Optic Disc and Visual Field Changes in a Prospective Longitudinal Study of Patients With Glaucoma

Comparison of Scanning Laser Tomography With Conventional Perimetry and Optic Disc Photography

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Objective: To investigate the relationship between optic disc changes measured with scanning laser tomography and those measured with conventional perimetry and optic disc photography.

Methods: In a prospective longitudinal study, we followed up 77 patients with early glaucomatous visual field damage. Scanning laser tomography (using the Heidelberg Retina Tomograph) and conventional perimetry (using the Humphrey Field Analyzer) were carried out every 6 months. Disc progression was determined by a procedure recently described by us for scanning laser tomography, with confirmed progression requiring repeatable changes based on probability limits for both the depth (using individual test-retest variability values) and size of change (determined in a group of 37 healthy individuals also followed up prospectively). Field progression was determined with the Statpac Glaucoma Change Probability Analysis. The agreement between scanning laser tomography and conventional disc photography was determined in a subgroup of patients.

Results: Patients were followed up for a median of 5.5 years, with a median of 12 sets of examinations with scanning laser tomography and conventional perimetry. Twenty-one patients (27%) showed no progression with either technique. Thirty-one patients (40%) progressed with scanning laser tomography only, while 3 (4%) progressed with conventional perimetry only. Of the 22 patients (29%) who progressed with both techniques, 10 (45%) progressed with scanning laser tomography first (median, 18 month earlier) and 9 (41%) with conventional perimetry first (median, 12 months earlier), while 3 (14%) progressed at the same time. Of the 16 patients with disc photographs that closely overlapped the follow-up, there was concordance between scanning laser tomography and disc photography in 13 patients (81%).

Conclusions: Glaucomatous disc changes determined with scanning laser tomography occur more frequently than field changes. Most patients with field changes also had disc changes; however, less than half of those with disc changes had field changes.

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Confocal scanning laser tomography was introduced approximately a decade ago primarily for quantitative imaging of the optic disc in glaucoma.¹ A topographic height map of the optic disc and peripapillary retina is produced with high spatial resolution. Advantages over conventional optic disc photography include quick image acquisition, quantitative analysis, and the ability to obtain good-quality images in most subjects without pupil dilation.² ³ Numerous studies have been carried out to assess the reproducibility of both the individual topographic height measurements and computed indices, such as cup-disc ratio and cup volume.⁴ ⁵ ⁶ The accuracy of the indices has been determined,⁸ as have studies comparing them with measurements obtained by stereo disc photography and planimetry.⁹ ¹⁰

Scanning laser tomography can identify glaucomatous and normal discs with generally a high degree of precision ¹¹ ¹² ¹³ however, the true sensitivity and specificity of the technique in a population screening with unbiased samples remains to be reported. Automatic nonsubjective detection of an abnormal disc depends on comparison of a disc index with that in a population of normal discs. Detection of a statistically significant change in the same optic disc over time requires comparison of the change in an index with the variability in its repeated measurement (test-retest variability). Since scanning laser tomography provides imaging data with high spatial resolution (about 10 µm per pixel), regional variability of the measurements can be characterized.⁵ ¹⁰ Furthermore, since
SUBJECTS AND METHODS

SUBJECTS

Data for this study were obtained from a longitudinal prospective study that began in 1991 in which a variety of psychophysical tests and scanning laser tomography are performed in a group of patients with glaucoma and healthy control subjects. Patients with glaucoma were recruited on a consecutive basis from the practice of one of us (R.P.L.) and the Glaucoma Clinic of the Eye Care Centre of the Queen Elizabeth II Health Science Centre, Halifax, Nova Scotia. Healthy control subjects were recruited from seniors’ groups, local church organizations, and employees of a local telephone company. The study was approved by the Queen Elizabeth II Health Science Centre Research Ethics Committee. All subjects gave written informed consent.

