Detecting Glaucoma With Visual Fields Derived From Frequency-Domain Optical Coherence Tomography

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PURPOSE. To compare the assessment of glaucomatous damage based on visual fields (VFs) derived from frequency-domain optical coherence tomography (OCT) to actual VFs obtained from static automated perimetry.

METHODS. A total of 84 eyes from 84 glaucoma patients or suspects and 128 eyes from 128 healthy subjects were included. The retinal ganglion cell (RGC) and retinal nerve fiber layer (RNFL) thicknesses measured with macular and disc RNFL cube scans were combined and decomposed into 48 principal components (PCs). For each eye, an OCT to VF transformation map was built using multiple linear regression (MLR) and the OCT and VF data from the other eyes. Using this transformation map, the combined 24-2- and 10-2-derived VF for this eye was then obtained.

RESULTS. With 98.0% specificity, the sensitivity of the derived VF reached 78.0% for all hemifields, whereas 74.4% of the actual VF hemifields were classified as abnormal. The agreement between the derived and the actual VFs was 82.2%. For each VF location, the derived VF values were linearly related to the actual values.

CONCLUSIONS. The derived VF based on the OCT data appears as sensitive as the actual VF for detecting glaucomatous damage. Because the derived and actual VFs should have largely independent sources of variability, the combination of the two should provide a more powerful diagnostic tool.

Keywords: OCT, visual field, glaucoma

Until recently, glaucomatous damage and its progression were diagnosed primarily based on visual fields (VFs), typically obtained with static automated perimetry (SAP) and fundus photos of the optic disc. Although SAP has the disadvantage of being time consuming and difficult for some patients to perform reliably, it is a direct measure of visual function and provides a topographic representation. In fact, decades of experience and sophisticated analytical tools have established SAP as the gold standard for glaucoma diagnosis. More recently, with the improvements in optical coherence tomography (OCT) technology, scans of the optic disc and macular regions have become routine adjuncts to VFs and fundus photos. However, to realize the full diagnostic power of OCT, we need ways to compare and integrate VF and OCT information.

Comparing OCT and VF results presents a challenge. First, healthy individuals show considerable variability in retinal structure, including overall thickness and the distribution of nerve fiber bundles around the optic disc.^{1–4} Second, the retinal ganglion cells in the central macula are displaced relative to their correspondent VF locations.^{5,6} Third, it is impossible to associate a local thinning in the retinal nerve fiber layer (RNFL) of a peripapillary disc scan to a specific local visual defect, because local RNFL damage is associated with a pattern or an arcuate of VF loss. Finally, OCT provides different scans (e.g., macular and disc cube scans), each of which contains multiple retinal layers. Combining these highly correlated pieces of information poses a statistical challenge.

An approach based on multiple linear regression (MLR) provides a way for addressing these problems. The math behind the MLR technique is straightforward and has been used for transforming disc RNFL thickness that was obtained from scanning laser polarimetry (SLP) image into a VF format used by SAP.⁷ In our approach, the VF sensitivity in linear units is derived from the concatenation of three OCT images: macular retinal ganglion cell plus inner plexiform layer (RGC+IPL), macular RNFL, and disc RNFL thickness. The OCT to VF transformation map used to generate the derived VF of a test eye is obtained using MLR and the OCT and VF data from the other eyes in the study. Using this approach, Zhang et al.⁸ showed that there was good qualitative agreement between the derived and actual VFs when 10-2 VFs were used and the derived VFs were obtained from RGC+IPL and RNFL thicknesses of macular OCT scans. However, they were unable to compare the specificity and sensitivity of the actual and derived VFs due to the lack of an age-similar control group.

In the present study, the MLR approach was extended. First, the RNFL thickness information from disc cube scans was used, as well as the macular RGC+IPL and RNFL information previously employed. Second, while previously the derived VFs were compared only to 10-2 VFs, here we compared them to the combined 10-2 and 24-2 VFs, as well as to the 24-2 VFs alone. Finally, with an age-similar control group, the sensitivity and specificity of the derived VFs were assessed.

