Fourier Analysis of Optical Coherence Tomography and Scanning Laser Polarimetry Retinal Nerve Fiber Layer Measurements in the Diagnosis of Glaucoma

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Objective: To evaluate a new Fourier-based analysis method for diagnosing glaucoma using retinal nerve fiber layer (RNFL) thickness estimates obtained from the optical coherence tomograph (OCT) (OCT 2000) and the scanning laser polarimeter (GDx).

Methods: We obtained RNFL thickness estimates from 1 eye of 38 healthy individuals and 42 patients with early glaucomatous visual field loss using the OCT and GDx devices. The shape of the RNFL double-hump pattern was assessed using Fourier analysis, and values were entered into a linear discriminant analysis. Receiver operating characteristic (ROC) curves were used to compare the performance of the Fourier-based metrics against other commonly used RNFL analytical procedures. Reliability was assessed on independent samples by the split-half method. Correlations were calculated to determine the extent to which the Fourier discriminant measures and other RNFL measures covaried between the 2 devices and the relationship between these RNFL measures and visual field measures.

Results: Sensitivity and specificity for the linear discriminant function (LDF) based on the Fourier analysis of the OCT data were 76% and 90%, respectively, and the area under the ROC curve was 0.925 (SEM, 0.028). For the GDx data, the Fourier-based LDF yielded sensitivity and specificity of 82% and 90%, respectively, with an ROC curve area of 0.928 (SEM, 0.029). These values were better than those determined using the GDx number, a previous discriminant function using GDx variables and OCT thickness values. The Fourier-based LDFs and numerous other measures were significantly correlated between the 2 devices. For each device, the visual field measures correlated most highly with the Fourier-based LDF measure.

Conclusions: For both devices, the LDF based on the output from a Fourier analysis of RNFL data resulted in better diagnostic capability compared with other common RNFL analytical procedures. That this technique improves RNFL analysis is also supported by the better correlations between visual field measures and the Fourier-based LDF measures.
on radial (sector) mean thickness values, and the GDx device provides the GDx number that is based on relational and direct measures.

Previously, we have emphasized that the shape of the distribution of the RNFL thickness estimates may be a more useful way to characterize the normal RNFL and detect deviations from it. Analyzing the RNFL in terms of shape variables rather than raw thickness, sector thickness, or even normalized thickness or simple relational measures may provide variables that are based on regional characteristics less affected by noise and individual differences. Shape analysis of data from new polarimetry devices that account for individual differences may provide variables that are based on regional characteristics less affected by noise and individual differences. Shape analysis of data from new polarimetry devices that account for individual differences may provide variables that are based on regional characteristics less affected by noise and individual differences.

In the present study, we apply a shape-based polarimetry device that accounts for individual differences. Shape analysis of data from new polarimetry devices that account for individual differences in anterior segment polarization may help even more. In the present study, we apply a shape-based RNFL analysis approach that is based on a 1-dimensional Fourier analysis of the double-hump RNFL thickness pattern. We use an LDF version of the Fourier method to combine the shape components generated by the Fourier analysis as reported in preliminary reports. The first goal of this study is to compare the extent to which this method improves glaucoma detection with polarimetry and tomography data. The second goal is to compare the output of the OCT and GDx devices in terms of these shape components and their raw output.