Patients were included according to the following criteria: (1) diagnosis of open-angle glaucoma with characteristic glaucomatous optic disc damage, such as notching or progressive thinning of the neuroretinal rim, typically recorded photographically; (2) visual field with a Mean Deviation index between −2 and −10 dB; (3) open angles by gonioscopy; (4) best-corrected visual acuity of 20/40 or better; and (5) 5 or more sets of good-quality examinations with scanning laser tomography. Exclusion criteria for patients were as follows: (1) concomitant ocular disease; (2) systemic disease or systemic medication known to affect the visual field; (3) refractive error exceeding 5 diopters (D) equivalent sphere or 3 D of astigmatism; and (4) contact lens wear.

Healthy control subjects were included according to the following criteria: (1) normal results of ocular examination; (2) best-corrected visual acuity of 20/40 or better; (3) intraocular pressure of 21 mm Hg or less; (4) negative family history of glaucoma; and (5) 5 or more sets of examinations with scanning laser tomography. Exclusion criteria for controls were as follows: (1) systemic disease or systemic medication known to affect the visual field; (2) refractive error exceeding 5 D equivalent sphere or 3 D of astigmatism; and (3) contact lens wear.

SCANNING LASER TOMOGRAPHY

Scanning laser tomography was performed with the Heidelberg Retina Tomograph (Heidelberg Engineering GmbH, Dossenheim, Germany). The device contains a low-intensity diode laser (wavelength, 670 nm) and a confocal imaging system. The principle of the technique has been described elsewhere. Essentially, 32 confocal sections of the imaged area, centered on the optic disc and perpendicular to the optical axis of the eye, are automatically captured from the level of the posterior vitreous to the retrolaminar optic nerve. The transverse image resolution is 256 × 256 pixels in a 10 × 10°, 15° × 15°, or 20° × 20° image frame. After alignment of the 32 section images for lateral eye movements, a 3-dimensional reconstruction of the imaged area is performed, yielding a topographic image with discrete topographic height values at the 65536 pixels.

RESULTS

There were 77 patients with glaucoma (41 men and 36 women), whose median age at baseline was 58.0 years (range, 29-87 years). The median follow-up was 5.5 years (range, 2-25 years). Each optic disc is unique, regional variability will be different for different individuals. A variability template against which changes can be gauged can be personalized for each optic disc. These theoretical considerations suggest that scanning laser tomography may be well suited to detect small changes in the optic disc.

Recently, a statistical technique was described for detecting topographic changes in the optic disc and peripapillary retina with scanning laser tomography. This technique does not require the user to outline the optic disc border (contour line) and does not rely on an arbitrary depth for the definition of disc cupping (reference plane). Computer simulation experiments showed that the technique has good sensitivity while maintaining a high level of specificity. The purpose of this study is to report data from a prospective longitudinal study of patients tested every 6 months and followed up for a median of 5.5 years with scanning laser tomography. We compare these results with those of conventional perimetry and disc photography.
was closest in time to the last optic disc photograph was cho-

was chosen as the final examination for this subset of analysis to ob-

tain follow-up times that overlapped maximally between the 2 imaging techniques.

DATA ANALYSIS

Analysis of changes in optic disc topography was per-

formed with a method described recently. Briefly, the

256 × 256-pixel array from each topographic image was di-

vided into a 64 × 64-superpixel array where each super-

pixel contained 16 (4 × 4) pixels. An analysis of variance

was conducted to analyze change in topographic heights

from one set of images (3 baseline images at 1 visit) to an-

other (3 follow-up images at 1 visit). For statistical testing

we adjusted the degrees of freedom for spatial correlation

by means of the Satterthwaite correction. The analysis

output is a probability map in which the probability that

the difference in topographic height (follow-up compared

with baseline) within a given superpixel occurs by chance

alone is shown on a gray scale. Therefore, a probability

map was simplified to show magenta superpixels when there was a reduction in top-

graphic height compared with baseline with P < .05 and to show

green superpixels when there was an elevation in top-

ographic height compared with baseline with P < .05. The

magenta and green superpixels were superimposed on the

reflectivity image so that the location of the changes could

be visualized easily.

