisher, Butterworth – Heinemann, and the first author, Arthur Bradley. *Ophthalmic Physiol Opt.* 1992;12:20.[20])

to fixation point. For example, data from the patient whose fluorescein angiogram (FA) is displayed in Figure 4A saw four spots. Two of the spots were scaled as size 1, and two of the spots as size 2 (Fig. 5). In comparing the drawing (Fig. 5) to the FA in Figure 4A, remember the entoptic field of view is inverted along the horizontal meridian through fixation with respect to the FA.

After drawing any visible defects, patients were asked to decrease the field stop diameter until the edge of the stop defined the edge of the FAZ (Fig. 3). The angle the field stop subtended at the eye's entrance pupil (x) served as the quantitative measure of FAZ diameter and could be converted easily to micrometers in the plane of the retina by assuming that the eye's posterior nodal distance was 16,670 μm ($FAZ = tan(x) \cdot 16{,}670$).

Immediately after entoptic testing, routine color fundus photography and fluorescein angiography were obtained for comparison with the entoptic data. FAs were performed only on the patients with diabetes.

Photographic Imaging of the Fundus

A Zeiss FF-3 30° fundus camera (Zeiss Strasse 73446; Carl Zeiss, Oberkochen, Germany) was used to obtain color fundus photographs and perform the fluorescein angiography. Care was taken by the retinal photographer to obtain the best photodocumentation of the parafovea during the capillary phase of the FA to optimize the visibility of the capillaries defining the FAZ.

Image Processing

Fundus images (color and FA) were digitized and stored on photograph computer disks, and the entoptic drawings were scanned and digitized using an Apple scanner and a Macintosh computer (Apple, Cupertino, CA). The digitized entoptic images then were traced using a standard object-based graphic package (MacDraw; Claris, Santa Clara, CA) to create high-contrast images with transparent backgrounds, which then were superimposed onto the fundus images for comparison.

To compare the photographic and angiographic images with the entoptic drawings, traced entoptic drawings were superimposed onto the photographic images. Before super-position, the entoptic images had to be top–bottom inverted to convert the personal view to the same coordinates as that of the clinical view. Scaling was achieved by following a standard rule for each instrument. For example, the circular

field limit to the entoptic image (for 8.1° instrument) was scaled to equal 52% of the distance from the foveola to disk center (15.5°) and centered on the presumed foveal center.

RESULTS

Of the 70 patients with diabetes whose eyes we tested, 61 (87%) had angiographically or photographically visible pathology or both within the central 8.1° or 10.1° (depending on the instrument used) field. Of these 61 patients with diabetes, 31 (50.8%) report seeing either spots, blobs, or other abnormalities in the entoptic image. That is, the entoptic method was successful in detecting 51% of the patients with pathology within the field of view. Thirty-eight patients (9 patients with diabetes and 29 control subjects) had no defects within the entoptic field of view. Of these 38 patients, 7 reported seeing parafoveal area defects not visible with photographic documentation, or an 18% false-positive rate. We can calculate from Table 1 that the entoptic method, when used by untrained patients, has a sensitivity of 51% and a specificity of 82%.

Simply because untrained patients can detect their retinal pathology 51% of the time does not indicate necessarily that the entoptic method provides an accurate image of the pathology. To evaluate the accuracy with which patients with diabetes can locate retinal defects, we used a super-position approach. That is, we scale and superimpose the patients' entoptic drawings onto digital images of their FAs or field 2

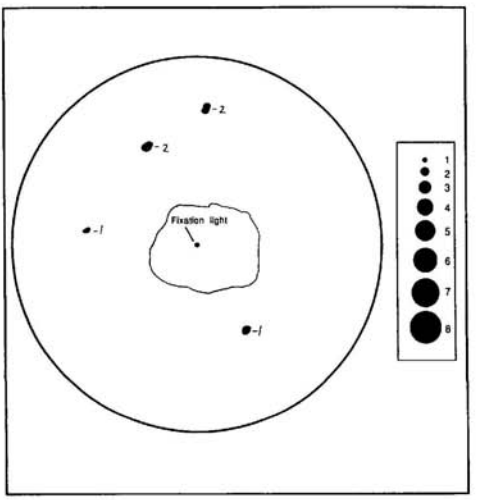

FIGURE 5. Entoptic drawing of a patient with diabetes whose fluorescein angiogram (FA) is displayed in Figure 4A. The patient saw entoptic images of four prereceptor retinal defects within the field of view. The locations of the defect with respect to fixation and the edge of the field were drawn on a sheet of paper and the size of the defect labeled using an eight-level scale. In this case, the patient labeled the defects as size 1 or size 2. The entoptic drawing is inverted along the horizontal meridian through fixation with respect to the FA (Fig. 4A).

