BACKGROUND AND OBJECTIVE: To compare rates of abnormal peripapillary retinal nerve fiber layer (RNFL) and macular ganglion cell layer scans acquired with Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA) and RTVue-100 (Optovue Inc., Fremont, CA) in healthy myopic eyes.

PATIENTS AND METHODS: Forty-one non-glaucomatous myopic eyes (41 individuals) were scanned with Cirrus to measure RNFL and ganglion cell-inner plexiform layer (GCIPL) and with RTVue to measure peripapillary RNFL and ganglion cell complex (GCC) thicknesses. Rates of abnormal scans were calculated and compared between devices. Inter-device agreement in falsely classifying scans as abnormal was also assessed.

RESULTS: The rate of abnormal average and four-quadrant RNFL was 4.8% to 7.3% on Cirrus and 2.4% to 9.7% on RTVue (P > .05). The overall rate of abnormal scans was 19.2% on Cirrus and 29.3% on RTVue (P = .3). Rates of abnormal Cirrus average and segmental GCIPL (12.2% to 17%) were similar to those of RTVue average and segmental GCC (9.7% to 14.6%) (P > .05). The overall rate of abnormal GCIPL (36.6%) was higher than that of GCC (14.6%) (P = .023). The inter-device agreement was poor for average RNFL (κ = -0.09), very good for average ganglion cell (κ = 0.81), and fair for overall RNFL (κ = 0.35) and overall ganglion cell (κ = 0.34).

CONCLUSION: The high rates of abnormal RNFL and ganglion cell layer scans on both devices call for caution, particularly when attempting to diagnose glaucoma in myopic eyes using these devices. The RNFL and ganglion cell layer analyses may not be interchangeable on either of these devices. These two devices are not interchangeable for classifying healthy myopic eyes based on RNFL or ganglion cell layer analysis.

From the Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Florida. Drs. Mwanza and Budenz are currently affiliated with the Department of Ophthalmology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. Dr. Aref is currently affiliated with the Illinois Eye & Ear Infirmary, University of Illinois at Chicago School of Medicine, Chicago, Illinois.

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Address correspondence to Donald L. Budenz, MD, MPH, Department of Ophthalmology, UNC-Chapel Hill, 130 Mason Farm Road, 5151 Bioinformatics Bldg., CB# 7040, Chapel Hill, NC 27599. E-mail: donald_budenz@med.unc.edu
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Rates of Abnormal Retinal Nerve Fiber Layer and Ganglion Cell Layer OCT Scans in Healthy Myopic Eyes: Cirrus Versus RTVue

Jean-Claude Mwanza, MD, MPH, PhD; Fouad E. Sayyad, MD; Ahmad A. Aref, MD; Donald L. Budenz, MD, MPH
INTRODUCTION

Major population-based studies have found a significant association between myopia and glaucoma. A recent review based on a meta-analysis of data from 11 population-based studies concluded that both low and high myopia increase the risk of developing open-angle glaucoma. Millions of individuals are diagnosed as having glaucoma worldwide each year. However, the risk of falsely classifying a normal individual as glaucomatous or a glaucomatous individual as normal may be high, particularly in early stages of the disease. Falsely diagnosing a truly normal individual as having glaucoma, with potential subsequent lifelong treatment, may have tremendous psychological, economic, and physical consequences. It is also well established that glaucomatous cupping is difficult to assess in myopic discs due to shallow cup, thin pre-laminar tissue, oblique implantation of the optic nerve resulting in tilted disc, and areas of peripapillary atrophy. In addition, non-glaucomatous myopic individuals may exhibit visual field defects similar to those seen in glaucomatous individuals.

Following recent advances in ocular imaging, optical coherence tomography (OCT) has developed rapidly to become an important clinical diagnostic and monitoring tool for glaucoma, mainly through quantitative analysis of peripapillary retinal nerve fiber layer (RNFL) thickness. In addition, studies are available to indicate that analysis of ganglion cell complex (GCC) and ganglion cell-inner plexiform layer (GCIPL) can successfully discriminate normal individuals and individuals with glaucoma. There is also indication that a substantial proportion of non-glaucomatous myopic eyes have thinner RNFL and GCC, and their thicknesses are falsely classified as outside normal limits on OCT. The current study was designed to compare the rate of abnormal peripapillary RNFL and macular ganglion cell scans obtained with two different spectral-domain OCT devices in healthy myopic eyes. The study was also designed to determine the agreement between devices and between peripapillary RNFL and macular ganglion cell scans in classifying individuals as abnormal.