### METHODS

#### SUBJECTS

Data from 1 eye, chosen at random, of 38 healthy control individuals and 42 patients with glaucoma (hereafter referred to as glaucoma patients) were used for the study. All subjects were required to have GDx and OCT scans within a 3-month period (average time between scans, 11 days; SD, 19 days). The 42 glaucoma patients were all of those from the University of California–San Diego (UCSD) glaucoma clinic who had the 2 scans available within 30 days and had repeatable abnormal visual field results on standard automated perimetry, with Glaucoma Hemifield Test results outside normal limits or a corrected-pattern SD (CPSD) outside 95% normal limits. The 38 healthy controls were mainly UCSD employees and relatives of patients who had undergone GDx and OCT scanning within 30 days of each other and met the criteria stated in this paragraph. Table 1 gives the demographic information for the patient and control groups as well as the global visual field indices. All participants underwent an ophthalmologic examination including visual field testing (standard automated perimetry) and imaging of the peripapillary RNFL with GDx and OCT. The ophthalmologic examination included slitlamp biomicroscopy, applanation tonometry, gonioscopy, and dilated indirect ophthalmoscopy. Visual field testing was performed with the Humphrey Field Analyzer 24-2 or 30-2 program (Zeiss Humphrey Systems). The healthy control group had normal results of the ophthalmologic examination, visual field results within normal limits, and an intraocular pressure of less than 22 mm Hg at the time of examination. These individuals also had no history of optic neuropathy or surgery and no history of diabetes or other systemic disease; the glaucoma patients had no relevant medical history except glaucoma. Informed consent was obtained from all participants, and the study was approved by the Human Subjects Committee of UCSD. Research followed the tenets of the Declaration of Helsinki.

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<thead>
<tr>
<th>Table 1. Patient Demographics and Visual Field Variable</th>
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<td><strong>Healthy Eyes</strong></td>
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<td>(38 Eyes)</td>
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<td>Age, mean (SD), y</td>
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<td>CPSD, mean (SD)</td>
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**Abbreviations:** CPSD, corrected-pattern SD; MD, mean defect.

#### RETINAL IMAGING

Polarimetry was conducted with a standard GDx device, which provides an array of 256 × 256 thickness estimates (15° field) based on polarization retardation. We used the number calculated by the GDx software, a value from 0 to 100 based on a trained neural network analysis of the scan (0 indicates completely normal; 100, advanced glaucoma). The present study used the average thickness estimates from the 32 (11.5°) angular sectors on a ring (a 10-pixel-wide band) located at 1.7 disc diameters distant from the disc on the baseline images (mean of 3 scans) for all additional data analysis.

The OCT device estimates RNFL thickness using low-coherence interferometry to differentiate the retinal layers on the basis of the different echo time delays that occur for the different layers. The OCT (circle scan mode) generated RNFL thickness estimates at 100 points in a 3.4-mm circle diameter centered on the optic disc that were averaged to provide values at 12 radial sectors around the disc. These values were used for all further data analysis. Three OCT scans were performed and averaged in each case.

#### FOURIER ANALYSIS

Fourier analysis is a mathematical procedure whereby a complex waveform pattern (eg, the double-hump pattern of nerve fiber distribution) is broken down and described as a set of harmonically related sine waves of specified frequencies, amplitudes, and phases. If all of the component sine waves are added together, point by point, the original waveform is reproduced. Also produced by Fourier analysis is the DC component, which is the overall level or mean value of all amplitude measures. In our application of Fourier analysis to the RNFL, the DC component is synonymous with mean thickness. The lowest-frequency component, the fundamental (F1), corresponds to a sine wave pattern with 1 cycle (ie, 1 hump), and the harmonics are sine waves whose frequencies are integer multiples of the fundamental (eg, the second harmonic, F2, has a frequency that is 2 times that of the fundamental, and thus has 2 humps; the third harmonic has 3 humps, etc). The amplitude value of each sine wave is the peak-to-trough distance, and the phase value describes where the waveform begins (eg, at the peak, at the trough, or somewhere between, relative to some reference). When a Fourier analysis is performed on a set of data (that describe some complex waveform), the number of sine waves generated to describe that waveform equals half the number of data points. For example, a waveform based on 12 data points, the present standard for the OCT, will generate 6 sine waves and a single DC component. Because the present GDx data are based on 32 data points, there are 16 resulting sine waves from the Fourier analysis. Each sine wave will have a specific amplitude and phase...
value. A more complete description of Fourier analysis can be found in Bracewell, and its application to RNFL thickness estimates can be found in Essock et al. The Fourier analysis was performed on data from each eye from each device (GDx and OCT), using the Fast-Fourier Transform procedure in MATLAB, version 5.0 (The Math Works, Natick, Mass).