We considered confirmed change in the topographic

height within a given superpixel to be present if the sig-

nificance value associated with it was always .05 or less in

3 consecutive sets of follow-up images. We devised a com-

puter program to provide this display. By computing the

incidence of confirmed change in healthy control subjects

in terms of the size of superpixels in a cluster, we were able

to devise probability limits (P < .05) for the patients with

glaucoma. The P < .05 cutoff value was a cluster of 20 su-

perpixels, ie, less than 5% of healthy control subjects had

a cluster of 20 or more significant superpixels in 3 con-

secutive images. There was no relationship between age and

the average or largest cluster of significant superpixels in

3 consecutive images in the healthy control subjects (P > .40). Any patient who showed a cluster of 20 or more significant superpixels where the topographic change com-

pared with baseline was outside normal limits in 3 con-

secutive sets of follow-up images was considered to have

confirmed progression. The date of confirmed progres-

sion was taken as the progression date.

We analyzed progression of the visual field by means

of the Glaucoma Change Probability Analysis described by

Heijl and colleagues. This analysis, which is available in

the Statpac program of the Humphrey Field Analyzer, es-

establishes a mean baseline visual field from 2 examinations.

Any location at which the difference in threshold de-

viation between a given follow-up examination and baseline

falls outside the 95th or 5th percentile for test-retest vari-

ability in patients with stable glaucoma is indicated as a white

triangle (probable “improvement”) or black triangle (prob-

able “deterioration”), respectively. Our criterion for pro-

gression was identical to one used in a recent study in

which first all the edge points were removed from the pro-

gram 30-2 pattern, leaving 50 locations in total. Con-

firmed progression occurred when there was complete over-

lap in the location of 4 or more black triangles in 2 of 3

consecutive follow-up visual fields. The date of confirmed

progression was taken as the progression date.

Since scanning laser tomography was introduced to the

study at a later date than conventional perimetry, we recal-
culated the baselines for the latter such that the first of the 2

baseline examinations exactly matched the date of the base-

line scanning laser tomography examination. Therefore, the

earliest confirmed progression with either technique could

occur after 18 months of follow-up. We compared the fre-

quency of progression with both scanning laser tomography

and conventional perimetry and the time to progression in

patients who progressed with both techniques.

To study the potential confounding effects of intra-

ocular pressure changes on optic disc topography, we con-
ducted a comparative analysis of several intraocular pres-

sure variables during the follow-up in patients who showed

progression with scanning laser tomography compared with

those who remained stable.

Two of us (M.T.N. and R.P.L.) independently evalu-

ated the disc photographs for each of the patients in whom
disc photographs that closely overlapped the follow-up with

scanning laser tomography were available. The investiga-
tors were masked to patient identity and had to indicate if

and where progression had occurred (superonasal, supero-
temporal, inferonasal, inferotemporal, or temporal). In cases of

disagreement, a consensus decision was made. These re-

sults were then compared with those obtained by scan-

ning laser tomography.

We used parametric statistical tests when respective
distributions were Gaussian and when there was homoge-

neity in group variances. When these conditions were not

met, equivalent nonparametric tests were used. All statisti-
cal tests were 2-tailed, and statistical significance was as-

sumed when P < .05.

years (range, 3-6 years), with a median of 12 sets of

examinations (range, 7-13) with scanning laser tomog-

raphy and 12 (range, 7-13) corresponding examinations

with conventional perimetry. The subset of 37 control

subjects who had scanning laser tomography performed

in addition to conventional perimetry included 18 men

and 19 women. Data from these subjects were used to

drive the 95th percentile for significant superpixel

cluster size in 3 consecutive examinations. Their median

age was 51.0 years (range, 31-72). The median follow-

up with scanning laser tomography was 2.8 years

(range, 2-6.5 years), with a median of 6 sets of examina-

tions (range, 5-14) with scanning laser tomography. The

visual field in all of these subjects remained nor-

mal as judged by the Glaucoma Hemifield Test and

with the use of the normal limits for Mean Deviation

and Corrected Pattern Standard Deviation with the

Statpac program.