MATERIALS AND METHODS

Subjects

This study included 84 eyes from 84 patients (58.6 ± 14.4 years) and 128 eyes from 128 healthy control subjects (38.8 ± 14.2 years) supplied by Topcon, Inc. (Oakland, NJ). The inclusion criteria for control included a correction of between +3.0 diopters (D) and -6.0 D; IOP less than 21 mm Hg; axial length between 22 and 26 mm; and a normal clinical examination. Exclusion criteria included a history of ocular disease or a family history of glaucoma. The patients had glaucomatous optic neuropathy (GON) with (glaucoma) or without (suspects) abnormal VFs. GON was defined by consensus of two glaucoma experts looking at optic disc stereophotographs based on the presence of focal or diffuse neuroretinal rim thinning, focal or diffuse nerve fiber layer defects, vertical cup-to-disc ratio greater than 0.6, or vertical cup/disc intereye asymmetry greater than or equal to 0.2 not due to optic disc size asymmetry. A subset of 50 of the healthy controls served as an age-similar group (53.9 ± 7.6 years) for the specificity measures. All subjects had OCT scans. In addition, the patients had 24-2 and 10-2 VFs and the age-similar controls had 24-2 VFs. When multiple VF tests were available, the one closest in time to the OCT tests was used. To be included, the VFs had to be reliable (indices <30%). When both eyes had the required data, the eye with better data quality was chosen, prior to the data analysis. For the patient eyes, the mean and SD of the mean deviations (MDs) were -5.0 ± 5.8 and -5.5 ± 6.4 dB for 24-2 and 10-2 VFs, respectively, and the mean and SD of the pattern SDs (PSDs) were 4.8 ± 5.5 and 3.5 ± 4.3 dB for 24-2 and 10-2 VFs, respectively. For the 24-2 VFs of the control eyes, the means and SDs were -0.4 ± 1.2 dB and 1.5 ± 0.4 for MD and PSD, respectively.

Written informed consent was obtained from all participants. Procedures followed the tenets of the Declaration of Helsinki and the protocol was approved by the institutional review boards of Columbia University and New York Eye and Ear Infirmary.

RGC+IPL and RNFL Thicknesses and VF Measures

The thicknesses of the RGC+IPL and the RNFL were measured using frequency-domain OCT (3D-OCT 2000/1000; Topcon, Inc.) and 6×6 -mm macular and disc cube scans. The layers of retinal structures were segmented with an automated segmentation algorithm⁹ without manual correction. Individual scans were inspected to remove those with gross acquisition/algorithm failures, where a segmentation line was drawn at least one layer away from the correct layer, or the center of the structure was 0.37 mm away from the center of the 6-mm image. The thicknesses of the RGC+IPL and RNFL were determined from these segmented borders. The centers of both scans were determined manually. The OCT images had a resolution of 512×128 , but this was reduced to 64×64 to decrease the memory demand for computation. The OCT images were further trimmed into 58×58 to remove the edges because some scans were not perfectly centered and thus data at the edges were missing. The data of disc scans within a radius of 1.17 mm from the center of the optic disc were masked and excluded from the analysis due to variable disc sizes limiting the availability of data in this region. Figure 1 shows the average thickness of RNFL and RGC+IPL for 128 normal eyes in a form similar to Figure 2 in Hood et al.¹⁰

For the MLR analysis, the total deviation values, obtained from the 24-2 and 10-2 VFs, were combined into a single composite VF with 120 points. If the local value of a patient's

FIGURE 1. For 128 normal eyes, the average thickness for both the RNFL and RGC layers of the macula scans and the RNFL of disc scans. The radius of the mask that covers the center of optic disc was 1.17 mm. The color range for OCT is 5% to 95% percentile for the normal eyes is the same for all subsequent figures.

VF was greater than 0 dB,¹¹ it was set to 0 dB. The only VF data available for the control eyes were the 24-2 VFs for the age-similar control group. The actual 24-2 VF values of all other control eyes, as well as the 10-2 VF values for all control eyes, were set to 0 dB. For all eyes, the data from left eyes were flipped to coincide with those of a right eye.

The MLR Method

The MLR method is identical to the method we previously reported⁸ with three exceptions. First, we added RNFL thickness from the disc cube scans to the RGC+IPL and RNFL macular thickness measures previously used and, second, we used a composite VF with 120 locations (24-2 and 10-2) instead of only the 68 locations of the 10-2 VF. Third, the dimensions of OCT data were reduced to 48 principal components (PCs) instead of the 24 PCs in the previous article so as to represent more complex disc RNFL.