DISCRIMINANT ANALYSIS

The Fourier coefficients (DC component and all amplitude and phase values) from all individuals were subjected to a stepwise discriminant analysis using SPSS for personal computers (version 10.0; SPSS Inc, Chicago, Ill). The absolute value of the phase coefficients was used for this procedure to emphasize deviations in shape regardless of direction. The significance of each variable (coefficient) in the discriminant analysis was determined using Wilks’ $\Lambda$, and only those variables that contributed significantly at the level of .05 were retained in the final function. The final LDFs were then applied to the data, and receiver operating characteristic (ROC) curves were generated. This procedure was performed for both the GDx and OCT data.

STATISTICAL ANALYSIS

Mean thickness comparisons between healthy and glaucomatous eyes were conducted using an unpaired, 2-tailed $t$ test for the GDx and OCT data. The $\alpha$ was set at .05. The ROC curves were generated from the LDFs from both devices and from various other metrics such as mean thickness, the UCSD LDF, and various GDx variables. Significant differences between ROC curves were determined by the method described in DeLong et al. Pearson product moment correlation coefficients were used for all correlations, and the $\alpha$ was adjusted using Bonferroni corrections based on the number of comparisons made.

A standard split-half technique was used to test the reliability of the Fourier-based LDFs for detecting glaucoma. For this split-half analysis, each subject in the total sample was randomly assigned to 1 of 2 groups of equal size. The same Fourier LDF analysis procedure was performed separately on each of the 2 independent samples, and sensitivity and specificity were calculated for each group by applying to 1 sample the discriminant function calculated independently on the other sample. Thus, the LDF was derived with one sample and tested on another for both of the samples, thereby providing 2 independent estimates of the performance of the procedure. The 2 sensitivity and specificity values were then averaged to provide an overall assessment of performance. Other than for this check of reliability, the full-size sample was used in all analyses throughout the report.

RESULTS

The mean RNFL thickness estimates for the healthy ocular controls and glaucoma patients determined with the GDx and OCT devices are shown in Figure 1. Both devices show the general double-hump pattern, but also show a difference in mean thickness between glaucomatous and healthy eyes ($t=2.8 [P<.01]$ for GDx; $t=7.2 [P<.001]$ for OCT). Although the shape of the distribution (double-hump pattern) is generally similar, differences between the thickness estimates produced on the same set of individuals by the 2 devices are apparent. To allow the comparison of the output of the 2 devices, the data were normalized by dividing all points on an individual curve by the maximum value, and data from both devices were plotted together (Figure 2). The most striking difference between the devices is that, although the location of the nasal and temporal minima correspond in 2 devices, the GDx device yields average curves with both peaks shifted nasally (ie, toward each other) compared with the OCT device for glaucomatous and healthy eyes. (This is a consistent difference between the machines, as 57 [71%] of all 80 subjects showed this shift.) A pervasive and systematic difference such as this finding of matching minima and shifted maxima would be unlikely to be related to individual differences in anterior segment polarization uncompensated for by the GDx device.

