Diagnosis of Early Glaucoma with Flicker Comparisons of Serial Disc Photographs

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We evaluated flicker comparison, a technique for detecting differences in serial fundus photographs. Serial optic disc photographs and computerized threshold visual fields were obtained every 3 months for an average of 40 months in 131 eyes of 81 patients with elevated intraocular pressure and normal visual fields. Two serial monophotographs were projected, optically aligned, and superimposed; analysis was done by alternately viewing first one and then the other image. We found flicker analysis of serial disc photographs to provide results which were closely correlated with those of computerized threshold perimetry. Thus, of those 12 eyes which developed field defects, eight showed definite change and two showed highly suspected change in optic disc configuration. Only two eyes showed a definite alteration in optic disc anatomy without the development of field loss, and field defects appeared in only one of 109 eyes in which there was no change or suspected change on flicker comparison. The flicker method was more sensitive than conventional nonflickered comparisons, but changes could usually be seen also with conventional inspection once they had been detected by the flicker method. Our findings suggest that flicker analysis may offer a considerable improvement over current standard methods of analyzing serial photography and may be a useful complement to routine perimetry. However, this method requires special equipment; requires that the photographs be similarly centered; and is time-consuming. Alignment of photographs by means of computerized image analysis techniques could make the method clinically practicable. Invest Ophthalmol Vis Sci 30:2376–2384, 1989
Materials and Methods

Patients

Patients in the study were considered at risk of developing glaucoma, and had untreated intraocular pressures of 22 mm Hg or more and normal visual fields. Intraocular pressure was the mean of three daytime measurements with the Goldmann tonometer. Visual fields were classified as normal only after testing with computerized static threshold perimetry using the central field threshold program of the Competer perimeter (Bara Elektronik, Lund, Sweden) and after kinetic testing of the periphery and nasal midperiphery on the Goldmann perimeter. Since only a small percentage of nonselected patients with ocular hypertension develop glaucoma, we included only patients where the patient or at least one eye met one or more of the following risk criteria:

1. positive family history of glaucoma
2. diabetes
3. pseudoexfoliation or pigment dispersion syndrome
4. observed optic disc hemorrhage
5. localized complete or incomplete rim notch or marked vertical cup asymmetry
6. cup:disc ratio ≥ 0.6 or cup:disc ratio discrepancy ≥ 0.2 between the two eyes. Cup:disc ratio was defined by the contour of the cup.
7. untreated intraocular pressure (mean of three daytime measurements) of 27 mm Hg or higher.

Many patients were included in the study because one eye met one or more of criteria 3–7 above, while the other eye had no extra risk factors. In these cases only the high risk eye was evaluated. The present investigation includes 131 eyes of 81 patients with a follow-up time of at least nine months.

Patients were randomly treated with topical timolol or a placebo. Treatment was masked to the patient and to the investigator. All subjects gave informed consent. The study was approved by the Ethics Committee of the University of Lund. Patients who developed definite glaucomatous visual field defects, or in whom the intraocular pressure (the mean of three daytime measurements) reached 35 mm Hg, left the study.

Perimetry and Disc Photography

Patients were prospectively followed at three-month intervals for a period ranging from 9 to 72 months. The average follow-up time was 40 months.

At each visit visual fields were tested with the threshold program of the Competer perimeter. Eyes which showed suspicious or pathologic results at field testing were retested the same day using the identical program and, if necessary, with automated profile perimetry and manual perimetry.

Monocular optic disc photographs were obtained through a dilated pupil using a Zeiss fundus camera and Kodachrome II slide film. At least two photographs were taken of each eye at each visit. We tried to place the disc in the approximate center of the photograph, but no special aiming devices were used.

Methods of Analysis

Approximately 1800 visual fields and twice as many fundus photographs were included in the analysis. Field charts were classified as normal, suspicious, or definitely abnormal. Interpretation focused on the detection of areas of decreased sensitivity and nasal steps. The measured differential light threshold value at each point was compared with those of surrounding points and with points in the opposite, superior, or inferior hemifield. It was not considered ethically acceptable to keep patients with known field defects in the study; exact numeric criteria for visual field interpretation therefore were not specified in the study protocol, since we anticipated that the frequent visual field examinations would allow us to recognize developing field loss at an earlier stage than would predetermined criteria. The rules actually followed were similar to previously used criteria. An important difference, however, was that in the present study a high level of suspicion was maintained, such that tests were repeated where field charts showed even shallow depressions. No eye was considered to have developed definite glaucomatous field loss until defects had been confirmed by repeating the automated standard threshold program and by submitting the patient to manual perimetry and, usually, to computerized profile perimetry. Studied eyes were classified into one of two categories: eyes which developed definite glaucomatous field defects during the period of follow-up, and eyes which did not develop field defects.