This approach has two basic assumptions. First, the combined data of three thickness measures, macular RGC+IPL and RNFL and disc RNFL, can be represented with a linear combination of 48 PCs (i.e., 48 basic patterns). Those PCs cover both the anatomical variability among subjects and the variation of glaucomatous defects. In other words, OCT data of any normal or glaucomatous eye can be associated with 48 values, referred to as the scores of the PCs. The OCT data are the summation of 48 PCs, each scaled by the corresponding score. Second, we assume that the VF values are linearly related to the scores of these PCs. In other words, the visual function is assumed to be linearly related to OCT thickness.

Leave-One-Out Approach

The OCT data for each test eye were transformed into the derived VF using the OCT to VF transformation matrix obtained with the data from the other eyes.

VF Analysis

The probability values for the actual VF were provided by SAP (Humphrey Field Analyzer; Carl Zeiss Meditec, Inc., Dublin, CA). The upper and lower hemifields were separately categorized as either normal or abnormal. A hemifield was considered abnormal if at least three contiguous points reach a 5% significance level with at least one of them reaching a 1% significance level. This rule is referred to as the 551 criterion. For the derived VF, the z score was calculated with the mean and the SD obtained for each location and for the age-similar control eyes. The P value of a derived VF was then calculated from the z score assuming a normal distribution.

FIGURE 2. The OCT and VF data for the patient eyes where both the derived and the actual VFs were normal. For this and all the subsequent figures, a *gray dot* in VF indicates a normal ($P \geq 0.05$) point, whereas *yellow* ($P < 0.05$), *light red* ($P < 0.01$), and *red* ($P < 0.005$) indicate an abnormal point. OCT data is in field view. All eyes are presented as right eyes.

RESULTS

Sample results are displayed in Figures 2 to 7 in field view. For each of the three eyes in each figure, the upper row of the left column shows the raw OCT thickness plots for the macular

RNFL (left panel), macular RGC+HPL (middle), and disc RNFL (right) scans, and the lower row the reconstructed plots based on 48 PCs. Note that, in most cases, the reconstructed OCT based on the 48 PCs of the other eyes fairly represented the raw OCT thickness data of the test eye despite the extensive

FIGURE 3. Patient eyes with both abnormal derived and actual hemifield VFs. An abnormal hemifield is marked with an *enclosing square*.

FIGURE 4. Patient eyes with both normal derived, but abnormal actual, hemifield VFs.

variability in glaucomatous damage and variation in the distributions of RGC+IPL and RNFL thicknesses. The middle and right columns of Figures 2 to 7 show the derived and actual VFs. Each point of the combined 10-2 and 24-2 VFs is shown as an individual dot, with the probability coded by color. A gray dot indicates a normal test point ($P \geq 0.05$),

whereas yellow ($P < 0.05$), light red ($P < 0.01$), and red ($P < 0.005$) indicate abnormal points.

In general, there is reasonable agreement between the actual VFs and the VFs derived from the OCT data. To obtain a quantitative measure, we called a VF hemifield, actual or derived, abnormal if it met the 551 criterion. The abnormal

FIGURE 5. Patient eyes with both abnormal derived, but normal actual, hemifield VFs.

FIGURE 6. Control eyes that show either abnormal derived VF or abnormal actual VF

hemifields are indicated by gray rectangles. For the combined 24-2 and 10-2 VFs (Table 1), the derived and actual VFs were both classified as normal in 14.9% of the hemifields and as abnormal in 67.3%, for an overall agreement of 82.2%. Figure 2 shows the results of three eyes for which all six hemifields are classified as normal on both the derived and actual VFs. Figure 3 shows five hemifields (marked with square borders) for which both were abnormal. For the 30 (17.8%) hemifields showing disparate results in Table 1, 12 (7.1%) of them were normal on the derived VF and abnormal on the actual VF. These hemifields are shown in Figure 4. On the other hand, 18 (10.7%) of the hemifields were normal on the actual VF, but abnormal on the derived VF. Figure 5 shows four examples. For the combined 10-2 and 24-2 VFs, the sensitivity of the derived VF was 78.0% as compared to 74.4% for the actual VFs. As only 1 of the 50 patients was classified as abnormal, the specificity of the derived VF was taken as 98%. Note that, due to limited sample size, the “specificity” can be affected by a few incidents and thus is only an approximation. A much larger healthy population is needed for a more accurate estimation of the specificity. Figure 6 shows the only control eye associated with an abnormal derived VF and two of four control eyes

associated with abnormal actual VFs. None of the control eyes showed abnormality for both the derived and actual VF.

