Structural Measurements for Monitoring Change in Glaucoma: Comparing Retinal Nerve Fiber Layer Thickness With Minimum Rim Width and Area

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Submitted: February 17, 2015

Accepted: September 27, 2015

Citation: Gardiner SK, Boey PY, Yang H, Fortune B, Burgoyne CF, Demirel S. Structural measurements for monitoring change in glaucoma: comparing retinal nerve fiber layer thickness with minimum rim width and area. *Invest Ophthalmol Vis Sci*. 2015;56:6886–6891. DOI:10.1167/iovs.15-16701

PURPOSE. Minimum rim width (MRW) and area (MRA) have been introduced as anatomically defensible measures of neuroretinal rim tissue observable using spectral-domain optical coherence tomography (SDOCT). They have been reported to change earlier than retinal nerve fiber layer thickness (RNFLT) in glaucoma. This study sought to determine which is better to distinguish subsequent change from variability, using the previously described longitudinal signal-to-noise ratio (LSNR).

METHODS. Data from 157 eyes of 157 participants with high-risk ocular hypertension or non-end-stage glaucoma (mean deviation [MD] from -22 to $+3$ dB) were used. Participants were tested approximately every 6 months for at least six visits. For each eye, MRW, MRA, and RNFLT were regressed linearly against time. Longitudinal signal-to-noise ratio for each eye was defined as the rate of change over time (signal) divided by the standard deviation of residuals from this trend (noise). These were compared between parameters using a Wilcoxon signed rank test.

RESULTS. The median LSNRs were -0.58y^{-1} for RNFLT (bootstrapped 95% confidence interval -0.69 to -0.48y^{-1}); -0.44y^{-1} (-0.59 to -0.32y^{-1}) for MRW; and -0.23y^{-1} (-0.32 to -0.08y^{-1}) for MRA. Longitudinal signal-to-noise ratios were significantly more negative for RNFLT than for MRW ($P = 0.025$) or for MRA ($P < 0.001$).

CONCLUSIONS. Retinal nerve fiber layer thickness measured by SDOCT had a better LSNR than MRW or MRA. Although MRW and MRA may be more sensitive for early detection of glaucomatous damage, these data suggest that RNFLT may be preferable for monitoring change.

Keywords: OCT, retinal nerve fiber layer thickness, neuroretinal rim measurement, progression, glaucoma

For many years, it has been appreciated that both structural and functional changes occur in glaucomatous eyes. Cupping/rim thinning can be observed using ophthalmoscopy and is predictive of loss of visual field sensitivity.¹ In recent years, quantitative structural measurements of tissues such as the neuroretinal rim area of the optic nerve head (ONH) have become possible, provided by confocal scanning laser tomography and now optical coherence tomography (OCT). In particular, the retinal nerve fiber layer thickness (RNFLT) measured by OCT has become a standard measurement, and has been shown to be closely related to the number of retinal ganglion cell axons remaining.²

Use of spectral-domain OCT (SDOCT) has for the first time permitted reliable visualization and quantification of clinically relevant subsurface structures such as Bruch's membrane opening (BMO). Using this technique, it has been noted that the structure referred to as the disc margin when the ONH is viewed with an ophthalmoscope or in stereophotographs does not correspond to a consistent anatomical structure. The edge of the rim tissue can correspond to any one of several different structures at different regions around the ONH, and/or in

different eyes.³ Similarly, the inner border of the rim tissue (traditionally referred to as the border of the optic "cup") is difficult to define without a fixed, reliable axial reference plane since it is often "sloped" in depth. These problems have led to interest in a more anatomically correct measure of neuroretinal rim tissue. It has been suggested that "rim" should be defined as a ribbon-like surface whose width extends from BMO to the inner limiting membrane (ILM).⁴ The parameter minimum rim width (MRW) relative to BMO, also known as BMO-MRW, has been defined as the shortest distance between the BMO and the ILM within SDOCT scans, averaged around the disc.^{5,6} The radial scans can also be used to estimate the minimum rim area (MRA) through which the axons must pass.⁷ Minimum rim area attempts to adjust for the fact that MRW will be related to disc size and not just the number of axons. It has been shown that these new measures correlate better with function and with other structural measures than the previously used "horizontal" rim measurements.^{6,7}

Peripapillary RNFLT is a measurement of predominantly neural tissue (the retinal ganglion cell axon bundles), made adjacent to the optic disc, typically approximately 1.7 mm from