We analyzed disc photographs with flicker chronsocopy using an instrument designed in our laboratory (Fig. 1). With this method, two images of the same optic disc, obtained at different times, are projected one atop the other. The two slides are flickered (ie, projected alternately, first one and then the other, in rapid succession). They are then aligned such that observed translational and rotational shifts between them are minimized. In the flickered image, unchanged areas appear stable, while changes appear...
Fig. 1. Schematic diagram of the instrument for flicker comparisons. The fundus photographs (2) are illuminated by two condenser-and-lamps systems (1). The two images are projected on a screen (7) via two lens systems (3), two mirrors (4, 6) and a beam splitter (5).

rapidly moving between two alternative views. With our instrument, the disc images are back-projected on a screen using a magnification of approximately 11 times that of the slide. The instrument contains two slide projectors, a beam splitter, and a number of mirrors. The instrument allows one of the slides to be moved along x and y axes and to be rotated. In this way, the two images, obtained at different times, can be superimposed, aligned, and flickered. The flicker frequency may be varied, but approximately 2 Hz is often quite appropriate.

Each slide taken during follow-up was compared to a baseline photograph and classified into one of four categories:

0 = no discernible change in disc anatomy from baseline
1 = slight suspicion of change
2 = high suspicion of change
3 = definite change

In this classification, only changes of optic disc configuration were taken into account; the occurrence of disc hemorrhages were not regarded as proof of change. Change was usually detected as minor displacements of small vessels or of other high contrast features, such as sharp cup borders. Color changes were not used. In category 3, changes were distinct, could be seen in several slides, and had usually been suspected at earlier examinations. In category 2 they were also visible in several pairs of slides but not as clearly as in category 3. Changes in category 1 were small and questionable. Photographs taken from slightly different angles were often difficult to align, and when flickered they sometimes initially gave a false impression of change (see Discussion). Therefore, every time when definite or suspect change was encountered, other pairs of photographs obtained at the same or approximately the same time were analyzed in order to see if suspected changes were also present in these.

To measure the degree of agreement between observers, a small sample of 22 pairs of photographs was selected and classified into one of the four categories, independently by two observers. In 15 cases the classification of photographs was in perfect agreement. The remaining 7 were classified within ±1 of the defined categories. In six of these cases discrepancies in classification were between categories 0 and 1.

All eyes were classified into one of four categories, from 0 to 3. We then counted the total number of eyes which had developed field loss in each of the four categories. The temporal relationship between disc changes and field defects was illustrated in a composite graph; all eyes which had developed definite change of disc anatomy or definite field loss were included.

The sensitivity of the flicker method was compared to that of conventional methods of comparing consecutive disc photographs. Three experienced ophthalmologists judged 50 pairs of disc photographs, including those ten which showed definite change on flicker chronoscopy (see Results). Forty pairs were unchanged controls. Pairs of control slides usually had been obtained at the same follow-up visit. Both slides of each pair were projected simultaneously side by side. The observers were free to inspect the images for as long as they wanted. They were masked for change and had not taken part in the flicker comparisons. They were not masked for sequence, however, and knew that the first photograph was always projected on the left side.

Results

Twelve of the 131 eyes developed glaucomatous visual field defects during the study period (one example is shown in Fig. 2). Corresponding disc
changes in these and the remaining 119 eyes are shown in Table 1. Eight of the eyes developing field defects showed definite changes in disc anatomy compared to baseline. In another two eyes with field loss, there was a strong suspicion of change. One eye developed glaucomatous field loss without any detectable alteration of disc configuration (Fig. 3). The spatial correlation between disc and field findings was high. In seven of eight eyes which developed definite changes in disc appearance and visual field defects, the largest observed alteration in disc anatomy occurred in a direction opposite to that of the field defect. In this analysis upper and lower hemifields were compared with the lower and upper halves of the optic nerve head. In the group without definite field loss, 108 of 119 showed no change of disc appearance (Table 1), and only two cases showed a definite change in disc anatomy.

Disc changes were often too small to be detected with conventional methods of comparing pairs of disc photographs (Table 2). Of course, some alterations were more difficult to detect than others. When the three ophthalmologists judged pairs of photographs projected on a screen (see Methods), in two pairs of slides the differences were missed by all three observers; in three pairs they were missed by two observers; and in another three pairs they were missed by only one observer (Fig. 4). The changes identified by the flicker method were usually visible also on conventional nonflicker comparisons once attention had been directed to the altered area.