Often only 24-2 VFs are obtained in the clinic. Table 2 shows the results of the analysis with only the 24-2 data. The outcome was similar, although as expected the sensitivity values were slightly lower than those of the combined VFs. In particular, the overall agreement was 78.5% and the sensitivity/specificity values were 72.0%/98.0% and 68.5%/92.0% for the derived and actual VFs, respectively. Thus, with a higher specificity, the sensitivity of the derived VF was slightly higher than that of the actual VF.

Figures 7 and 8 show the scatter plots of actual versus derived VF values for each test location of the 10-2 VF and 24-2 VF, respectively. A simple linear regression was performed between the individual derived and actual VFs to evaluate the agreement between the two measures. Overall, the median R^2 was 0.34 (Fig. 7) and 0.24 (Fig. 8). Although these are modest correlations, the following should be kept in mind. First, the R^2 values were calculated on the individual points, not the binned data (open circles), which show less variability and a clear linear trend. Second, given the large variability inherent in actual VF measures, we should not expect high correlations, even if the underlying agreement was perfect. Third, the

TABLE 1. Number (%) of 168 Hemifields Classified as Normal or Abnormal, for Both the Actual and Derived Combined 10-2 and 24-2 Total Deviation VFs

Combined 10-2 and 24-2 Total Deviation, Agreement = 82.2%	Actual VF (Specificity Not Available)		
	Normal	Abnormal	Total
Derived VF specificity = 98%			
Normal	25 (14.9)	12 (7.1)	37 (22.0)
Abnormal	18 (10.7)	113 (67.3)	131 (78.0)
Total	43 (25.6)	125 (74.4)	168 (100.0)

The specificity of the actual VF is not available because the actual 10-2 VFs for age-similar control eyes were not available. Specificity is 98% because abnormality is found in only 1 of the 50 upper fields.

FIGURE 7. Scatter plots showing the actual VF (x-axis) versus the derived VF (y-axis) for the patient eyes and for the 68 locations of the 10-2 VF. VF sensitivities are presented in linear values. The axes for each box ranges from 0 to 1.0 (−30 dB to 0 dB loss). Each circle is the mean of a 10-eye bin, where the vertical line represents the range of data. The number in each panel is the R^2 value. A red outline indicates the R^2 value for the MLR was smaller than 0.2. A green line indicates the fifth percentile of normal eyes. In other words, any derived VF below it will be significant at P value of 5%.

lowest correlations are, in general, associated with the most restricted range of VF losses. In particular, the locations within the red boxes have an R^2 less than 0.20 and a median VF loss of −8.7 dB as compared with the rest of the locations, which have a median loss of −14.2 dB.

DISCUSSION

The OCT data of patients can be reasonably well reconstructed with 48 PCs (e.g., left column of Figs. 2–7). In other words, the anatomical variability across subjects and the variability in the region of glaucomatous damage across patients can be

expressed with a limited number of basic patterns. However, the reconstruction will never be perfect. (See, e.g., the data in the top row of Fig. 4, which is one of poorest reconstructions in our data set.) First, the OCT data reconstructed with the 48 PCs (e.g., Fig. 4, top row) may lack some detail because details of high spatial frequency are represented in higher-order PCs, which are not included. In addition, some details of structural damage in a particular eye may not be well represented in the data of the other 83 patient eyes. Therefore, a sufficient amount of data that include most patterns of glaucomatous defects is the key to the success of this approach.

MLR has been previously applied by Zhu et al.⁷ to transform SLP disc RNFL data into VFs formatted as 24-2 grayscale plots.