FIGURE 1. Examples of longitudinal series for minimum rim width (MRW) for two participants.

its center. For example, the circular scan used in this study is performed at a radius of 6° from the center of the optic disc as placed by the operator. By contrast, MRW is a measurement of the thickness of the neuroretinal rim tissue, and thus is contained within the optic disc. It has therefore been suggested that MRW may be more sensitive to conformational changes occurring within the ONH tissues such as the lamina cribrosa. It is possible that these aspects of glaucomatous ONH structural change occur separately from, and perhaps precede, retinal ganglion cell axon loss. In a nonhuman primate unilateral experimental glaucoma model, the onset of MRW change preceded the onset of RNFLT change.⁸ In a study comparing human eyes with open-angle glaucoma against healthy controls, for 95% specificity, the sensitivity of MRW was reported to be 81%, compared with 70% for RNFLT.⁶

While early detection of glaucomatous damage is clearly important, it is also important to be able to monitor eyes for subsequent change. To be useful for this task, the rate of change of a parameter must be sufficiently rapid to distinguish it from measurement noise. We have previously described the use of a longitudinal signal-to-noise ratio (LSNR) for this purpose.⁹ The principle is that the rate of change of a progressing eye should be a relatively large multiple of the variability. The aim of the LSNR technique is to determine how easy it is to distinguish change from variability, and a highly negative LSNR indicates that the eye is changing too rapidly for the change to be plausibly caused by variability alone. This formulation enables comparisons between parameters measured on different scales, and indeed using different instruments, if the same eyes and same testing dates are used for both. In this study, we use the LSNR to compare the abilities of MRW, MRA, and RNFLT to distinguish longitudinal change from variability.

METHODS

Data for this study were taken from participants in the Portland Progression Project, a prospective longitudinal study of the course and risk factors for glaucomatous progression. Individuals with non-end-stage glaucoma or with ocular hypertension plus risk factors for glaucoma undergo testing with a variety of methods, including automated perimetry and SDOCT, approximately every 6 months. Participants were tested at a tertiary glaucoma clinic at Devers Eye Institute. Inclusion criteria were a diagnosis of primary open-angle glaucoma and/or likelihood of developing glaucomatous damage (e.g., high-risk ocular hypertension), as determined by each participant's clinician. Exclusion criteria at entry included an inability to perform reliable visual field testing, best-corrected visual acuity worse than 20/40, or other conditions or medications that may affect

the visual field. If both eyes were eligible, one was chosen for delineation and analysis, using the eye with the better-quality series of SDOCT scans if there was a substantial difference, or choosing an eye at random otherwise. All protocols were approved and monitored by the Legacy Health Institutional Review Board, and adhered to the Health Insurance Portability and Accountability Act of 1996 and the tenets of the Declaration of Helsinki. All participants provided written informed consent once all of the risks and benefits of participation were explained to them.

Spectral-domain OCT was performed with a Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). Peripapillary RNFLT represents the mean distance between the ILM and the posterior boundary of the retinal nerve fiber layer, along a 6° radius circle scan centered on the ONH. The instrument's automated delineations were manually adjusted by experienced technicians when necessary to address obvious delineation errors. Minimum rim width was calculated as the minimum distance from BMO to the ILM, averaged over 24 hand-delineated radial scans.⁷ Minimum rim area was calculated by minimizing the area of a trapezium between BMO and the ILM within sectors centered on each radial scan, as previously described.⁷ Follow-up scans were colocalized to the baseline reference scan for an eye by matching key vessel features in the infrared images (transverse alignment). Automated white-on-white perimetry was performed using a Humphrey Field Analyzer (HFA II; Carl Zeiss Meditec, Dublin, CA, USA), with a size III stimulus, Swedish Interactive Threshold Algorithm (SITA) standard algorithm, and 24-2 test pattern. Sensitivities were summarized using mean deviation (MD).

For each structural parameter (RNFLT, MRW, or MRA), the LSNR was calculated for individual eyes that had a series of at least six SDOCT scans of high quality. Ordinary least-squares linear regression was performed to derive the trend over time. The slope of this line was used as the measure of "signal." Note that while least-squares regression does not take into account autocorrelation in a longitudinal sequence, this affects only the standard error and *P* value of the slope estimate; it does not affect the validity of the estimated rate of change. The residuals from this trend line were calculated, and their standard deviation was used as the measure of "noise." The LSNR for a given eye is defined as the slope of the trend line divided by the standard deviation of residuals from that line.

