An optimal reference plane to detect glaucomatous nerve fiber layer abnormalities with computerized image analysis

Joseph M. Miller and Joseph Caprioli

Glaucoma Service, Department of Ophthalmology and Visual Science, Yale University School of Medicine, 330 Cedar Street, New Haven, CT 06510, USA

Received April 5, 1991 / Accepted June 7, 1991

Abstract. Nerve fiber layer height measured with respect to a standardized retinal reference plane is diminished by glaucoma. The definition of the reference plane influences the nerve fiber layer measurements. We empirically determined the best reference plane for measurement of nerve fiber layer height. Optimal parameters for measurement reproducibility were determined for a group of 6 normal and 6 glaucomatous eyes each imaged nine times. Optimal ability to distinguish normal from glaucomatous eyes was determined for a group of 33 normal eyes and 36 glaucomatous eyes each imaged once. Measurements with the smallest variability (root mean square error = 32 μm) and the highest sensitivity (83%) and specificity (88%) were achieved when the reference plane is defined by portions of the image from a peripheral temporal area 32° wide, and for two peripheral nasal areas of 55° width centered 30° above and below horizontal. These parameters for the definition of the reference plane should provide measurements of nerve fiber layer height with the least variability and the greatest ability to discriminate between eyes with early glaucomatous damage and normal eyes.

Introduction

Glaucoma produces clinically detectable changes in the appearance of the optic nerve [3, 16, 22] and nerve fiber layer [1, 13, 17] by virtue of the damage it causes to retinal ganglion cells. The desire to detect early structural damage and small interval changes has led to the development of image analysis systems to measure the topography of the optic nerve head and nerve fiber layer [2, 6, 10, 15, 18-21, 23].

The analysis of contour maps derived from image analysis may prove more difficult than actually making the measurements. When the map is analyzed to develop summary parameters such as cup/disc ratio, the measurements are more reproducible than subjective estimates [4, 14, 15] but do not discriminate well between normal and glaucomatous eyes [6]. The structural parameters cup volume and disc rim area may contain more information, but still lack diagnostic predictive power because of the wide overlap between normal and glaucomatous populations [6]. These measurements are conveniently made with image analysis since they do not require a physical reference level other than the disc edge.

Contour measurements of the papillary and peripapillary surfaces are of little value unless there is an adequate reference level. While elevation measurements may be made with high precision relative to each other, there is no absolute reference level inherent in the image. Cartographers make measurements relative to sea level, but no such ready reference level exists in the posterior pole of the eye.

A method to make measurements of the peripapillary surface relative to a retinal reference level established in the peripheral portions of videographic images has been developed [7]. This reference level facilitates comparison of maps for change over time, and allows multiple measurements made at a single session to be combined for better resolution. Measurements made with this technique have an enhanced diagnostic capability compared with standard structural parameters (cup-disc ratio, rim area, cup volume) [3, 8]. The reference plane definition was based on assumptions about locations thought to change least with progressive glaucoma. A priori, it is conceivable that a single definition might improve reproducibility at the expense of sensitivity by including areas affected by glaucomatous atrophy e.g., the nerve fiber layer bundles). Inclusion of such areas would diminish the ability to distinguish eyes with early glaucoma from normal eyes, as the reference level itself might be influenced by the disease. This study was performed to empirically determine the optimal reference plane in order to enhance reproducibility and diagnostic predictive power.

Offprint requests to: J. Caprioli
Patients and methods

Image analysis

Maps of optic nerve head contour were generated from data acquired with a computerized image analysis system (Roentgenstok Instruments, Munich, FRG). The illumination system projects seven vertical stripes onto the optic nerve head. A simultaneous stereoscopic image is recorded and surface contour measurements are calculated from stereoscopic disparities. A total of four vertically striped images are acquired; two of the four images are used in the topographic analysis. The two selected for analysis have the stripes projected with slightly different horizontal offsets so that when the two sets are superimposed, there is an even separation between all stripes (Fig. 1). The elevation measurements along the two sets of seven stripes, the relationship of these stripes to the center of the optic disc, and the corrected disc dimensions are transmitted to an IBM PC/AT (IBM Corp., Armonk, NY) for analysis. The two stripped images are combined to form a higher resolution elevation map. A surface is generated by interpolating horizontally between the measurement locations. Measurements are then corrected for the optical magnification of the eye and an interpolated map, in units of μm, is generated. The method for correction of image size has been previously described [4].

The average nerve fiber layer height of a 200 μm diameter annulus surrounding the optic disc is then calculated. This measurement is one of several structural parameters under investigation [5, 8], and was chosen because it is the area where the nerve fiber layer is thickest and is sensitive to glaucomatous damage [7]. The measurements of nerve fiber layer height are made at 64 locations around the disc, then averaged to yield a mean elevation.