TABLE 2. Number (%) of 168 Hemifields Classified as Normal or Abnormal for Both the Actual and Derived 24-2 Total Deviation

24-2 Total Deviation Agreement = 78.5%	Actual VF (Specificity 92%)		
	Normal	Abnormal	Total
Derived VF specificity = 98%			
Normal	32 (19.0)	15 (8.9)	47 (28.0)
Abnormal	21 (12.5)	100 (59.5%)	121 (72.0)
Total	53 (31.5%)	115 (68.5)	168 (100.0)

They found that the MLR approach did not work as well as a neural network algorithm they devised. However, in their case, there were extra challenges for achieving a high-quality transformation with MLR. In particular, the information from the disc scan was essentially the thickness of RNFL in a ring. Thus, they used 1-dimensional data to predict the 2-dimensional VF data. Second, around the optic disc, there are many

blood vessels that generate high-intensity and high spatial frequency signals. It is possible that many of the higher-order PCs of the 228 PCs used in their study represented blood vessels and that MLR might have worked better with considerably fewer PCs so that high spatial frequency signals not representing the RNFL profile were removed. In contrast, we used a richer frequency-domain OCT dataset, which included 2-dimensional RNFL and RGC+IPL thicknesses in the macula and RNFL thickness at the disc, 48 PCs, and assumed that retinal structural measures could be linearly transformed into visual function.

Consistent with this linear assumption, the VF scatter plots (Figs. 7, 8) of actual VFs versus derived VFs show a linear trend. However, notice that there is a substantial nonzero intercept on the y-axis (derived VF) and that the derived VFs have values less than 1.0 when the actual VFs of the patients are normal, similar to previous findings.⁷ In other words, while the relationship is linear, it is not proportional. Based on our linear assumption, this result is not surprising. The derived VF essentially

FIGURE 8. Scatter plots showing the actual VF versus the derived VF values as in Figure 7, but for the 52 locations of the 24-2 VF.

represents the relative thickness of the retinal structure. The value of 1.0 for the derived VF indicates normal thickness and the value of zero indicates zero thickness. Because there are structures that are relatively unaffected by glaucoma, such as glial cells and blood vessels, it follows that even after total loss of visual function, there will be some OCT thickness remaining, as has been observed in patients with extreme visual loss, originally shown by Sihota et al.¹² (see Ref. 11 for other references). There is another reason for the nonzero y-intercept. Due to the structural variability among eyes, the locations of RGCs and retinal nerve fibers corresponding to a given VF location are not identical in different eyes.^{4,13–15} The OCT to VF transformation matrix represents not only the transformation between the two measures, but also the distribution of structural variability among subjects. The structural variability can be manifested in two ways in the linear transformation approach. First, a derived VF value will not be zero until all the related retinal structures become zero. Second, a derived VF value will not be 1.0 until all the related retinal structures are normal. On the other hand, normal eyes with significantly different distributions in the RNFL, such as those shown in the second and third rows in Figure 6, will be predicted as normal.

Overall, our study showed reasonably good agreement (82.2%) between the derived VF and the actual VF in terms of normal and abnormal hemifields. Note that we did not expect perfect agreement given the independent sources of variability in both tests. If there were perfect agreement, there would be little value-added in combining information from both tests. In fact, the derived VF and actual VF disagree in 18.6% for the combined 10-2 and 24-2 format. In some cases the derived VF was a false negative (e.g., Fig. 4, top). In other cases, the actual VF was clearly a false negative (e.g., Fig. 5, top). The latter is more common. Given the derived VF is reasonably sensitive and specific and the OCT data are often acquired more quickly and easily, it is possible that OCT scans can play an important role for some screening purposes. In general, it has been shown that more diagnostic information can be gleaned by combining the structural and function information.^{16,17} Our technique of expressing the OCT data as a VF makes combining the data much easier, for instance, by a simple point-to-point multiplication of the *P* values, since the OCT to VF transformation map already has many of the corrections built in, such as ganglion cell displacement, that would be needed otherwise to compare the data in an optimal manner.

Our study is not without its limitations. First, the patients we included had abnormal-appearing optic discs, while their VFs could have appeared normal. Therefore, our measure of sensitivity of the derived VFs might be greater than one would expect for a general glaucoma population. Second, as mentioned above, a larger sample of healthy controls is needed for a more accurate determination of specificity. Finally, a larger sample of patterns of glaucomatous defects should further improve the agreement between the derived and actual OCT maps.

CONCLUSION

Our data show that the derived VF calculated from the OCT data is topographically consistent with the actual VF and as sensitive as the actual VF. This suggests that OCT can be used to supplement the SAP VF measure for the diagnosis of glaucoma, and perhaps with suitable modification for detecting progression as well.

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