When our Fourier analysis procedure is applied to the data of each individual and the linear discriminant analysis procedure is applied, each eye can be classified as glaucomatous or normal on the basis of the resultant discriminant function. The stepwise procedure yields an equation consisting only of terms that contribute significantly to the discrimination of glaucoma from healthy eyes. For the OCT device, the function was $0.041 \times DC + 0.077 \times F2$ amplitude $+ 0.648 \times F3$ phase $- 6.378$. For the GDx device, the function was $0.260 \times F2$ amplitude $+ 1.366 \times F12$ amplitude $+ 0.681 \times F12$ phase $- 1.912 \times F13$ amplitude $+ 0.798 \times F14$ phase $- 5.942$. The most important variables in the equations (in terms of discriminative power) were, for OCT, the DC level, then, approximately equally, F2 amplitude and F3 phase, whereas for GDx they were...
F2 amplitude and F14 phase. Only the amplitude of the second Fourier coefficient is present in both functions. However, because the 2 functions are based on a different number of input coefficients, it is not surprising that the relevant coefficients are different (i.e., there are only 6 amplitude and phase coefficients for the OCT data, and there are 16 for the GDx data). From these functions, sensitivity and specificity values and associated ROC curves were obtained. The ROC curves from application of the Fourier metrics and the most prevalent metrics in the literature are shown in Figure 3 for the GDx device and in Figure 4 for the OCT device. For the GDx data, the areas under the curve for the GDx number, the UCSD LDF, and the Fourier-based LDF were 0.734, 0.773, and 0.928, respectively (SEM, 0.056, 0.052, and 0.029, respectively). For the GDx device, the Fourier-based LDF performed significantly better, with the area under the ROC curve significantly larger than that obtained from the GDx number or the UCSD LDF (P < .05). For the OCT device, we evaluated the standard measures of mean thickness, inferior sector thickness, and the Fourier-based LDF and obtained areas under the ROC curves of 0.872, 0.888, and 0.925, respectively (SEM, 0.041, 0.038, and 0.028, respectively), as shown in Figure 4. Again, the discrimination ability (ROC area) was greater for the Fourier-based LDF measure (but not significantly [P > .05]). The split-half reliability analysis (Table 2) shows that these findings are reproducible. When the various measures are tested on the half-size independent samples, the Fourier measures still outperform the GDx number and the UCSD LDF, with best performance for the OCT Fourier-based LDF and poorest performance for the GDx number.

An anatomical measure that accurately reflects RNFL integrity presumably should be strongly associated with visual function measures. Hence, a GDx or OCT measure that relates better to a visual field metric may suggest a more meaningful RNFL variable. Correlations were calculated between visual fields and both OCT and GDx variables to assess the degree of such associations and are shown in Table 3. For the GDx measures, only the Fourier-based LDF and UCSD LDF values correlated significantly with the mean defect (MD) or CPSD. For the OCT measures, the Fourier-based LDF value and average thickness significantly correlated with the MD and CPSD. For both devices, the Fourier-based LDF correlations tended to be higher than the other measures (Table 3).

To the extent that the data from the 2 devices actually reflect the true RNFL thickness distribution, the thickness estimates and the metrics developed based on them (e.g., the GDx number or the LDF values) should significantly covary between the 2 devices. In actuality, average thickness as measured by each device was not correlated across individuals (r = 0.10 [P > .05]) as shown in Figure 5.
Presumably, the lack of individual compensation for anterior segment polarization for each subject by the GDx device is the basis for part of this discrepancy. A more important finding is that, despite average thickness not being significantly correlated across the 2 devices, the various measurements of abnormal characteristics from the 2 devices correlated very well. All GDx measures tested (and the GDx-based LDF measures) were significantly correlated with both the OCT average thickness measure and the OCT Fourier-based LDF values, except for GDx average thickness and GDx ellipse average variable, both of which are direct RNFL thickness estimates (Table 4). The highest relationships, however, are between the Fourier-based LDFs (OCT and GDx), the UCSD GDx LDF, and the OCT average thickness measures.