The selection of the image locations to determine the reference plane was varied with a computer program. Peripheral elevations were constructed as those calculated from the most nasal and temporal stripes in the image (Fig. 1). Each plane was defined by a best fit through three areas of the peripheral image: temporal, superior nasal, and inferior nasal elevation measurements. The reference plane thus defined has a height of 0; positive measurements lie below the plane and negative measurements lie above it. The possible temporal areas were varied from those enclosed by an area 10° above and below the horizontal, in 10° steps, to 80° above and below the horizontal. The nasal definition areas were symmetrically extracted from one of 28 possible areas of 10° step size. These areas were characterized by a sweep width centered about a mean angle. A total of 224 different ways of defining the reference plane were investigated for each of the patient groups.

One eye each of 6 normal and 6 glaucomatous patients was imaged nine times within several days to determine the effects of reference plane definition on reproducibility. The mean nerve fiber layer height was calculated for the nine image sets of each patient 224 different ways (once for each of the reference plane determinations). The average nerve fiber layer height and the parameters used to define the reference plane were recorded for each analysis.

A separate group of patients was studied to determine the effect of reference plane definition on the ability to discriminate glaucomatous from normal eyes. The mean nerve fiber layer height was measured in 33 eyes of 33 normal volunteers and 36 eyes of 36 patients with early glaucomatous visual field damage. The characteristics of this population have been previously reported [7]. Normal subjects were recruited from hospital staff and families of patients. All were of the age of 40, had a normal eye examination and normal computerized static threshold perimetry, and were age-matched to the glaucoma patients. Glaucoma patients had a history of elevated intraocular pressure on or prior to treatment and visual field defects characteristic for early glaucomatous damage as measured by automated static threshold perimetry. Eyes with advanced visual field loss (mean defect > 15 dB) were excluded. All eyes had mean nerve fiber layer height calculated for each of the 224 different reference plane definitions.

Reproducibility was defined for each eye by the root mean square error (μm) of the nine repeated measurements of nerve fiber layer height. Individual values were averaged for the 12 eyes in the reproducibility study. An average measure of reproducibility was obtained for each of the 224 possible reference planes. The optimal reference plane for reproducibility was defined as the plane which exhibited a minimum mean square error.

The ability to discriminate between glaucoma and normal was evaluated with the Z statistic in the larger group of normal and glaucomatous subjects [12]. This statistic is a function of the means, standard deviations and number of subjects, and increases as the populations become more distinct. For each of the 224 different reference plane definitions considered, the Z statistic was computed. The optimal reference plane for predictive power was defined as the plane which maximized the Z value.

Optimal reference planes were determined independently for the reproducibility dataset and the predictive power dataset. The three parameters which defined the reference plane (temporal sweep, nasal angle, nasal sweep) were independently plotted against root mean square error (for reproducibility data) and Z-statistic (for predictive power). A second-order polynomial (a curve with a single smooth maximum or minimum) was fitted to the data. The maximum or minimum was found for each curve by solving for the location where the derivative of the second-order polynomial was zero. For the optimum to be considered significant, the second-order term had to be statistically significant and the maximum or minimum had to lie within the measured range of data. Data analysis was performed with a multivariate general linear hypothesis program (SYSTAT, Systat Corp., Evanston, Ill.).

Results

The average reproducibility (root mean square error) was best (32 μm) when the reference plane was defined with a nasal mean angle of 30° (P = 0.000) and a nasal area of 58° (P = 0.014). The reproducibility was insensitive to the size of the temporal area (P = 0.212). Figure 2 shows the plots of observed RMS errors as a function of reference plane definition parameters.

Summary data for the subjects in the predictive power study are given in Table 1. No significant differences existed between the two groups for age, refractive error, or disc size. Significant differences (P = 0.000) were found between the groups for visual field mean defect, corrected loss variance and short-term fluctuation, cup-disc ratio, disc rim area, and cup volume. These differences reflected the selection criteria for the glaucoma patients. Curve fitting and localization of the maximal
value of each parameter showed that the optimal temporal area was 32° ($P = 0.029$), the nasal angle was 24° ($P = 0.000$), and the nasal area was 56° ($P = 0.058$). Figure 3 shows the plots of the Z statistic as a function of reference plane definition parameters.

The plane definition which provided the best reproducibility was similar to the definition which provided the best predictive power. The reference plane which optimized both reproducibility and predictive power was defined by a peripheral temporal area of 32° wide and nasal area of 55° wide centered 30° above and below horizontal (Fig. 4).