PATIENTS AND METHODS

Patients

This prospective study was conducted on non-glaucomatous myopic volunteers aged 18 years and older recruited among University of Miami medical students, ophthalmology and optometry trainees, and employees. After individuals provided written informed consent to participate in the study, they underwent a screening eye examination that included visual acuity, automated refraction, slit-lamp examination, intraocular pressure (IOP) measurement, ophthalmoscopy, and visual field testing using the screening mode of frequency-doubling technology (software version 4.00.0 Welch Allyn Humphrey Systems; Carl Zeiss Meditec, Inc., Dublin, CA).

Individuals were excluded for the following reasons: best-corrected visual acuity worse than 20/40, contraindication to dilation or intolerance to topical anesthetics; IOP 22 mm Hg or greater, history of raised IOP, or any type of glaucoma in either eye, history of intraocular surgery in the study eye (except cataract or refractive surgery performed more than 1 year prior to enrollment), cup-to-disc area ratio interocular asymmetry 0.2 or greater, evidence or history of non-glaucomatous neuropathy or other optic nerve abnormalities in either eye, or retinal diseases including diabetic retinopathy, macular edema, or other vitreoretinal disease. Abnormal frequency-doubling technology test results, defined as one or more locations identified as abnormal at a P value of .05 or less at the same location(s) on repeated testing, was also an exclusion criterion.

OCT Instrumentation and Rates of Abnormal Scans

Following the screening eye examination, individuals underwent OCT peripapillary and macular scanning sequentially with Cirrus HD-OCT (Carl Zeiss Meditec, Inc.) and RTVue-100 (Optovue Inc., Fremont, CA). Only one eye randomly selected was scanned per individual. Six scans including three peripapillary scans centered on the optic disc were obtained with Cirrus OCT (Optic Disc 200 × 200 axial protocol) and with RTVue (Optic Nerve Head protocol). In addition, the same number of macular scans centered on the fovea was acquired using the Macular Cube 200 × 200 cube protocol for Cirrus OCT and GCC protocol for RTVue. Macular scans obtained with Cirrus OCT were processed with the ganglion cell analysis algorithm, which was a pre-release version of software version 6.0.

Only good quality images, defined by a signal strength of 6 or greater for Cirrus OCT and a signal strength index of 30 or greater for RTVue were used for
analysis. For peripapillary RNFL, the overall average and quadrant thicknesses were used in the analysis. For macular ganglion cell analysis, the overall average and hemispheric (superior and inferior) GCIPL for Cirrus OCT and GCC for RTVue were considered. In addition, the minimum GCIPL was analyzed for Cirrus OCT and compared with focal loss volume measured with RTVue.

To determine the frequency of abnormal scans, the average and quadrant significance maps for RNFL and the average and hemispheric maps for GCIPL for each participant were examined. Any yellow or red color on any of the maps was considered abnormal. An individual was considered positive when at least two of the three scans consistently showed a thickness value lower than the given percentile of the instrument intrinsic normative database it was compared to, specifically, less than 5% indicated in yellow or less than 1% level in red.

**Statistical Analysis**

All analyses were performed using SPSS version 19.0 (SPSS, Inc., Chicago, IL). The actual percent agreement, without the adjustment for agreement that would have occurred by chance, was calculated as follows using only the actual observations: % agreement = (number of agreements / number of cases compared) × 100%. The statistical significance of the difference between rates of abnormal scans was calculated using the chi-square test. *P* values of less than .05 were considered significant. The degree of agreement between instruments in classifying individuals as normal or abnormal was assessed with kappa (κ) statistic. The classification proposed by Altman was used to determine the degree of agreement between instruments and between peripapillary and macular scans: poor (κ < 0.2), fair (κ = 0.21 to 0.40), moderate (κ = 0.41 to 0.60), good (κ = 0.61 to 0.80), and very good (κ = 0.81 to 1.00).

**RESULTS**

**Demographic and Ocular Characteristics**

Forty-one non-glaucomatous myopic eyes of 41 individuals were included in the study. Mean age was 31.7 ± 8.3 years (range: 24 to 64 years), axial length was 25.2 ± 1.2 mm (range: 23.1 to 28.4 mm), spherical equivalent was -4.6 ± 1.9 diopters (range: -2.0 to -10.0 diopters), and IOP was 13.4 ± 2.2 mm Hg (range: 9 to 17 mm Hg). The mean signal strength was 8.3 ± 1.1 (range: 7 to 9) for RNFL scans and 8.8 ± 0.9 (range: 8 to 10) for macular scans on Cirrus OCT; the mean signal strength index was 74.0 ± 8.6 (range: 55.4 to 89.8) for RNFL and 65.3 ± 10.8 (range: 48.5 to 83.9) for macular scans on RTVue.