Figure 1 illustrates the premise behind the LSNR technique. The rates of change differ markedly. Participant A has a rate of change of $-1.90 \mu\text{m/y}$, whereas participant B has a rate of change of $-0.93 \mu\text{m/y}$. However, visual inspection of these series suggests that the evidence that MRW is decreasing is very similar for both eyes. While participant B has a slower rate of change, the series is also less variable. Correspondingly, the

TABLE. Summary of the Characteristics of the Cohort

	Mean	95% Range	Full Range
Series length, no. of tests	8.6	6 to 10	6 to 11
Age, y	69	51 to 87	44 to 91
Most recent MD, dB	−1.2	−9.5 to 2.3	−21.9 to 3.0
Rate of change of MD, dB/y	−0.10	−0.89 to 0.32	−2.16 to 1.12
Most recent MRW, μm	247	121 to 359	87 to 390
Rate of change of MRW, $\mu\text{m}/\text{y}$	−1.6	−9.4 to 3.3	−24.5 to 9.9
Most recent MRA, mm^2	1.04	0.54 to 1.48	0.37 to 1.66
Rate of change of MRA, mm^2/y	−0.005	−0.035 to 0.020	−0.077 to 0.037
Most recent RNFLT, μm	84	43 to 110	38 to 117
Rate of change of RNFLT, $\mu\text{m}/\text{y}$	−1.0	−3.2 to 1.0	−8.6 to 2.1

Columns show the mean of the sample, and the ranges covering 95% and 100% of the data. Rates of change were calculated by linear regression over the entire series for an eye. Rates of change for structural parameters are not age corrected. Only eyes with at least six reliable tests were included. MD from automated perimetry; MRW from optical coherence tomography radial scans; MRA from optical coherence tomography radial scans; RNFLT from optical coherence tomography peripapillary circle scans.

LSNRs are very similar: -0.56y^{-1} for participant A and -0.55y^{-1} for participant B.

Longitudinal signal-to-noise ratios can be compared between parameters using a nonparametric Wilcoxon signed rank test. Note that ordinary least-squares regression aims to minimize residuals, and therefore the true variability is greater than the noise measure used here. However, this is the same for all of the parameters and so should not affect comparisons between them. The median LSNR for each parameter was calculated, together with a 95% confidence interval generated from 10,000 bootstrapped resamplings.

RESULTS

Data were obtained from one eye each of 157 participants with series of at least six SDOCT scans of sufficient quality.

Characteristics of the cohort are summarized in the Table. The median rate of change of MD (from linear regression) was -0.048 dB/y , similar to reports from a clinical population of patients with glaucoma.¹⁰

The median LSNR was -0.58y^{-1} for RNFLT (with a 95% confidence interval -0.69 to -0.48 from bootstrapping). The median LSNR for MRW was -0.44y^{-1} (with 95% confidence interval -0.59 to -0.32) and for MRA was -0.23y^{-1} (-0.32 to -0.08). Using a paired analysis for the same eyes, LSNRs were significantly more negative for RNFLT than for MRW ($P = 0.025$, Wilcoxon signed rank test) or for MRA ($P < 0.001$). This indicates that RNFLT was able to detect longitudinal change better than either MRW or MRA, since the rate of change was a more negative multiple of the variability.

Residuals from the single-eye trend lines are plotted against the parameter values in Supplementary Figure S1. There is no evidence of heteroscedasticity either for MRW ($P = 0.211$ from a Breusch-Pagan test¹¹) or for RNFLT ($P = 0.127$). However, MRA appeared to be more variable at higher values ($P = 0.001$), resulting in reduced LSNRs in eyes with more rim. Supplementary Figure S2 shows plots of noise against signal for the three structural measures.

Figure 2 shows histograms of the LSNRs for each of the three structural parameters. Data with an LSNR below -0.5y^{-1} are highlighted in gray, indicating the proportion of eyes for which that parameter was deteriorating more rapidly than half a standard deviation per year. This comprised 86 eyes (54%) for RNFLT, 76 eyes (48%) for MRW, and 49 eyes (31%) for MRA. Of these, 35 eyes for RNFLT, 35 eyes for MRW, and 16 eyes for MRA had an LSNR below -1y^{-1} . Figure 3 compares the LSNRs between the structural parameters. In both cases, the majority of points lie above the line of equality, showing that the LSNR is lower for RNFLT than for MRW or MRA.