The temporal relationship between the detection of changes in optic disc anatomy and the development of visual field defects is illustrated in Figure 5. Only those eyes developing definite changes at the optic nerve head or definite field defects were considered. In 5 of the 14 eyes, disc changes were noticed before any disturbances of the field were measured; in two eyes the alterations appeared simultaneously; and the remaining seven eyes showed suspected visual field disturbances before any changes of the optic disc could be detected.

Upon entry into the study, 6 of the 12 eyes which later developed glaucomatous field loss met at least one risk criterion relating to a suspicious appearance of the optic disc (criteria 4–6). One of these showed a hemorrhage plus a large cup; one showed cup:disc ratio discrepancy ≥ 0.2; the other four showed large cupping. Several of these could easily have been classified as normal after development of field loss, even though the flicker analysis had shown that they had undergone definite topographical change (eg, 1, 3, 5 in Fig. 4). By comparison, in 21 of the 119 eyes not developing glaucomatous field loss, discs met one or more risk criteria related to appearance at baseline. A majority of the eyes which developed field loss never
showed any disc hemorrhages although several had been observed and photographed 15 times or more.

Table 2. Detection of change by conventional comparison of disc photographs

<table>
<thead>
<tr>
<th>Changed pairs (N = 10)</th>
<th>Unchanged pairs (N = 40)</th>
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<tr>
<td>Correctly identified</td>
<td>Not identified</td>
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<tr>
<td>Identified as unchanged</td>
<td>Identified as changed</td>
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<tr>
<td>Observer 1</td>
<td>6</td>
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<tr>
<td>Observer 2</td>
<td>6</td>
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<td>Observer 3</td>
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* No single pair of slides was falsely classified as changing by more than one observer.

Discussion

The apparent usefulness of a diagnostic technique and its correlation with other methods depend on the stage of the disease. In more advanced stages, signs tend to be more obvious and pathology easier to detect, regardless of the methods of examination. Advanced glaucoma, for instance, often may be diagnosed even by casual disc inspection or by a crude perimetric screening test. The high correlation between disc and field classifications in glaucoma that has been documented in cross sectional studies\(^1\)\(^-\)\(^3\) can thus be explained partly by the large proportion of middle- or late-stage cases in these studies.

The detection of early disease, such as incipient glaucoma in the ocular hypertensives we studied, constitutes a more difficult task, both in terms of the...
Fig. 4. Disc photographs of those ten eyes in which definite disc change occurred. Areas where changes were most obvious on flicker comparison have been marked with arrows. Hemorrhages were not taken into account. With conventional nonflicker comparison all three observers detected changes in pairs 4 and 7, while one observer missed the changes in pairs 6, 8, and 9. The changes in pairs 1, 3, and 10 were missed by two observers, and those in pairs 2 and 5 by all three observers.
which developed definite field defects or distinct changes of disc defects and changes in optic disc configuration in those 14 eyes.

There were also definite changes of disc topography. Disc topography change, but without definite field loss, was seen in two eyes.

The results of the flicker method were also highly specific, probably in large part because a positive result required the demonstration of changes from a baseline photograph. This baseline comparison precluded the faulty classification of discs with unusually large physiological cups as glaucomatous.

The documentation of an increase in cup size has traditionally been considered to be a hard sign in the diagnosis of glaucoma. Nevertheless, some studies indicate that some enlargement of the cup can occur physiologically with age. We were concerned that such age-induced changes might complicate the process of making flicker comparisons. In this study, however, demonstrable increases in optic nerve excavation were closely linked to the appearance of visual field defects. This result suggests that age-related changes are small, given the time frame studied and relative to the progression rates of many if not most glaucomas.

Several earlier studies, including results from histological studies, have indicated that alterations in optic disc anatomy often precede visual field defects. One may therefore question the high correlation between optic disc changes and field defects in the present study. A critical difference between the cited studies and the present one is the type of perimetric technique employed. All studies mentioned above relied on standard kinetic manual field testing. One investigation comparing retinal nerve fiber layer photography with automated static threshold perimetry has shown a much closer correlation between axonal and functional loss. Computerized threshold testing is a considerably more sensitive method than manual perimetry for the detection of early glaucomatous field loss. Odberg and Rilse were aware of this difference and speculated, "It is likely that some more small field defects might have been detected with automatic perimetry." The likelihood of finding early field loss should be particularly large in the present study because of the prospective study design, the frequent visual field tests, and the ability to retest all suspect field findings, which permitted us to employ sensitive criteria of field interpretation. High specificity was maintained by repeating questionable fields and by requiring the presence of similar defects in several field charts.