The average and hemispheric ganglion cell thickness for both OCT devices are displayed in Table 1. All GCIPL measurements were significantly thinner than GCC measurements (all *P* < .001), but correlated well with each other (Pearson r = 0.84 to 0.87, all *P* < .001). Table 2 shows the proportions of individuals classified as having abnormal RNFL and ganglion cell thickness scans based on each parameter that was analyzed. For RNFL, the rate of abnormal scans was 4.8% on Cirrus OCT versus 9.7% on RTVue for average, and ranged from 4.8% to 7.3% on Cirrus OCT and from 2.4% to 9.7% on RTVue for quadrants. The rate of abnormal scans calculated based on the presence of any abnormal quadrant was comparable on the two instruments. The overall rate based on any abnormal parameter was 19.2% on Cirrus OCT and 29.3% on RTVue. The differences in rates of abnormal RNFL parameters between devices were all not statistically significant (all *P* > .05). The ganglion cell layer analysis showed that Cirrus OCT average, minimum, and hemispheric GCIPL were abnormal in 12.2% to 17% of the individuals, whereas the rate of abnormal scans ranged from 2.4% to 14.6% for RTVue average, focal loss vol-

### Table 1

**Comparison and Correlation of Average and Hemispheric Ganglion Cell-Inner Plexiform Layer (GCIPL) and Ganglion Cell Complex (GCC) Thickness**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GCIPL</th>
<th>GCC</th>
<th><em>P</em></th>
<th>Pearson r (<em>P</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>81.9 (6.1)</td>
<td>94.8 (7.4)</td>
<td>&lt; .001</td>
<td>0.86 (&lt; .001)</td>
</tr>
<tr>
<td>Superior hemisphere</td>
<td>82.4 (6.0)</td>
<td>94.7 (7.5)</td>
<td>&lt; .001</td>
<td>0.84 (&lt; .001)</td>
</tr>
<tr>
<td>Inferior hemisphere</td>
<td>81.5 (6.4)</td>
<td>94.9 (7.6)</td>
<td>&lt; .001</td>
<td>0.87 (&lt; .001)</td>
</tr>
</tbody>
</table>
volume, and hemispheric GCC, with no significant differences compared to Cirrus OCT GCIPL rates ($P = .09$ to 1). However, the ganglion cell analysis produced a higher overall abnormal rate on Cirrus OCT than on RTVue ($P = .023$).

The actual percent agreement between the two devices (not shown in Table 1), without the adjustment for agreement that would have occurred by chance, in classifying individuals as abnormal was 20% for average, 50% for superior quadrant, 12.5% for nasal quadrant, 0% for temporal and inferior quadrants, and 33.3% for any abnormal parameter based on RNFL analysis. For ganglion cell analysis, these values were 71.4% for average, 66.7% for superior hemisphere, 57.1% for inferior hemisphere, 62.5% for any hemisphere, 20% for minimum GCIP/ GCC focal loss volume, and 31.3% for any abnormal parameter. On both instruments, 33.3% of eyes with abnormal average ganglion cell layer thickness had abnormal average RNFL thickness. Kappa statistic for agreement between instruments was fair ($\kappa = 0.34$) for any abnormal ganglion cell