**Discussion**

Recent technological advances have facilitated the analysis of digitized images to extract quantitative information about optic nerve head and nerve fiber layer structure [2, 5, 6, 9, 10, 15, 18-21, 23]. There are two reasons for obtaining accurate quantitative measurements: (1) to identify early structural damage; and (2) to provide a sensitive measure of progressive damage. Markers for structural optic nerve damage should be sensitive, specific, objective, and quantitative. Early clinical studies were confined to measurement of “standard” structural parameters such as cup-disc ratio, disc rim area, and cup volume. The poor sensitivity and specificity of these measurements, and the lack of strong correlations between functional measurements and structural measurements was disappointing [6]. The standard parameters conformed to the usual qualitative descriptions of the optic nerve head, and were not designed to optimize the information to be gained from topographical measurements.

Novel parameters of optic nerve head structure were sought that might be more sensitive and specific, and that might correlate better with functional defects in early glaucoma [5, 7, 8, 11, 21]. Since the variability of normal optic nerve head structure was great, and since
glaucoma causes atrophy of the nerve fiber layer, measurements of juxtapapillary nerve fiber layer height were made [7]. This required the establishment of a retinal reference plane to standardize the measurements. The reference areas initially chosen were three distinct peripheral regions of the imaged retinal surface located temporally, inferonasally, and superonasally of the disc, and outside the normally thick areas of the superior and inferior nerve fiber bundles. We believed that these were the thinnest areas of nerve fiber layer available in the images and changed least with progressive glaucomatous damage, since they did not include the arcuate bundles. Normal optic nerves had a typical double-hump configuration when the profiles of nerve fiber layer surface height were plotted two dimensionally; that is, the thickest areas of the nerve fiber bundles were located superiorly and inferiorly, while the temporal area tended to be lowest because of slight tilting of the optic nerve head in almost all cases. Glaucomatous atrophy was typified by loss of the double-hump pattern with flattening and lowering of the nerve fiber layer surface profile. Localized defects of the nerve fiber layer could also be demonstrated with this technique [7]. In a study of 53 normal subjects, 87 glaucoma suspects, and 112 patients with early glaucoma, the mean differences of nerve fiber layer height between normal and glaucoma groups were 70 µm, while the differences at the superior and inferior poles averaged 106 µm [5].

In these experiments, we empirically determined the optimal image locations to define the reference plane to reduce variability and increase sensitivity and specificity (predictive power). Reproducibility was insensitive to the temporal areas chosen, but was dependent on the nasal mean angle (optimum 30°, \( P = 0.000 \)) and nasal area (optimum 58°, \( P = 0.014 \)). These reference plane parameters provided an average root mean square reproducibility of 32 µm. The Z statistic, which increases as the populations of normal and glaucomatous eyes become increasingly distinct, was used to determine the optimum settings for the reference plane for predictive power: these showed that the optimal temporal area was at 32° (\( P = 0.029 \)), nasal angle 24° (\( P = 0.000 \)), and nasal area 56° (borderline significance, \( P = 0.058 \)). The plane definition that provided the best reproducibility was similar to the definition that provided the best predictive power. The reference plane that optimizes both reproducibility and predictive power was defined by a temporal arc 32° wide and nasal areas 55° wide, centered 30° above and below the horizontal.

Useful information can be obtained by developing new structural parameters for optic nerve damage which do not conform to the classic ways of qualitatively describing the optic disc. The inherent variability of measurements made of the optic disc is great, owing to the large variations in the scleral infrastructure of the optic nerve head. More stable and less "noisy" measurements might be made outside the disc, such as the contour or thickness of the nerve fiber layer. The empirical approach used here could also be used to develop similar optimal parameters for digital image analysis with other cameras or instruments. A major goal should be to im-

prove the utilization of computerized image analysis by developing more robust measures of structural damage. Further work is required to establish which of the structural parameters are most sensitive to progressive glaucomatous damage. It will not be surprising if the relative sensitivities of various methods change with the stage of glaucoma: that is, some measurements may be sensitive indicators of early glaucomatous damage, while others may be more sensitive indicators of progressive damage in its advanced stages.

Acknowledgements: This study was supported by grants from The National Institutes of Health EY07353 (Dr. Caprioli), The Robert Leet and Clara Guthrie Patterson Trust, The Connecticut Lions Eye Research Foundation, Inc., and Research to Prevent Blindness, Inc.

References

of the optic disc in glaucoma: the natural history of cup progression and some specific disc-field correlations. Trans Am Acad Ophthalmol Otolaryngol 78:OP255-OP274