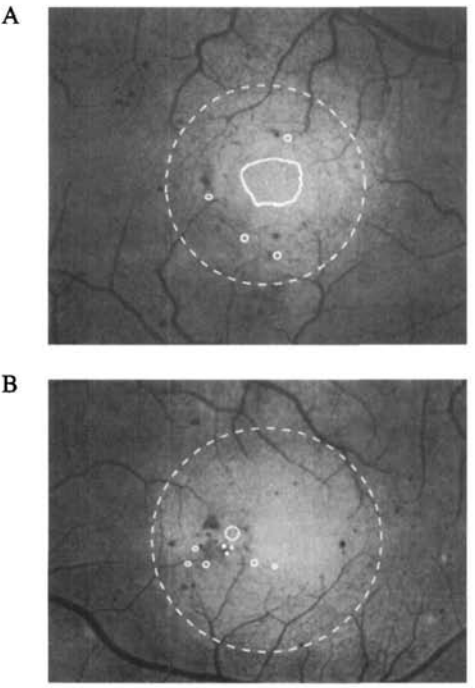

FIGURE 4. Examples from two different patients (**A, B**) showing the super-position of the entoptic image (*white lines and circles*) onto a negative view of the capillary phase of the macular fluorescein angiogram. The dashed circles indicate the entoptic field of view. The small circles are entoptically visible dark "spots" or "blobs." The large irregular shape in the center of Figure 4A is the patient's drawing of the capillary arcade forming the foveal avascular zone.

TABLE 1. Entoptoscopic Reports

	Detect Disease	*Fail to Detect Disease*
Patients with diabetes with photographically visible disease in the entoptic field	31	30
Controls and patients with diabetes with no photographically visible disease in the entoptic field	7	31

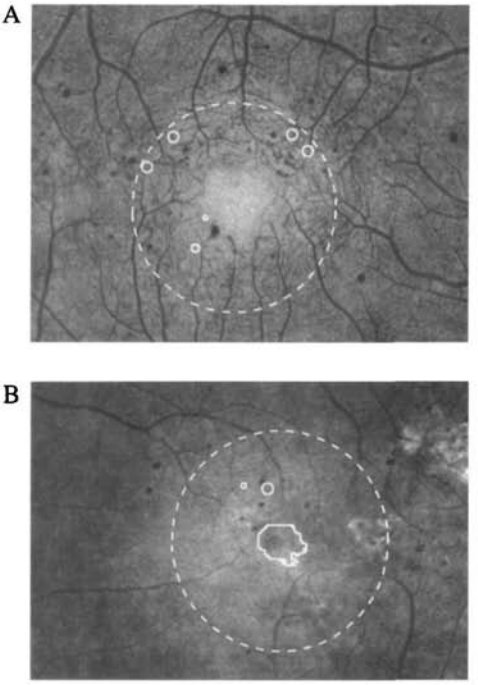

FIGURE 6. Examples from two additional patients showing the super-position of entoptic and angiographic images of the central retina.

of their color photographs or both. Examples of this procedure can be seen in Figures 4, 6, and 7 from subjects where both entoptic data and FAs were of good quality.

Figure 4 shows examples from two different patients (Figs 4A, 4B) in whom the macular region of the angiogram is shown as a photographic negative. We have chosen to use the negative because this is the view seen entoptically by patients where vessel shadows and opaque pathology appear dark on an otherwise light (blue) field. Superimposed onto the angiograms in white are the entoptic drawings made by the patients, which include numerous spot opacities drawn as small circles. The dashed white circle describes the entoptoscope field of view, and the large irregular shape in the center (Fig. 4A) is the FAZ traced by the patient.