Twenty-one patients with glaucoma (27%) showed

no progression with either scanning laser tomography

or conventional perimetry. Fifty-three patients (69%)

showed progression with scanning laser tomography, of

whom 22 (42%) had visual field progression; 25 (32%)

showed progression with conventional perimetry, of
whom 22 (88%) had optic disc progression. Overall concordance between the 2 techniques was attained in 43 patients (56%). A large number of patients (31 patients [40%]) showed progression with scanning laser tomography only (Figure 1), while the number of patients showing progression with conventional perimetry only was much lower (3 patients [4%]).

Of the 22 patients (29%) who showed progression with both scanning laser tomography and conventional perimetry, 10 (45%) showed progression first with scanning laser tomography, 9 (41%) showed progression first with conventional perimetry, and 3 (14%) showed progression at the same time (Figure 2). Of patients showing progression with scanning laser tomography first, the median delay in progression with conventional perimetry was 18 months, while of those showing progression with conventional perimetry first, the median delay in progression with scanning laser tomography was 12 months. The median 6-month difference in the ability of scanning laser tomography to detect progression earlier in those who had progression with both techniques was not large enough to reach statistical significance (P = .60, Mann-Whitney test).

The maximum elevation and maximum reduction in intraocular pressure from baseline during follow-up in patients classified as stable or progressing with scanning laser tomography were similar and not statistically significantly different (Table 1). In addition, there were no significant group differences in the mean, maximum, SD, or range of intraocular pressure during the follow-up.

Optic disc photographs that were close in time to the baseline scanning laser tomography examination were available in 16 patients. The mean (±SD) time difference between these 2 dates was 7.25 (±1.18) months, while the corresponding value between the last disc photograph and closest scanning laser tomography was 1.31 (±0.34) months. There was independent agreement (stable or progression) in 9 patients (56%), while a consensus agreement was necessary in the remaining patients. Concordance between the consensus agreement and analysis with scanning laser tomography was obtained in 13 patients (81%) (Table 2). One patient (6%) showed disc progression with photography only. In this case, change in the topographic height values in the region where change was seen graphically was not statistically significant given the relatively high regional test-retest variability. Two patients (13%) showed progression with scanning laser tomography only. In both cases, the change occurred within the cup, which was not in the focal plane of the photograph; hence, while the neuroretinal rim and peripapillary retina were in focus, the location of the changes was out of focus.

The following is a representative case report. A 55-year-old woman with open-angle glaucoma had progressive optic disc cupping documented photographically before enrollment in the study. The baseline optic disc
photograph showed a thin inferior neuroretinal rim (Figure 3, A). The baseline visual fields (Figure 4) showed a corresponding dense superior arcuate scotoma, while the inferior hemifield was normal. The final optic disc photograph (Figure 3, B) showed a narrowing of the superior temporal rim, with independent consensus reached by the 2 observers. The probability maps with scanning laser tomography during the same time frame detected the changes seen in the photographs in addition to demonstrating progressive confirmed changes in almost the whole temporal rim (Figure 4) that are not apparent in the disc photographs. The corresponding visual fields did not show progression according to the study criteria (Figure 4). The inferior visual field remained normal.

Figure 3. A, Right optic disc photograph of a 55-year-old woman in November 1994 shows a denuded neuroretinal rim inferiorly. B, The final optic disc photograph (May 1998) shows change in the superior temporal rim (arrow).

Clinical and scientific evidence suggests that structural changes, including disc hemorrhages, nerve fiber layer loss, and optic disc morphologic changes, occur before alterations in the visual field are seen on conventional perimetry. Clinical examination of the optic disc by means of the slitlamp or ophthalmoscope, although quick, cannot be easily or accurately transcribed for use in the follow-up of patients. Optic disc photography allows the archiving of slides or prints and effective evaluation of disc progression in glaucoma; however, pupil dilation, flash photography, and waiting time make it difficult to undertake routinely at each visit. Scanning laser tomography offers a theoretically viable adjunct or alternative to disc photography for the routine follow-up of patients with glaucoma because of ease of use and immediate access to the data. The availability of quantitative and objective data is an important advantage over subjective evaluation of disc photographs. Scanning laser tomography has been shown to detect small changes in the optic disc after surgical and medical intraocular pressure reduction. Furthermore, with the analysis technique used in this study, changes in optic disc topography were detected in dogs in whom small alterations in either intraocular or cerebrospinal fluid pressure were made. It is likely that acute pressure changes around the optic disc do not reflect the type of changes seen in progressive glaucoma. The purpose of this study, therefore, was to test the hypothesis that the promising short-term results with scanning laser tomography could be repeated in a prospective study of patients with glaucoma.