DISCUSSION

In this study we found a better (more negative) LSNR for RNFLT than for MRW or MRA. This indicates that when using SDOCT to assess glaucomatous structural change, RNFLT may be more useful, since true change related to axon loss should be easier to distinguish from noise. Detecting glaucomatous damage and monitoring glaucomatous change are essentially different tasks. Therefore there is no reason to assume that the same methods, parameters, or analyses will be optimal for both. Our results do not contradict findings that MRW may show a difference from healthy, “normal” structural characteristics sooner than RNFLT in early glaucoma,^{6,8} since our LSNR

FIGURE 2. Histograms of the longitudinal signal-to-noise ratios for each eye in the study (in units of y^{-1}) for three structural parameters, defined as the rate of change over time divided by the standard deviation of residuals from that trend line. Bars shaded in gray highlight those eyes deteriorating more rapidly than 0.5 standard deviations per year. OCT, optical coherence tomography; RNFL, retinal nerve fiber layer.

FIGURE 3. Comparison of longitudinal signal-to-noise ratios (LSNR) between structural parameters. RNFL, retinal nerve fiber layer. Points above the line of equality (*solid black line*) have a more negative (i.e., better) LSNR for RNFL thickness than for the other parameter.

method is designed to look at a later stage of the disease once both structures may be changing.

When comparing different measures for monitoring change, a common framework must be used to remove the effect of differences in units. Efficient detection and monitoring of change require that the amount of change be as large as possible compared with the variability. This is what the LSNR aims to assess. The signal that we wish to detect is the rate of change over time, hence the need for longitudinal series. The noise that we wish to minimize could be assessed by the repeatability of results over a short period, but it is just as valid to use the repeatability over a longer period so long as any change in that period has been accounted for, and this is achieved by using residuals from the trend line. An ideal measure would have a rate of change of sufficient magnitude in a progressing eye that the change is clearly distinguishable from variability, and this will be reflected in a greater magnitude LSNR.⁹ The LSNR technique cannot assess the accuracy of measures, since it is based on the rate of change and so will not detect systematic errors. It also is not designed to distinguish between measures with different resolutions, although a higher resolution may be associated with lower variability. However, while LSNR does not definitively determine the optimal measure for assessing change, a greater-magnitude LSNR is certainly a desirable property of such a measure.

One plausible explanation for the results is that MRW and MRA are affected not only by axon loss but also by conformational changes in response to short- or long-term IOP fluctuations. It is known that a higher IOP during an SDOCT scan can influence ONH structural conformation in a manner that manifests as posterior displacement of the ONH surface and thinning of both MRW and MRA.^{12–14} This may cause stretching and/or compression of axons at the location where they enter the ONH, mechanical effects that remain incompletely characterized or understood but that could reasonably be hypothesized to be deleterious. Glaucomatous changes in ONH structural conformation are further thought to include active remodeling of connective tissues.^{15,16} By comparison, peripapillary RNFLT is less affected by the IOP at the time of scanning or the earliest stages of glaucomatous ONH conformational changes.^{8,17–20} This hypothesized mechanism would result in early, detectable changes in MRW and MRA due to these conformational changes, before detectable

axon loss, but also more variability due to IOP in later measurements (if made without manometric IOP control),⁸ which would hamper change detection. Since RNFLT should be less affected by these issues, it may be less sensitive to the earliest changes but also more repeatable, making it easier to distinguish changes due to axon loss. The possibility of these kinds of conformational changes is still under investigation, and that work may help explain our findings in the near future.

While RNFLT demonstrated significantly more negative LSNRs than the other measures, the median LSNRs for all parameters are quite small due to the predominance of stable eyes that exist in any well-managed clinical group. The cohort used in this study consisted primarily of participants with very early glaucomatous damage, or ocular hypertension. Indeed, 75 eyes (48%) had MD at their last visit > 0 dB, although this is likely due to the fact that many individuals had been participating in the study for several years and were exceptionally well practiced visual field takers.²¹ In addition, greater technician attentiveness in a detail-oriented clinical study²² can result in measured visual field sensitivities that are above the population-wide normative levels. In this cohort, the average rate of functional change was very similar to that recently reported from a typical glaucoma clinical population.¹⁰ Our cohort cannot be used to determine which parameter is best for detection of the earliest glaucomatous change, because many of the participants would already have passed that stage by the time they entered the study and SDOCT testing commenced. Studies in human eyes are almost always affected by the inclusion criteria; results showing that one type of change preceded another may say more about the clinical characteristics that caused recruitment into the study than they do about the actual course of the disease. In a nonhuman primate model of the disease, which does not have this constraint, and in which SDOCT imaging is performed under manometric IOP control, it was reported that MRW changed prior to RNFLT.^{8,17} Neuroretinal rim measurements may also be more variable in humans since they are not measured at a fixed IOP.

