A comparison of retinal nerve fiber layer (RNFL) thickness obtained with frequency and time domain optical coherence tomography (OCT)

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Abstract
To diagnose glaucoma and other diseases of the retinal ganglion cell/optic nerve, the thickness of the retinal nerve fiber layer (RNFL) is routinely measured with optical coherence tomography. Until recently, these OCT measurements were made almost exclusively with a time domain OCT (tdOCT) machine from a single manufacturer. Recently, a number of OCT machines, based upon an improved frequency domain OCT technology (fdOCT), have appeared. We compared measurements made using a new fdOCT machine to those from the older tdOCT machine. The results were comparable. More importantly, we learned that the key factor determining whether results from different machines will be comparable is the algorithm used to segment RNFL thickness, not the type of OCT.

1. Introduction
Glaucoma damages retinal ganglion cells and their axons. These axons travel in the retinal nerve fiber layer (RNFL) and become part of the optic nerve as they enter the optic disc. Optical coherence tomography allows for the fast and noninvasive measurement of RNFL thickness. (See recent reviews [1–3].) In the relatively short time since it was first introduced [4,5], OCT RNFL thickness, measured around the optic disc, has become an important clinical tool for diagnosing and following glaucomatous damage.

Numerous clinics and laboratories have been following patients with glaucoma and other disease of the retinal ganglion cell/optic nerve with OCT machines manufactured largely by a single source. Until recently, these machines employed a version of the OCT technology referred to as time domain OCT (tdOCT). To measure RNFL thickness with tdOCT, a circular scan is made around the optic disc and an algorithm determines the portion of the scanned image attributable to the RNFL. More recently, a number of manufacturers have employed a faster OCT technology referred to as Fourier domain or frequency domain OCT (fdOCT). Because it is faster, multiple line scans can be made across the optic disc in the same time that it takes to make a single circle scan with the tdOCT.

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As fdOCT machines replace tdOCT machines, the question naturally arises about the comparability of the measurements. To compare the new measures with the old tdOCT records, one can derive RNFL thicknesses around a circle located in the same location as the circle scan of the tdOCT. Here we compare the standard tdOCT circular scans to comparable information obtained from fdOCT measurements of the optic disc. While this project started as a simple comparison of one new fdOCT machine to the typically used tdOCT machine, we learned an important principle that is applicable to future comparisons among OCT machines. Namely, discrepancies between RNFL measures from different machines can result from differences in the way the machines’ algorithms determine the RNFL thickness.

2. Methods

2.1 Subjects

Forty-four eyes of 30 glaucoma patients, 39 eyes of 33 glaucoma suspects, and 27 eyes of 18 controls were scanned with tdOCT and fdOCT technology. The glaucoma patients had abnormal discs and abnormal visual fields (Humphrey Field Analyzer, program 24-2 SITA, Carl Zeiss Meditec, Inc. Dublin, CA) as defined by an abnormal glaucoma hemifield test (GHT) or an abnormal mean deviation (MD) or an abnormal pattern standard deviation (PSD). The patients were on average 62 ± 13 years of age and had average MDs of −6.85 ± 6.7 dB. The glaucoma suspects, on average 56 ± 16 years, had abnormal discs, but normal visual fields. The controls had normal disc exams and were 41 ± 16 years. The controls were not tested with visual fields and were thus “presumed healthy” based upon history and normal disc exam.

Written informed consent was obtained from all subjects. Procedures followed the tenets of the Declaration of Helsinki, and the protocol was approved by the Committees of the Institutional Board of Research of Columbia University and New York Eye and Ear Infirmary.

2.2 OCT measurements

For the tdOCT measurements, the thickness of the peripapillary RNFL was measured with the Stratus OCT (Carl Zeiss Meditec, Inc, Dublin, CA, USA) using version 4.0 software and the Fast Scan protocol. During a single recording with this protocol, three scans are made around a ring 3.4 mm in diameter (Fig. 1A). The software supplied by the machine segments the RNFL as shown by the white lines in Fig. 1B and determines the RNFL thickness as the distance between these white lines. The RNFL thickness profile, with a spatial resolution of 256 points, is the machine-averaged value for the 3 scans. Only scans with a signal greater than 5 were used. The 256-point RNFL thickness profiles were exported for further analysis. The profile for the scan in Fig. 1B is shown in Fig. 1C.