Figure 4A shows the angiogram from a diabetic right eye (scored 43 by the reading center) with several obvious microaneurysms (MAs) surrounding the foveal center. Three MAs, one directly superior, one inferior, and one directly temporal to the foveal center, can be seen easily. There are several other more peripheral MAs inferior and temporal to the foveal center and more outside of the entoptic field of view. The entoptic drawing made by this patient shows a central avascular zone (irregular shape in the circle center) and four visible spots: one superior, one inferior, one temporal, and one inferior-temporal. The locations of the drawn MAs do not correspond perfectly with those of the angiographic image, but they are close. This patient has seen as much pathology in the parafovea as the clinician might see.

Figure 4B shows an FA from the left eye of a different patient with numerous aneurysms just nasal and directly inferior to the foveal center. Entoptically, this is close to what the patient reports and draws. This patient drew a large blob with eight smaller dots distributed in a horizontal band. When superimposed, the spatial correspondence between the entoptic drawing and the angiogram is quite good.

Figures 6A and 6B show two more examples in which retinopathy can be seen clearly in the angiogram, and the patient in each case is able to report seeing opacities with similar spatial distributions. Figure 6A shows an FA with a large MA just inferior and temporal to the foveal center, and the patient draws two spots close to this location. The FA also shows two clusters of small aneurysms superonasal and superotemporal to the fovea. The patient has drawn a pair of spots in both locations. The left eye of a different patient (Fig. 6B) has retinopathy visible superior and also temporal to the foveal center, but the patient only draws pathology superior near where there are two easily visible microaneurysms.

During the pilot study for this project, we tested several subjects who were selected specifically because we knew that they had foveal retinopathy. Although not included in any of the data analysis described in this report, we have included a super-position image from one of these patients (Fig. 7) because it shows a

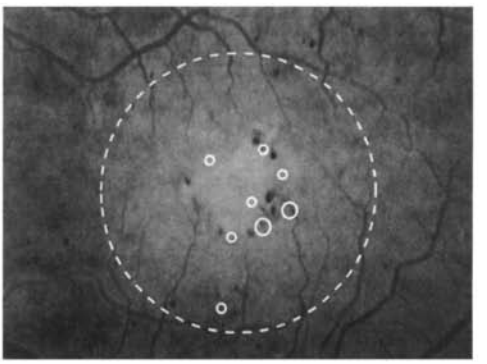

FIGURE 7. Super-position of entoptic (white) and angiographic images from the left eye of a patient with diabetes (trained to see his or her own defects using the fluorescein angiogram) with numerous microaneurysms in the fovea and parafovea.

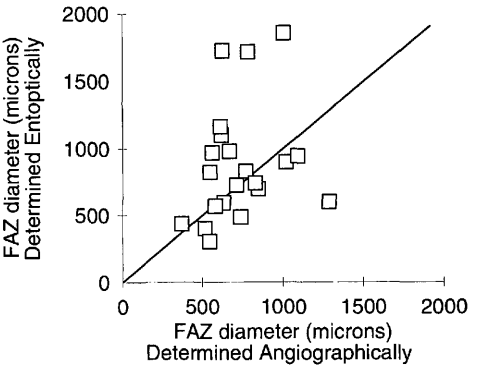

FIGURE 8. Scattergram of foveal avascular zone diameter obtained with entoptic (x) and angiographic (y) methods (diagonal line is the $y = x$ line).

patient can be trained to see the foveal pathology. The left eye of this patient has a clear arc of MAs just temporal to the central fovea, an obvious MA just nasal to the foveal center, and several MAs near to the inferior edge of the entoptic field. Entoptically, this patient draws an arc of spots just nasal to the fixation point and a visible spot just temporal and near to the inferior edge of the entoptic field. When superimposed, the angiographic and entoptic images show a clear similarity, indicating that this patient had an entoptic view of the pathology similar to that available to the clinician.

Size of Foveal Avascular Zone

It has been reported that in persons with diabetes, FAZ size increases and can become irregular in shape.[17,18] Because the capillary arcade forming the FAZ is one of the most striking characteristics of the entoptic foveal image in normal persons[9,13,19,20] and can be seen entoptically by most normal persons, we were motivated to see if patients with diabetes, were able to report their FAZ size correctly. To compare the entoptic estimates of FAZ diameter with the angiographic estimates, a quantifiable FAZ is required in both the angiographic and entoptic images. Forty of the patients with diabetes were able to measure reliably their FAZ entoptically. Of these 40, 22 had FAs with sufficient foveal capillary detail to quantify FAZ size. To examine the relation between the entoptically determined and the angiographically determined FAZ size, we have plotted the two measures of FAZ diameter in Figure 8.