Our technique for detecting changes in optic disc topography relies on defining test-retest variability in discrete parts (superpixels) of the area imaged. Changes during follow-up are always gauged on this variability and defined in probabilistic terms; hence, to attain the same probability value, change in an area that has inherently high measurement variability (such as at the edge of the cup) would be greater than that required in an area with low variability (such as the peripapillary retina). Using this approach, we can also define probability limits in a group of healthy control subjects for the size of cluster whose constituent superpixels repeatedly show changes that are outside the test-retest variability range. We acknowledge that the control group was not age matched to the patients; however, this is unlikely to significantly affect our findings, given the independence of the significant cluster size and age. Obtaining these data empirically in normal subjects is critical, since we can then determine the significance of not only the depth but also the area of topographic changes in patients. The criteria for progression in this study were such that the earliest time after baseline that changes could be confirmed in the disc and visual field was identical, ie, 18 months (1 baseline and 3 follow-up examinations with scanning laser tomography, and 2 baseline and 2 follow-up examinations with conventional perimetry, each examination being at 6-month intervals).

Our study showed that 69% of patients followed up for a median of 5.5 years showed disc changes that were outside the statistical limits of test-retest variability determined individually per patient. Furthermore, the area of change was repeatable over 3 examinations and was outside normal limits. Despite this conservative approach, the number of patients showing disc changes was remarkable. The number of patients showing field changes during this period was considerably lower (32%) and not incompatible with previous reports. In many cases, despite the extensive disc changes, there were no field changes during the follow-up. There are several possible

COMMENT

No relevant financial relationships.

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Figure 4. Scanning laser tomography and visual field examinations of the same eye shown in Figure 3 during the same period as the baseline and final optic disc photographs. A, Baseline scanning laser tomography examinations (first column) with the reflectivity (top) and topography (bottom) images obtained in May 1995. Baseline visual field examinations obtained in May and November 1995 show a superior arcuate defect (second and third columns). The Mean Deviation plot of the follow-up examinations is also shown (fourth column). B, Follow-up examinations with scanning laser tomography beginning with the first examination that confirmed progression could be determined (November 1996) and ending with the examination on the same day as the last optic disc photograph. Probability symbols are superimposed on the reflectivity images (magenta indicates significant superpixels with reduction in topographic height, and green, significant superpixels with elevation in topographic height). Progression is confirmed in November 1996. Corresponding visual field examinations were obtained on the same day as the scanning laser tomography examinations (second and third columns) with change in threshold deviations from baseline (fourth column) and their change probabilities (fifth column). The visual field was classified as stable.
explanations for these findings. First, optic disc changes precede visual field changes in progressive glaucoma and, eventually, field progression will follow. A second explanation is one of scaling, whereby there are more progressive events in the optic disc, not all of which have a consequence in the visual field, perhaps because the relative scale to measure perimetric changes is coarser compared with disc changes. A third explanation is that disc topographic changes may not always represent neuronal loss but reorganization of the extracellular matrix of the optic disc or laminar position. Consequently, these structural changes may not necessarily result in visual field changes. Fourth, the spatial sampling in conventional visual field testing is coarse. Evidence suggests that, in some cases, visual field defects that were undetected by conventional stimulus patterns can be detected by fine grid perimetry at the time structural changes are detected. Finally, it is logical to assume that, if optic disc changes always translate to neuronal loss, there must be a functional consequence of this loss and our ability to detect the earliest psychophysical changes in the visual field is not yet optimal. It is possible that receptive field organization in the retina is redundant with conventional perimetric stimuli. Indeed, empiric evidence supports the view that conventional perimetry is not the most sensitive technique to monitor visual field changes.

