Practitioners have a long tradition of describing structural glaucomatous damage by its observable effects on the optic nerve. *Cupping, cup-to-disc ratio, and glaucomatous optic neuropathy* are part of the everyday language of the clinician caring for patients with glaucoma. The optic nerve changes are the most dramatic clinical findings in the examination of an eye with glaucoma, but they are the secondary result of damage to and, ultimately, the death of retinal ganglion cells. Why don’t practitioners describe glaucoma in terms of the primary changes in the retinal nerve fiber layer (RNFL)?

I believe the answer is that it is very difficult to observe clinically the subtle changes that represent nerve fiber layer loss. The typical glaucomatous RNFL changes are a loss of the normal reflection from this layer and a change in the appearance of the striations. These observable changes are distributed over a relatively large area compared with the changes in the optic nerve. It is far more difficult, however, to appreciate the absence of the normal RNFL than it is to recognize the presence of glaucomatous abnormalities in the optic nerve.

Although a number of investigators have suggested that RNFL abnormalities may be the earliest detectable sign of glaucoma, an RNFL examination is not commonly performed at most clinics. The technique of observation at the slit-lamp biomicroscope with red-free light takes practice, and nerve fiber layer photography has proven impractical at all but a few major glaucoma centers. Nonetheless, the clinicians who want to advance the level of glaucoma care for their patients recognize that a practical method for RNFL examination and documentation would be valuable.

Several technologies can aid the clinician with RNFL examination. This article focuses on scanning laser polarimetry, the first computer-assisted imaging technique for this application.

**HISTORY**

Scanning laser polarimetry was developed at the University of California, San Diego, and introduced as a commercial instrument by Laser Diagnostic Technologies (San Diego, CA). This technology grew out of efforts to improve scanning laser ophthalmoscopy. An observation of unusual retinal patterns under certain optical conditions led to the hypothesis that the RNFL was a polarizing structure. It was already known that the thickness of polarizing structures such as fine lens coating or silicon microchips could be measured optically. A polarizing (or birefringent) structure shifts the polarized light in proportion to the thickness of the structure. The RNFL is birefringent; where it is thicker, it produces a greater shift in polarization. Measuring this shift provides an indication of thickness by means of a rotating, polarizing filter that detects the axis and magnitude of the shift or retardation.

The raw data from a scanning laser polarimeter are in arbitrary polarization-shift (retardation) units. A conversion factor was calculated based on the histologic measurement of some enucleated monkey eyes that had been imaged. The commercial instruments have reported results in microns based on this conversion.

The theory behind scanning laser polarimetry is very appealing, and it worked well in an experimental setting for enucleated eyes with the cornea and lens removed. The major challenge remaining was that the cornea and lens are also polarizing structures. Only by extracting the retinal signal from the total signal could one measure the RNFL thickness. Early efforts to correct each individual’s nonretinal signals were abandoned in the older scanning laser polarimeters, and an average correction based on known population values was applied.

The first commercial scanning laser polarimeter was the
Nerve Fiber Analyzer, followed by the Nerve Fiber Analyzer II and the GDx (all from Laser Diagnostic Technologies). Each generation improved on some of the recognized limitations of previous instruments, but early adopters remained frustrated with the technology, which seemed to work in some patients but not in others. In retrospect, that observation makes perfect sense. Because an average corneal polarization correction was applied, the instrument worked on average. If a patient’s nonretinal retardation were close to the population mean, the scanning laser polarimeter gave a valid reading. If the values were far from the mean, the device could not separate the signal from the noise, and the images were strange indeed. When a study of a group of patients was conducted, the average for the glaucoma patients differed from the average for the normals, but each group contained individuals in whom the imaging failed. Moreover, because investigators lacked the tools to recognize those individuals, the scanning laser polarimeter was of limited clinical utility.

In 2000, Greenfield et al published a study in which they measured the true polarization properties of the eyes of patients and illustrated the effects that the “outlier” corneas had on images obtained with a scanning laser polarimeter. It became clear that an individualized compensation technique had to be developed to make the scanning laser polarimeter valid in a broader population. One creative approach to this problem was based on the known anatomy of the normal retina. The RNFL in the macula is very thin and should contribute no signal to scanning laser polarimetry. If one measures the signal in the macula with no compensation, that signal should represent the nonretinal “noise” of the eye. If an “opposite” correction for the cornea is then applied for an eye, the macula’s signal should approach zero, and everything seen elsewhere in the retina should be predominantly the RNFL signal. This approach was validated by Weinreb et al and individualized compensation was introduced in 2003 as the GDx VCC (Variable Cornea Compensator; Laser Diagnostic Technologies). Finally, all of the fundamental issues had been addressed.