The studies by Sommer and co-workers, Quigley and co-workers, and Pedersen and Anderson were all retrospective. In the paper by Pedersen and Anderson, some figures show discs with configurations which are very likely to be associated with field defects readily detectable by computerized threshold perimetry. One figure shows a broad sector-shaped retinal nerve fiber defect. Standard computerized perimetry generally will find field defects in eyes with these obvious abnormalities in the retinal nerve fiber layer.

The sensitivity of flicker comparisons was clearly superior to that of conventional comparisons of disc photographs, even when the latter were done under optimum conditions. There is no reason to doubt the positive findings of the flicker methods; most changes...
were readily visible also on conventional nonflickered comparisons once attention was focused on the changing area. The correlation between definite changes demonstrated by flicker comparisons and the development of field loss also indicates that clear changes observed in the flicker method were real. The differences between the flicker method and conventional comparisons are similar to the recent findings of Varma and co-workers, who compared the detectability of changes through conventional comparisons and through image analysis. It is possible that similar results could have been obtained by image subtraction as described by Alanko and co-workers, or by serial measurements of optic disc pallor as described by Nagin and Schwartz. When a few masked rim area measurements were performed, these were not able to differentiate as conclusively between changing and nonchanging discs as was the flicker method.

The high correlation between development of field defects and change in optic disc configuration suggests that both perimetric and flicker methods combined similar high sensitivities and specificities. A contributing factor, however, may be that many of the studied high-risk eyes were in a rather late phase of ocular hypertension, and therefore that recognizable changes at the optic nerve head could have taken place before the study was started.

Flicker analysis has some definite disadvantages. It cannot show whether or not glaucomatous damage is present at the first visit, but rather only allows the detection of progression of the disease. It is our experience, however, that the most difficult decisions in the management of glaucoma revolve around exactly this issue, around possible progression in a patient already identified as being at risk. In the majority of those subjects who developed definite field loss or change of disc configuration, a definite diagnosis of glaucoma could not have been established at baseline, even on very careful disc inspection. Secondly, the flicker method is not entirely objective and numeric as are disc pallor measurements or measurements performed by modern optic nerve head analyzers. Thirdly, flicker analysis is time-consuming. Manual alignment of serial photographs is laborious, and this fact alone is probably enough to prevent our method from becoming a routine clinical method. Computerization may offer a solution to this problem (see below). Images, if photographed from different angles, may first seem to indicate change. We have found that there is almost no risk that such slides will be falsely classified as positive, however, since the alignment also of surrounding fundus areas will become impossible in this situation. A real consequence of this problem, nonetheless, is that a considerable number of pictures may have to be excluded from analysis. This is clearly a disadvantage. If prospective studies are planned in which flicker comparisons of serially obtained disc photographs will be performed, it will be advisable to use a special centering attachment on the camera. It is likely that such a modification can increase the sensitivity of the method even further. Using exposures locked in the same arterial pulse phase could constitute a further refinement. As shown by this study it is quite possible, however, to use the flicker technique for analysis of older fundus photographs which have been obtained in the conventional way without any auxiliary devices.

Although perimetry and flicker comparison each detected the majority of cases of developing glaucoma, it is important to emphasize their complementary diagnostic roles. Sometimes glaucoma was detected with only one method, or was detected earlier with one than with the other. It is nevertheless reassuring to find that few early glaucomas would have gone undetected if the patient had been followed regularly with either method alone. It is equally important, however, to recognize that the sensitivity and specificity of perimetry discussed here was associated with a perimetric approach which was more rigorous than that generally practiced clinically; the relative efficacy of this flicker comparison may be higher when compared to typical clinical perimetry.

The ability of the flicker method to diagnose glaucoma approximately as effectively as threshold perimetry is noteworthy. If alignment or comparisons could be facilitated through the development of computerized image analysis routines, the method could be used clinically both for diagnostic purposes and for the recognition of progression in eyes with known glaucoma. Recognition of early glaucoma in patients followed because of ocular hypertension could be based on small but definite changes of optic disc configuration. This method should preferably be used as an adjunct to perimetry. Judging from the results of this study, diagnosis could probably be equally early, and possibly more time-efficient, when based on disc photography as when it is based on computerized perimetry. Results from the earlier comparisons of disc changes and development of field defects may even indicate that flicker comparisons could be more effective than repeated perimetry, at least in patients who are identified and followed from a very early stage of the disease. The photographic method could be particularly valuable in the management of patients who have difficulties in producing reliable perimetric results.
Key words: glaucoma detection, optic disc photography, computerized perimetry, flicker chronoscopy, ocular hypertension

References