Although some persons suspected of having glaucoma with an abnormal disc appearance have normal results with short-wavelength automated perimetry, a systematic longitudinal comparison of the newer perimetric techniques with scanning laser tomography in progressive glaucoma has not yet been reported. We showed that, in the patients who showed both disc and field changes, disc changes were not detected statistically significantly earlier than field changes. This is an apparently paradoxical finding, given that substantially more patients showed disc changes only; however, it tends to support the scaling hypothesis posed herein. Correlating specific progressive events in the optic disc to those in the visual field may not be an accurate exercise in progressive glaucoma. In the present study, we attempted to conduct a corresponding spatial analysis of optic disc and visual field changes and found that the confirmed disc changes frequently occurred in more than 1 region of the disc. Correlating these changes to those in the visual field, even though changes may occur in 1 hemifield, may be misleading; if the changes do not occur at the same date, it is possible that field changes may be a result of previous disc changes that were not captured during the follow-up of the patient. Alternatively, it can be argued in this case that the field changes followed the disc changes. The latter is feasible in an undamaged field; however, in the case of preexisting field damage, it may be overly simplistic to attribute a given field change to a disc change or vice versa. Follow-up studies of patients with glaucoma, while crucial in our understanding of disease progression and for devising new techniques to detect the change, typically represent only a relatively short window during the disease span of a patient.

Since scanning laser tomography has been shown to be very sensitive to changes in intraocular pressure, we wanted to ensure that the changes observed in the optic disc were not due to pressure fluctuations in the follow-up and were hence false-positive findings. Requiring changes to occur in 3 consecutive examinations would likely eliminate any random effects due to pressure fluctuation, even if they were present. In addition, we were unable to find any significant relationship between a variety of pressure variables between patients classified as stable or progressing by scanning laser tomography, although we are limited by single measurements made in the clinic. Finally, Topouzis and colleagues showed that reduction in optic disc cupping after trabeculectomy is observed only in the short term and that the cupping indices return to preoperative values after 4 to 8 months. Because of our criteria for optic disc progression, it would seem unlikely, both from that study and from our observations (Table 1), that those undergoing large reductions in intraocular pressure would necessarily have a lower progression rate with scanning laser tomography.

The agreement between clinical judgment of disc progression using optic disc photographs and scanning laser tomography was generally very good (13 of 16 cases). It should be pointed out, however, that the time required to reach consensus was probably greater than can be afforded in routine clinical practice. We acknowledge the limitation of this study with respect to its inability to provide a definitive answer on the merit of scanning laser tomography when compared with conventional photography because of the relatively small sample size. We were, however, careful to ensure that the follow-up of these patients with the 2 imaging techniques overlapped as closely as possible.

In summary, we have shown that small changes in optic disc topography can be detected by using a previously described analytical technique with scanning laser tomography. These changes occur more frequently than do visual field changes and concur with the changes seen with conventional photography. Clinical trials in glaucoma frequently define end points based on development of a visual field defect or progression in an already damaged field. While measurement of the visual field with conventional perimetry remains the most important functional variable in glaucoma, there are several important limitations. First, long follow-up periods, often spanning many years, are required. Second, many examinations may be required to confirm the end point and detect meaningful changes. Finally, there is increasing evidence that conventional perimetry may not be the most sensitive method of monitoring the visual field in glaucoma. While evaluation of the visual field should remain an important method of monitoring patients, particularly with the newer psychophysical tests such as short-wavelength, automated, high-pass resolution and frequency doubling perimetry, focus should now be directed toward the real potential of scanning laser tomography as an alternative both to conventional disc photography and to traditional end points in clinical trials. The challenge with scanning laser tomography, as with any new technique, is to translate the empirical findings to clinical significance and to provide practical clinical guidelines to use the technique effectively in the management of patients with glaucoma.