For the fdOCT measurements, eyes were imaged with the 3DOCT-1000 (Topcon, Inc., Paramus, NJ, USA). This scan consists of 128 line scans [B-scans] 6 mm in width, covering a vertical distance of 6 mm. The machine’s software determined the RNFL thickness within the 6 mm by 6 mm region, the green square in Fig. 1D. The RNFL thickness is displayed as a 3D map in Fig. 1E. The interpolated image for a circle 3.4 mm in diameter (dashed black circle in Fig. 1E) is shown in Fig. 1F. The 256-point RNFL thickness profiles were exported for further analysis. The bold red curve in Fig. 1G shows the RNFL thickness profile for the image in Fig. 1F. The dotted, red curve was obtained by spatially averaging the RNFL profile using a Gaussian convolution function with an averaging window of 16.
2.3 Analysis

Using the 256-point fdOCT and tdOCT RNFL thickness profiles, the overall average RNFL thickness was computed, as well as the average thickness for 4 quadrants.

3. Results

Figure 2A shows a comparison of average fdOCT and tdOCT RNFL thicknesses. Each point represents the values for a single eye. There is a strong correlation between the two measures ($r=0.93$; 0.91 if only one eye per individual is included). The dashed line has a slope of 1.0. If there were no measurement error and if the two machines produced identical results, all points would fall on this line. In fact, the points fall close to the line. Figure 2B shows a Bland-Altman plot of the same results. Here the difference between the tdOCT and fdOCT measures for each eye is plotted against the average of these two measures. The mean of the differences here is $-0.7 \, \mu m$ (solid bold horizontal line), close to zero (dashed line), suggesting that there was no systematic error between the tdOCT and fdOCT measures.

To test for small differences between the two measures, only one eye of each individual was used. (If a subject had data for two eyes, only the right eye was used.) As seen in Table 1, the two machines produced similar results. The overall average thickness differed by less than 2 $\mu m$ for all 3 groups; these small differences were not significant.

Figure 3 shows the Bland-Altman plots for the quadrants (see inset upper right). Again the systematic difference between the two measures is relatively small. The means of the differences (solid bold lines) are close to zero (dashed lines), 3.9 (superior), $-2.4$ (inferior), $-5.8$ (nasal), and 1.5 $\mu m$ (temporal).

While the tdOCT and fdOCT showed good agreement, notice in Fig. 2A that there was a tendency for the points to fall above the dashed line for smaller average thicknesses and below for greater average thicknesses. This same trend can be seen in Figs. 2B and 3. The best fitting (red) lines have positive slopes suggesting that there is a slight tendency for fdOCT values to be greater than tdOCT values when RNFL thickness is relatively thin and the reverse occurs when RNFL is relatively thick.

The outliers are also consistent with this tendency. The dotted horizontal lines in Fig. 2B and Fig. 3 are $\pm 1.96\times$SD confidence interval (CI) (i.e. 95% of the points should fall within these lines). Note that the points falling above these lines tend to have an average thickness greater than 80 $\mu m$, while those falling below tend to have an average thickness less than 100 $\mu m$.

An examination of the outliers revealed that this tendency is due to differences in the algorithms used in the tdOCT and fdOCT machines. Figures 4 and 5 illustrate this point by examining the underlying data contributing to the two points circled in Figs. 2B and 3A,C. Figure 4 shows the scans for the outlier falling above the 95% CI in the figures, with panel A containing the RNFL profiles for the tdOCT scan (blue), fdOCT scan (red) and the difference between the tdOCT and fdOCT scans (green). The vertical dashed red lines indicate two locations at which the difference between the tdOCT and fdOCT RNFL thickness (green curve) was the largest. It is clear from the scan that these regions contain major blood vessels, as indicated by the shadows in Fig. 4C (red arrow). The fdOCT algorithm is sensitive to local changes in signal and thus does not include the BV shadow in Fig. 4C. The tdOCT algorithm, on the other hand, is less sensitive to local changes and largely includes the BV thickness.
For the point falling below the CI, and circled in Figs. 2B and 3A,C, the reverse is the case. Notice in Fig. 5 that the BVs are included between the white lines in the fdOCT scan (Fig. 5C), but not in the tdOCT scan (Fig. 5B). Because the tdOCT algorithm is not sensitive to local changes, it includes little of the BVs in regions where most of the axons are lost (Fig. 5B). Under these same conditions, the fdOCT algorithm incorporates most of the BV thickness (Fig. 5C). Consequently, the RNFL thickness is greater for the fdOCT scan under these circumstances.