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cirrus OCT</th>
<th>RTVue</th>
<th>$P$</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNFL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>2 (4.8%)</td>
<td>4 (9.7%)</td>
<td>.39</td>
<td>-0.09</td>
</tr>
<tr>
<td>Temporal quadrant</td>
<td>2 (4.8%)</td>
<td>2 (2.4%)</td>
<td>1.00</td>
<td>0.47</td>
</tr>
<tr>
<td>Superior quadrant</td>
<td>2 (4.8%)</td>
<td>1 (2.4%)</td>
<td>.55</td>
<td>0.66</td>
</tr>
<tr>
<td>Nasal quadrant</td>
<td>3 (7.3%)</td>
<td>5 (9.7%)</td>
<td>.46</td>
<td>0.45</td>
</tr>
<tr>
<td>Inferior quadrant</td>
<td>2 (4.8%)</td>
<td>3 (7.3%)</td>
<td>.64</td>
<td>0.36</td>
</tr>
<tr>
<td>Any quadrant</td>
<td>7 (17.0%)</td>
<td>9 (21.9%)</td>
<td>.58</td>
<td>0.47</td>
</tr>
<tr>
<td>Overall</td>
<td>8 (19.2%)</td>
<td>12 (29.3%)</td>
<td>.30</td>
<td>0.35</td>
</tr>
<tr>
<td>Ganglion cell&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>6 (14.6%)</td>
<td>6 (14.6%)</td>
<td>1.00</td>
<td>0.81</td>
</tr>
<tr>
<td>Superior hemisphere</td>
<td>5 (12.2%)</td>
<td>5 (12.2%)</td>
<td>1.00</td>
<td>0.77</td>
</tr>
<tr>
<td>Inferior hemisphere</td>
<td>7 (17.0%)</td>
<td>4 (9.7%)</td>
<td>.33</td>
<td>0.69</td>
</tr>
<tr>
<td>Any hemisphere</td>
<td>7 (17.0%)</td>
<td>6 (14.6%)</td>
<td>.76</td>
<td>0.73</td>
</tr>
<tr>
<td>Minimum/focal loss volume&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5 (12.2%)</td>
<td>1 (2.4%)</td>
<td>.09</td>
<td>0.31</td>
</tr>
<tr>
<td>Overall</td>
<td>15 (36.6%)</td>
<td>6 (14.6%)</td>
<td>.023</td>
<td>0.34</td>
</tr>
</tbody>
</table>

RNFL = retinal nerve fiber layer; OCT = optical coherence tomography.
<sup>a</sup>Denotes ganglion cell-inner plexiform layer and ganglion cell complex for Cirrus OCT and RTVue, respectively.
<sup>b</sup>Measured with Cirrus OCT and RTVue, respectively.
Cirrus OCT is manufactured by Carl Zeiss Meditec, Inc., Dublin, CA, and RTVue is manufactured by Optovue Inc., Fremont, CA.

Figure 1. Venn diagrams comparing (A) the number of eyes with overall abnormal retinal nerve fiber layer scans on Cirrus OCT (Carl Zeiss Meditec, Inc., Dublin, CA) and RTVue (Optovue Inc., Fremont, CA) and (B) the number of eyes with overall abnormal ganglion cell-inner plexiform layer scans on Cirrus OCT and abnormal ganglion cell complex scans on RTVue.
parameter (Figure 1A) and for minimum GCIPL/GCC focal loss volume ($\kappa = 0.31$), good ($\kappa = 0.69$ to 0.77) for GCIPL/GCC hemispheres, and very good ($\kappa = 0.81$) for average thickness. The agreement between instruments on classifying individuals was poor for average RNFL ($\kappa = -0.09$), fair to moderate for quadrants ($\kappa = 0.36$ to 0.56), and fair for any abnormal RNFL parameter ($\kappa = 0.35$) (Figure 1B). Average RNFL and average ganglion cell analyses showed moderate agreement on Cirrus OCT ($\kappa = 0.46$) and fair agreement on RTVue ($\kappa = 0.32$). When the analysis was based on any abnormal parameter, the agreement between RNFL and ganglion cell scans was poor on both devices. Examples of agreement between RNFL and ganglion cell scans on both instruments are illustrated in Figure 2.

**DISCUSSION**

Technological advances in ocular imaging in recent years have led to the development of OCT, which provides the clinician with information that has been shown to improve the diagnostic performance for early diagnosis and assist in the management of diseases affecting the optic nerve, retina, and choroid. Consequently, OCT has been introduced successfully for routine assessment of glaucoma. In recent evaluations of the glaucoma diagnostic accuracy of OCT, sensitivity values of 78% to 92% for Cirrus OCT and 80% to 88% for RTVue with specificities of 77% to 95% and 90% to 98%, respectively, have been reported. However, information about rates of abnormal OCT in healthy myopic eyes and normal OCT in glaucomatous myopic eyes...
is largely lacking. We chose to focus on the rate of abnormal OCT RNFL and ganglion cell analysis in non-glaucomatous myopic eyes because they have thinner RNFL\textsuperscript{13,31-33} and ganglion cell layers\textsuperscript{34,32,34} and therefore may fall outside normal limits because current OCT normative databases do not take refractive error into account. Although sensitivity and specificity are the most commonly used measures of test performance, the rate of abnormal OCT results is important to know, particularly in healthy myopic individuals because of the likelihood of them being falsely classified as glaucomatous by clinical examination.\textsuperscript{12,35}

It is important to note that the current study is not about the subtle discordance that can commonly occur between glaucoma diagnostic devices used for assessing structural changes, which are in this case the thicknesses of the RNFL and ganglion cell layer. Our main concerns are rather substantial inter-device differences and equivocal or abnormal OCT results in glaucoma-free individuals using devices approved by the U.S. Food and Drug Administration. Although it can be argued that some discordance is acceptable in myopic individuals when different OCT devices are used, it is potentially problematic if a substantial proportion of otherwise normal myopic individuals is classified as having abnormal RNFL and ganglion cells scans by these devices, which could result in initiation of treatment inappropriately.