It is possible that the relative abilities of the different measurements to assess change would vary with disease stage. The RNFLT reaches a floor, which it cannot go below even if all axons are lost, typically at 30 to 50 μm but varying between eyes.^{23,24} Minimum rim width and MRA may also reach a floor that is above zero, but this has not yet been determined. It has

been suggested that function becomes the best way to evaluate glaucomatous damage late in the disease process, once RNFLT approaches this floor²⁵; although it should be noted that perimetric sensitivity also reaches the floor of its reliable stimulus range at a similar stage of disease.²⁶ If a measure reaches its floor for a given eye, this will reduce the observed magnitude of its rate of change over time. This will tend to make the LSNR less negative (i.e., not as severe). A larger dynamic range would be considered a desirable property of a clinical measure, and so a measure with a greater magnitude of LSNR would still be preferred.

A further caveat with our results is that they implicitly assume that longitudinal change is linear over time. If change is actually nonlinear, this will tend to increase the residuals around a linear trend line and hence bring the LSNR closer to zero. There is evidence that nonlinear change may be the case for MD,²⁷ although over short sequences of six visual fields the nonlinearity has less effect.^{27,28} This nonlinear mode of change when sensitivities are expressed on a dB scale is equivalent to linear change when sensitivities are expressed on a linear 1/Lambert scale. Given that the structure-function relation also appears linear when using linear-scaled sensitivities,^{29–31} it is reasonable to expect structural change to be approximately linear. This, however, is not definitively known, and indeed it has been suggested that the relation between MRW and RNFLT may also be nonlinear.²⁰ Over the relatively short intervals evaluated in this study (six tests would cover approximately 2.5 years), a linear approximation of change is reasonable and would be difficult to distinguish from a nonlinear trend.

The LSNRs of MRW and MRA may improve with further refinements to their algorithms. Minimum rim area in particular is currently calculated as the sum of the areas of sectoral trapeziums, optimized for each radial scan individually.⁷ A continuous ribbon between BMO and the ILM could be defined, which would have a smaller area than the current MRA,⁴ and may be more closely related to the number of axons present. Such a refinement is computationally challenging, but could result in MRA outperforming MRW, as would be expected due to the confounding influence of disc size on MRW.

The LSNR technique used here assesses the ability to distinguish longitudinal change from variability. The premise is that a parameter with more negative LSNR will be more useful for detecting disease progression. It is, however, also important to assess the ability of different measures to distinguish damage from variability, as in event analyses aiming to determine whether an eye is normal. This task cannot be achieved using this longitudinal dataset but requires a test-retest dataset obtained from multiple visits over a short span of time, and data collection for such an analysis is ongoing.

In summary, this study suggests that RNFLT provides a more robust way to monitor glaucomatous structural changes over time than MRW or MRA. While changes in the neuroretinal rim have been reported to occur earlier in the glaucomatous disease process than changes to the nerve fiber layer, the lower variability of RNFLT may make it easier to subsequently distinguish true progression from conformational change and/or noise. The LSNR used in this study does not tell us which measure is best for detecting or staging glaucoma, and is not the only test of suitability of a measure for longitudinal analyses. However, the lower LSNR achieved with RNFLT suggests that it may be better than the other measures for assessing change. Clinically, measuring multiple parameters within the ONH, RNFL, and macula may maximize early detection of damage without compromising the ability to use the same or a different combination of measurements to determine whether changes are occurring.

Acknowledgments

Supported by National Institutes of Health Grants R01-EY19674 (SD) and R01-EY021281 (CFB); unrestricted research support from The Legacy Good Samaritan Foundation, Portland, Oregon (SKG, CFB, BF, SD); Heidelberg Engineering (CFB); Alcon Research Institute (CFB); and Sears Medical Trust (CFB). The sponsors/funding organizations had no role in the design or conduct of this research.

Disclosure: **S.K. Gardiner**, Carl Zeiss Meditec (C); **P.Y. Boey**, None; **H. Yang**, None; **B. Fortune**, None; **C.F. Burgoyne**, Heidelberg Engineering (F, R), Reichert (F); **S. Demirel**, None

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