**PERFORMANCE**

**Diagnosing Glaucoma**

Ideally, an automated structural examination accomplishes two tasks: (1) the identification of abnormal (glaucomatous) eyes (Figure 1) and (2) the detection of progression in cases of established glaucoma. The first task depends on comparing an individual with the known normal population, an area in which nerve fiber layer examination may have an advantage over optic nerve examination. One appealing feature of an RNFL examination is that the RNFL should be far less variable than the optic nerve structure in the population. A normal optic nerve can be large or small with a correspondingly large or small cup. The scleral canal can be oblique with a tilted optic nerve head. The range of normal is large. This variability makes it difficult to use statistical means to distinguish between early glaucoma and a healthy but atypical nerve. The typical RNFL should have approximately 800,000 to 1,200,000 nerve fibers. Because there should be less variability among healthy individuals’

![Figure 1. Short-wavelength automated perimetry demonstrated an inferior arcuate defect in the patient’s right eye (A) and a similar, inferior step defect in his left eye (B). Scanning laser polarimetry yielded abnormal values in both of the patient’s eyes that corresponded to the defects observed with short-wavelength automated perimetry (C).](image-url)
RNFLs, it may be easier to use statistical means to identify an abnormal nerve fiber layer.

The GDx VCC has a normative database collected in a multicenter, collaborative fashion. Based on these values, the clinician may compare an individual patient with this known population and thereby identify regions of the RNFL exhibiting a lower-than-expected signal. Does this finding represent early glaucoma? As with all new diagnostic technologies attempting to achieve earlier diagnosis, the question is whether they have truly detected disease or produced a false positive. The only reliable way to determine the answer is with large, long-term, prospective studies. The reality is that such investigations probably will never be completed due to their expense and complexity as well as the time needed to achieve meaningful endpoints for a slow, chronic disease such as glaucoma.

A second option is to compare the new test with established tests in known glaucoma patients and normals; if they correlate well, it is strongly supportive of the new test’s validity. This year’s ARVO annual meeting included several reports supporting the validity of the Variable Cornea Compensator’s strategy. Zegers et al.6 studied 77 normal subjects and 156 patients with known glaucoma. The sensitivity and specificity of the GDx VCC were 89% and 96%, respectively; the device missed some of the glaucomatous eyes but was usually correct when it classified an eye as abnormal. Fingeret et al.7 studied 15 subjects with optic-cup asymmetry and 24 with symmetric, large cups. Although 6% of the eyes with asymmetric cups had abnormal GDx VCC scans, 47% of those with large symmetric cups were abnormal. It is not known whether these abnormal scans represent early diagnosis or false positives.

Detecting GlaucomatousProgression

The second task for an imaging device is detecting progression over time. This task may actually be easier than detecting abnormality, because the technology only needs to compare an individual eye to itself and look for significant change over time. There is currently no change software available for the GDx VCC. The recent implementation of individualized compensation means that long-term studies must be conducted to collect data in patients with progressive disease. Until those data are compiled, software can be implemented to look for statistical change. The basic principles are to perform multiple scans in an individual over a short time and calculate the variability at each region of the retina. If values on subsequent examinations are statistically significantly different in excess of known, short-term variability, they may represent change. This software approach is used in visual field testing and in other imaging technologies. At ARVO this year, my colleagues and I reported the short-term reproducibility of measurements with the GDx VCC in 52 eyes that were imaged repeatedly.8 The majority of parameters demonstrated a variability of 5% or less. The newest scanning laser polarimeter appears to deliver reproducible results.

Reading The Data

The GDx VCC device presents data in an approachable format. The results for both eyes are given on a single page. At the top of the column is a reflectance image from which some optic nerve detail can be ascertained. Below that is the retardance (polarization) image, which uses color-coding to show the areas of greatest and least signal. In the next image down, clusters of pixels that have a statistically significantly lower value than the normative database are color-coded. Calculated parameters and a nerve fiber index from a neural network are also provided. The nerve fiber index was a particularly efficient parameter for discriminating between normal and glaucoma in a study by Zegers et al.6

Conclusion

Scanning laser polarimetry has evolved tremendously over the last decade. Due to the changes in hardware, there are no long-term studies on the current GDx VCC, and its images still do not seem to represent the anatomy of some patients. Nevertheless, recent reports (mentioned earlier) suggest that the instrument is performing as expected. This technology can now assist the clinician in evaluating the RNFL in a large number of patients. Further software development should allow valid scans in an even greater number of patients, more reliable discrimination between normal and abnormal, and new tools for detecting statistically significant progression.

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