Since the 2 devices’ measures of average thickness were unrelated (ie, with the relation accounting for only -2% of the total variance), we next considered whether thickness measures might correspond better in the thicker areas (ie, the superior and inferior regions) or the thinner areas (nasal and temporal regions). Comparisons were made using thickness estimates averaged across these 4 regions (90° quadrants) and using the single extreme value (maximum for superior and inferior quadrants and minimum for temporal and nasal quadrants) for the 4 regions. (The 90° quadrants were formed by combining 8 GDx sectors or 3 OCT sectors.) In general, the associations at the thicker regions (superior and inferior) were stronger (about 0.25) than the associations for the 2 thin-
The main finding of the present research is that the LDFs generated from a stepwise discriminant analysis of the Fourier coefficients derived from RNFL thickness estimates were found to effectively discriminate eyes with early glaucoma from healthy eyes for data obtained from either the GDx or OCT devices. In both cases, the area under the ROC curve was approximately 0.93, indicating that this method of analysis works equally well for both devices. When applied to the present patient sample, ROC comparisons show that the Fourier-based LDFs detected glaucoma better than other commonly used measures, including the GDx number and OCT mean thickness. The finding that the Fourier-based LDF values are more strongly associated with visual function measures (visual field indices) than are other measures such as average thickness or any of the various GDx variables provides further support that it is a sensitive measure for assessing RNFL integrity in early glaucoma.

A direct comparison between the RNFL measures of the 2 devices found that the overall thickness measures were not significantly correlated between the devices (an $r^2$ of only 0.01). A similar finding was reported by Zangwill et al.\textsuperscript{38} We assume that much of this discrepancy may be attributable to errors in the polarimetry measures resulting from individual differences in polarization from the anterior segment of the eye,\textsuperscript{31} and we suspect that some of the discrepancy between the 2 devices will be reduced as individual compensation of an eye’s corneal polarization becomes routine.\textsuperscript{39} However, although both devices purportedly provide estimates of

### Table 4. Correlations Between OCT and GDx Measures

<table>
<thead>
<tr>
<th>Thickness Amplitude Measures</th>
<th>Correlation</th>
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<tbody>
<tr>
<td>Average superior</td>
<td>0.34*</td>
</tr>
<tr>
<td>Average inferior</td>
<td>0.38*</td>
</tr>
<tr>
<td>Single-value superior</td>
<td>0.30*</td>
</tr>
<tr>
<td>Single-value inferior</td>
<td>0.40*</td>
</tr>
</tbody>
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* $P<.0125$ using Bonferroni adjusted $\alpha$.

### Figure 6

Average amplitude in the inferior quadrant (average of nasal and temporal quadrants subtracted from the average inferior quadrant thickness) determined by the ocular coherence tomograph (OCT) (OCT 2000; Zeiss Humphrey Systems, Dublin, Calif) and scanning laser polarimeter (GDx) (Laser Diagnostic Technologies, San Diego, Calif) devices plotted against each other for all subjects. Like other amplitude measures, the measurements from the 2 devices are significantly related. Least squares regression line is shown.

\[ y = 0.6547x + 10.769 \quad r=0.38 \]

**COMMENT**

The main finding of the present research is that the LDFs generated from a stepwise discriminant analysis of the Fourier coefficients derived from RNFL thickness estimates were found to effectively discriminate eyes with early glaucoma from healthy eyes for data obtained from either the GDx or OCT devices. In both cases, the area under the ROC curve was approximately 0.93, indicating that this method of analysis works equally well for...
RNFL thickness, the GDxs actually measures polarization retardance, thought to be proportional to RNFL thickness, but not a direct measure of RNFL thickness. The correlations reported in Table 4 and the tabulations indicate a regional aspect of the poor correlation between the thickness measures produced by the 2 devices. Much of the poor association between the 2 devices occurs at the nasal and temporal regions, as the association between the 2 devices' measures was stronger in thinner regions (inferior and superior) than in the nasal and temporal quadrants or for the total retina. Furthermore, the peak-to-trough amplitude measures from the 2 devices were more closely and significantly correlated, suggesting that the peak-to-trough measures across the 2 devices were more consistent across individuals than were absolute thickness measures. The Fourier-based LDF measures were among the most highly correlated measures across the 2 devices, suggesting that the overall shape or pattern of fiber distribution is more similar than specific thickness estimates. As in previous reports, this leads us to emphasize the utility of a shape-based analysis of quantitative RNFL measurements..