As shown in Figure 8, most of the 22 subjects report seeing an FAZ that is similar in size to that observed angiographically. Using entoptic visualization, three subjects report an FAZ diameter considerably larger than that seen angiographically, and one subject reports an FAZ much smaller than seen angiographically.

In an earlier sample of patients with diabetes,[12] we reported a decrease in high-contrast visual acuity as entoptically measured FAZ diameter increases. We examined the relation again here now that the sample size has increased by more than a factor of 5. Although there is considerable scatter (Fig. 9), those subjects with enlarged FAZs tend to have worse acuity ($P < 0.001$, $r = 0.53$).

DISCUSSION

Optimized entoptic viewing of the parafoveal retinal pathology and vasculature can be performed by untrained patients with diabetes. It is noninvasive and can be implemented as often as needed.

Previous experience with the Vascular Entoptoscope has shown that foveal capillary detail, especially the capillary arcade forming the FAZ, is visible to virtually 100% of normal persons. One demonstration of the ease with which persons can see foveal area capillary detail came at the annual meeting of the Optical Society of America in 1990, where we estimate that 400 attendees used the Vascular Entoptoscope and all but one (an older man with small pupils) were able to see their foveal area retinal vasculature and FAZ. This qualitative finding is consistent with our experimental findings on normal persons.[9,19,20] Further, we have shown that the smallest capillary detail was visible entoptically in the fovea and parafovea by taking FAs repeatedly on ourselves until we were able to get angiographic images of sufficient quality to see the inner capillary loops of the FAZ.

Given the success with educated normal per-

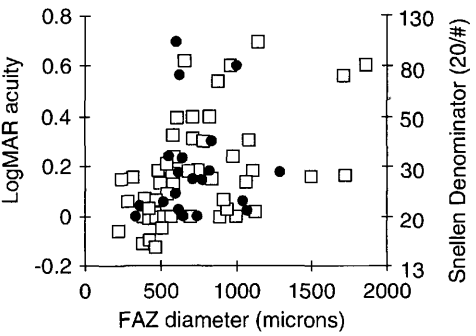

FIGURE 9. Best-corrected high-contrast visual acuity expressed as the log of the minimum angle of resolution as a function of foveal avascular zone diameter determined using entoptic techniques (*squares*) and fluorescein angiogram (*circles*).

sons, the failure of 49% of the patients with diabetes to detect their own parafoveal pathology entoptically was puzzling at first. There are at least three possible reasons for the failure of these patients with diabetes to see their own foveal or parafoveal pathology. First, they may fail to see their pathology because of reduced visual function caused by retinopathy. However, this is unlikely because most of our patients had good acuity (20/30), with a mean log of the minimum angle of resolution of 0.18. Second, it is likely that the difficulty of the task (i.e., seeing, locating, and drawing complex retinal features that cannot be fixated) may have been a contributor to these failures. Third, it is possible that more complex psychological reasons interfered with patient performance. For example, the low level of education and motivation of our clinic population (for this patient group, the average years of education is 10.6 and has a "no-show" rate for appointments of 50%).

We expect to find a higher sensitivity when testing patients who are better educated (the average years of education for the Optical Society American meeting demonstration probably was 20 or more years) and more motivated. Pilot work in our private-paying Consultants Clinic supports this belief, as does an analysis of our data set by level of education. That is, when we compared the retinopathy rating (from the reading center) of those who saw spots on the entoptoscope and those who did not, we found the following:

1. In all patients who saw spots (no selection for education level), there was a mean difference from those who did not see spots of 2.69 (P = 0.5).
2. For high school graduates who saw spots, there was a mean difference from those high school graduates who did not see spots of 9.84 (P = 0.08).

These results support our clinical impression by showing that patients with high school educations were more likely to see their retinal defects than were less-educated patients.