6. Conclusion

The RNFL thickness data obtained with the fdOCT (3DOCT-1000) machine can be compared to data previously collected with the widely used Stratus tdOCT. The absolute values produced by the two machines were not significantly different. In fact, the agreement is remarkably good given that different machines, different technologies, and different algorithms were used. This conclusion applies, of course, to only one type of fdOCT machine.

However, there is a more general finding here that is relevant to future comparisons of OCT machines from different manufacturers. In particular, the algorithm used to segment RNFL thickness will influence the measurements, especially as it interacts with BVs. Algorithms that have very little spatial averaging/filtering, such as the one used in the 3DOCT-1000, will tend to include BVs in patients with extreme RNFL loss when there are only local BV signals present. Under these conditions, the algorithms that have a lot of spatial averaging/filtering, such as the one in the Stratus tdOCT, will often exclude part of the local BV signal, as it is averaged with neighboring regions with little or no signal. On the other hand, in individuals with relatively thick RNFL layers, it is more likely that the shadows produced by BVs will be included by the algorithm with more spatial averaging/filtering. Given that BVs can make substantial contribution to RNFL thickness in patients [6,7] and contribute to the variability in RNFL profiles among controls [7,8], it is important to understand how segmentation algorithms treat local signals due to BVs.

With the introduction of different fdOCT machines, various strategies for segmenting retinal layers are being developed. For example, at recent meetings, various research groups and commercial companies have presented the results of different algorithms for segmenting the RNFL. The nature of these algorithms, in general, and how they treat BVs, in particular, will need to be closely analyzed if the results from different machines are to be compared.

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Fig. 1.
Sample data from a glaucoma suspect. A. Location of tdOCT circle scan. B. tdOCT single circle scan. Distance between white lines is RNFL thickness. C. RNFL thickness as a function of the distance around the optic disc for the scan in panel B. D. Fundus view showing location of the fdOCT line scans. E. 3-D representation of RNFL thickness. F. A reconstructed fdOCT scan for circle (dashed curve in panel E). Distance between white lines is RNFL thickness. G. RNFL thickness (thin red line) as a function of the distance around the optic disc for the scan in panel F. Bold red line is RNFL thickness for profile in panel F; thin dotted line is the same data after spatial smoothing. See View 1 for fdOCT data and View 2 for tdOCT data; additional datasets are also available for fdOCT (Case003) and tdOCT (Case004).
Fig. 2.
A. Scatter plot of fdOCT overall average RNFL thickness versus tdOCT overall average RNFL thickness. Each point represents the results for a single eye, controls (green), suspects (blue) and patients with glaucoma (red). Dashed line has a slope of 1.0 and is locus of equal fdOCT and tdOCT values. B. Bland-Altman plot showing the difference between overall RNFL thickness on fdOCT and tdOCT versus the average of the fdOCT and tdOCT values. Dashed line has a slope of 0 and is locus of equal fdOCT and tdOCT values. Bold solid line is the mean of the average fdOCT and tdOCT values.
Fig. 3.
Bland-Altman plots showing the difference between RNFL thickness on fdOCT and tdOCT versus the average of the fdOCT and tdOCT values for the superior (panel A), nasal (panel B), inferior (panel C) and temporal (panel D) quadrant. Each point represents the results for a single eye, controls (green), suspects (blue) and patients with glaucoma (red). Dashed line has a slope of 0 and is locus of equal fdOCT and tdOCT values. Bold solid line is the mean of the average fdOCT and tdOCT values.
Fig. 4.
A. tdOCT (blue) and fdOCT (red) RNFL profiles for a glaucoma suspect. The green curve is the difference between the tdOCT and fdOCT profiles. B. tdOCT scan for the blue curve in panel A. C. fdOCT scan for the red curve in panel A. Dashed red lines indicate the two places where the two scans differ the most.
Fig. 5.
A. tdOCT (blue) and fdOCT (red) RNFL profiles for a patient with glaucoma. The green curve is the difference between the tdOCT and fdOCT profiles. B. tdOCT scan for the blue curve in panel A. C. fdOCT scan for the red curve in panel A. Dashed red lines indicate the two places where the two scans differ the most.
Table 1

Overall Average and Standard Deviation of RNFL Thickness (μm)

|               | Controls 18 eyes | Suspects 33 eyes | Glaucoma 32 eyes |
|---------------|------------------|------------------|------------------|
| tdOCT         | 99.5 ± 12.3      | 88.3 ± 12.6      | 76.8 ± 18.8      |
| fdOCT         | 97.5 ± 11.7      | 88.5 ± 10.9      | 77.9 ± 16.4      |