One reason why the thickness estimates of the 2 devices were not correlated for the sample population in this study or for that of Zangwill et al.49 may be related to the severity of the glaucomatous damage. A study from Hoh et al.23 compared OCT and GDx data from the same group of individuals and found that the OCT thickness estimates correlated significantly (r = 0.29) with an estimate of RNFL thickness (the ellipse average variable), as well as with all other GDx variables tested. However, the patient sample used in that study consisted of patients with relatively more advanced glaucoma than the sample analyzed in the present study (MD average, −7.7 for the study by Hoh et al.23 compared with −4.0 for this study) and the study by Zangwill et al.46 (which included a number of patients with early glaucoma, with an MD average of −2.1). In addition, all 3 studies show a similar trend in the strength of the correlations, where the association of mean thickness values between OCT and GDx were weaker than the association between OCT mean thickness and other GDx variables (eg, modulation variables). The use of patients with more advanced glaucoma in the study by Hoh et al.23 can also explain why their test measures (mean thickness for OCT and the number, maximum modulation, ellipse modulation, and ellipse average for GDx) correlated more strongly with the global visual field indices than was found in the current study. Despite these differences due to stage of disease, a similar pattern was found for both studies (ie, the present study and that of Hoh et al.23) in that the OCT mean thickness correlated more strongly than any of the GDx variables with measures of visual function (MD and CPSD), suggesting that OCT measures may be a better indicator than the present versions of GDx polarimetry measures for retinal functional integrity (see also Zangwill et al.45 and Weinreb et al.46). In more advanced stages of glaucoma, present OCT and GDx measures correlate with functional loss (OCT more so than GDx), but the present results show that in even earlier stages of glaucoma, Fourier indices of either OCT or GDx data correlate with functional loss, whereas the other measures do not.

The ROC curve analysis suggests that other than the Fourier-based LDF approach, the measures from the OCT device are better at detecting glaucoma than the measures from the GDx device, despite the fact that the GDx uses more sophisticated analytical procedures when deriving its measures (eg, a neural network analysis) than present metrics typically used for analysis of OCT data (ie, direct measures of total or sector mean thickness). This may not be surprising, given our finding that the OCT measures were more strongly correlated with visual field indices than the GDx measures, a finding also reported by Hoh et al.23 Bowd et et al.26 also found the area under the ROC curve was significantly higher for the best OCT measure compared with the best GDx measure; however, Zangwill et al.45 did not find a significant difference. However, the Fourier-based LDFs from the 2 devices resulted in similar discriminating ability for the 2 devices. That is, although current measures commonly used from the 2 devices generally result in better discriminating ability for the OCT device (see also Zangwill et al.45), if Fourier analysis is used to characterize the shape of the RNFL, then the resulting LDF works equally as well for both devices.

The weightings of the factors varied less between the 2 halves for the OCT data, possibly suggesting further that, at present, the values obtained from the OCT device are more internally consistent than those from the GDx device.

This procedure emphasizing characteristics of the shape of the double-hump pattern is a way to improve the utility of RNFL measurements, whether from a polarimetry or a tomography device. In particular, the present procedure for analyzing shape by means of Fourier analysis with application of an LDF improves the performance of both the OCT and GDx devices. The split-half analysis shows that these Fourier-based LDFs are robust and can accurately discriminate glaucoma on samples independent of their derivation, although their degree of robustness is likely to improve when the LDFs are generated on larger patient samples. Like the other metrics in use, the Fourier-based LDF method needs to be established on the largest sample possible in the future to maximize its performance. With further refinement, this analysis method may be useful for assessing risk for conversion from a glaucoma suspect to glaucoma, in addition to improving the detection of glaucoma as shown in the present results.

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