We are particularly encouraged by the fact that even in this difficult patient population, capillary detail of the FAZ was quantifiable entoptically in 40 of 70 patients compared to 22 of 70 from the optimal frame of the capillary phase of the FA. That is, the number of entoptically visible FAZs was 1.8 times the number of FAZs visible in the FAs. This finding is not new. Bird and Weale,[23] our group,[9,19,20] and others[24] have noted that even very good FAs miss a lot of capillary detail.

Of the 22 eyes in which we were able to quantify the FAZ both entoptically and with FA, most report an FAZ seen entoptically that matches approximately that seen angiographically (Fig. 8). Three patients reported larger FAZs entoptically and one smaller. Although we do not know the exact reasons for these errors, we suspect three possible causes. First, as Weinhaus et al[24] have shown, even on excellent angiograms, many capillaries are not visible. Compound this with the fact that typical angiograms on diabetics, where the media may not be ideal, foveal capillaries may or may not be visible and, if they are, what one believes to be the capillary loop defining the FAZ may or may not actually be the defining loop. Second, given that many of our patients with diabetes were unable to report seeing highly visible pathology in the fovea, it is not surprising that some would not see some of the inner-most capillary loops forming the FAZ. Therefore, we might expect overestimates of the FAZ size in some of our patients with diabetes. Third, because naive subjects generally try to fixate the retinal details to which they are attending, the FAZ will always tend to appear larger because its edge will move away from the entoptic field center every time the patient tries to fixate the FAZ edge.

The fact that many patients (see five examples in Figs. 4, 6, and 7) can detect and locate and judge accurately the size of foveal and parafoveal MAs is encouraging. In fact, a sensitivity result of 51% and a specificity result of 82% are similar to other clinical test results that have had years of development and refinement. For example, in 182 eyes, it was found that the Henson perimeter had a sensitivity of 59.4% and a specificity of 88%, the Humphery perimeter a sensitivity of 64.2% and a specificity of 64.2%, and the Perikon perimeter a sensitivity of 55% and a specificity of 90.4% for screening for glaucomatous field defects.[25] Similarly, it has been found that applanation tonometry alone has a sensitivity of 47.1% and a specificity of 92.4% for screening for glaucoma.[26]

Our findings confirm our theoretical expectations that MAs, exudates, and other opacities that are larger than are the capillaries should be visible in the parafoveal area. Combine this with a high specificity of 82% and we reasonably can be assured that untrained patients who see abnormalities entoptically in their parafovea warrant further clinical evaluation. That is, if untrained patients say they see something, then they probably do (high specificity). However, given a sensitivity of 51%, we can not be comfortable saying that further testing is not warranted if untrained patients do not see defects.

In monitoring patients with known abnormalities, sensitivity can be improved significantly by training patients to see their own parafoveal defects using feedback. Thus, entoptic testing may prove to be valuable particularly for monitoring motivated patients between routine examinations to gain a better understanding of the natural history of the disease process.

In summary, we have shown, in a double-masked

experimental paradigm, that untrained patients with diabetes can detect entoptically their own parafoveal retinal defects with a sensitivity of 51% and a specificity of 82%. Prior work,[14] as well as unpublished work in our laboratory, shows that sensitivity can be increased with feedback training. A sensitivity of 51% with a specificity of 82% is not ideal. These levels of sensitivity and specificity are encouraging given the nature of our test population and the fact that this is our first clinical attempt at using the device, and they are similar to accepted well-developed clinical tests for glaucoma screening. We also have shown that FAZ detail was seen more often entoptically (1.8 times) than was angiographically. These observations reinforce our belief that entoptic monitoring of the parafoveal area by at-risk patients can be an effective, low-cost method for documenting the natural history of diabetes before a visual acuity loss as well as for monitoring therapies designed to alter the disease course.

Key Words

diabetic retinopathy, entoptic images, fluorescein angiography, microaneurysms, visual acuity

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References

1. Cotton P. Advances in diabetic retinopathy could save sight, money with more frequent eye exams. *JAMA.* 1990;264:2608–2611.
2. Kahn HA, Moorehead HB. Statistics on blindness in the model reporting area 1969–1970. *DHEW Publ No. (NIH) 73–427.* 1973.
3. National Society to Prevent Blindness Operational Research Department. *Vision Problems in the U.S.: A Statistical Analysis.* New York: National Society to Prevent Blindness; 1980:1–46.
4. Patz A, Smith R. The ETDRS and Diabetes 2000. *Ophthalmology.* 1991;98:739–740.
5. Javitt JC, Canner JK, Sommer A. Cost effectiveness of current approaches to the control of retinopathy in Type I diabetics. *Ophthalmology.* 1989;96:255–264.
6. Delori F, Pflibsen K. Spectral reflectance of the human ocular fundus. *Applied Optics.* 1989;28:1061–1077.
7. Ditchburn R. What is psychophysically perfect image stabilization? Do perfectly stabilized images always disappear?: Comment. *J Opt Soc Am A.* 1987; 4:405–406.
8. Helmholtz H. In: Southall JPC, ed. *Treatise on Physiological Optics.* New York: Dover Publications; 1962:217–218.
9. Applegate RA, Bradley A, van Heuven WAJ. Entoptic visualization of the retinal vasculature near fixation. *Invest Ophthalmol Vis Sci.* 1990;31:2088–2098.
10. Duke-Elder S, Smith RJH. Entoptic Methods. In: Duke-Elder S, ed. *The Foundations of Ophthalmology, Heredity, Pathology, Diagnosis, and Therapeutics.* St. Louis: Mosby; 1962:454–458.
11. Murrillo-Lopez F, Maumenee A, Guyton D. Perception of Purkinje vessel shadows and foveal granular pattern as a measure of potential visual acuity. ARVO Abstracts. *Invest Ophthalmol Vis Sci.* 1993;34:1422.
12. Bradley A, Applegate R, van Heuven W, Nair P. FAZ enlargement and visual acuity in diabetic retinopathy. ARVO Abstracts. *Invest Ophthalmol Vis Sci.* 1994; 35:1395.
13. Nunez R, Applegate R, Bradley A, Hendricks J. Clinical version of the Vascular Entoptoscope. *Vis Sci Appl Tech Digest (Optical Society of America).* 1996;1:160–163.
14. Kluxen G, Wilden E. An entoptic test in diabetic patients. *Diabetes Care.* 1987;10:800–801.
15. Klein R, Meuer S, Moss S, Klein B. The relationship between microaneurysm count to the 4-year progression of diabetic retinopathy. *Arch Ophthalmol.* 1989;107:1780–1785.
16. Klein R, Meuer S, Moss S, Klein B. Retinal microaneurysm counts and 10-year progression of diabetic retinopathy. *Arch Ophthalmol.* 1995;113: 1386–1391.
17. Bresnick GH, Condit R, Syrjala S, Palta M, Groo A, Korth K. Abnormalities of the foveal avascular zone in diabetic retinopathy. *Arch Ophthalmol.* 1984;102:1286–1293.
18. Mansour M, Schachat A, Bodiford G, Haymond R. Foveal avasculature zone in diabetes mellitus. *Retina.* 1993;13:125–128.
19. Zeffren BS, Applegate RA, Bradley A, van Heuven WAJ. Retinal fixation point location in the foveal avascular zone. *Invest Ophthalmol Vis Sci.* 1990;31:2099–2105.
20. Bradley A, Applegate RA, Zeffren BS, van Heuven WAJ. Psychophysical measurement of the size and shape of the human foveal avascular zone. *Ophthalmic Physiol Opt.* 1992;12:18–23.
21. Early Treatment of Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic fundus photographs—an extension of the Modified Airlie House Classification. *Ophthalmology.* 1991;98:786–806.
22. Early Treatment of Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. *Ophthalmology.* 1991;98:823–833.
23. Bird AC, Weale RA. On the retinal vasculature of the human fovea. *Exp Eye Res.* 1974;19:409–417.
24. Weinhaus RS, Burke JM, Delori FC, Snodderly DM. Comparison of Fluorescein Angiography with microvascular anatomy of Macaque retinas. *Exp Eye Res.* 1995;61:1–16.
25. Marraffa M, Marchini R, Albertini R, Bonomi L. Comparison of different screening methods for the detection of visual field defects in early glaucoma. *Int Ophthalmol.* 1989;13:43–45.
26. Tielsch JM, Katz J, Singh K, et al. A population-based evaluation of glaucoma screening: The Baltimore eye survey. *Am J Epidemiol.* 1991;134:1102–1110.