Although a few studies are available that have compared RNFL thickness between Cirrus OCT and RTVue, this is the first report to establish a comparison between GCIPL and GCC in both thickness and rates of abnormal scans in myopic individuals. As expected, average and hemispheric GCIPLs were significantly thinner compared with GCC measurements. This finding is understandable because, unlike the GCC algorithm, the Cirrus OCT ganglion cell analysis algorithm leaves the RNFL out to segment and measure only the GCIPL as previously described.\textsuperscript{23} The only available study that compared the ability of macular ganglion cells and peripapillary RNFL scans acquired with RTVue for glaucoma diagnosis in highly myopic eyes is by Kim et al.\textsuperscript{32} In that study, false-positive rates were not reported, but the data suggest that they ranged between 53.3% and 45.8% in highly myopic eyes and between 16.3% and 24.5% in non-highly myopic eyes for average, hemispheric, and focal loss volume of GCC. False-positive rates based on average RNFL thickness were 25% and 10.2% in highly and non-highly myopic eyes, respectively. Direct comparison of these rates with ours is difficult because we did not separate our study population into high and non-high myopic eyes.

Our results showed that approximately one in every five myopic individuals had a false-positive RNFL scan on Cirrus OCT. This rate is far lower than the 52% found on time-domain OCT by Rauscher et al.,\textsuperscript{13} Vernon et al.,\textsuperscript{20} Leung et al.,\textsuperscript{19} and Qiu et al.\textsuperscript{22} assessed the proportion of abnormal peripapillary RNFL scans in myopic eyes using time-domain OCT. None of those studies reported the overall proportion of abnormal RNFL, but a careful look at their results tends to suggest abnormal time-domain peripapillary RNFL scans in more than 40%, approximately 45%, and more than 20%, respectively. In addition, more than 20% of the individuals had abnormal RNFL on Cirrus OCT in the study by Qiu et al.\textsuperscript{22} Overall, results of the current study and those of previous studies indicate high rates of abnormal RNFL scans in healthy myopic eyes.

The lack of difference in rates of abnormal RNFL scans between Cirrus OCT and RTVue may be in line with earlier findings that the two devices have a similar ability to distinguish normal eyes and eyes with glaucoma using peripapillary RNFL,\textsuperscript{36} although RTVue yields thicker measurements than Cirrus OCT, as reported in the current study and elsewhere.\textsuperscript{37,38} It is important to emphasize that the high rate of abnormal results obtained with both instruments does not necessarily lessen the usefulness of OCT in myopic individuals. In addition, the overall lower rate of abnormal results based on ganglion cell analysis on RTVue compared to Cirrus OCT does not indicate with certainty that measurements obtained with RTVue in myopes are correct or that those obtained with Cirrus OCT are erroneous. Another important aspect to keep in mind is that although a high specificity is desirable because it influences the significance of a finding, a test with high specificity such as RTVue GCC may be prone to missing true glaucomatous change in comparison with a test that has a low specificity, such as Cirrus OCT GCIPL in this study. Overall, the findings call for caution when interpreting OCT results in this group of individuals based on both RNFL and ganglion cell layer thickness measurements.

One interesting observation in the current study is the level of agreement between Cirrus OCT and RTVue for classifying individuals as having abnor-
normal scans based on RNFL and ganglion cell analysis, and the agreement between RNFL and ganglion cell analysis on Cirrus OCT and RTVue. Because of the anatomical relationship between retinal ganglion cell bodies and their axons, one would expect a good agreement between RNFL and ganglion cell layer in classifying individuals. If we consider average thicknesses, the agreement was moderate on Cirrus OCT, suggesting that to some extent the performance of RNFL reflected that of GCIPL. In contrast, agreement between GCC and RNFL parameters in classification was poor with RTVue.

It is difficult to explain this discrepancy, but it is possible that combining RNFL and GCIPL the way that is done with RTVue, and assuming that the thickness of this complex represents just the ganglion cell layer, may account for the observed lack of agreement. Another factor that may have contributed to low agreement between macular ganglion cell and peripapillary RNFL analysis is that the former is only based on a sampling containing approximately 50% of the retinal ganglion cell population, whereas the latter results from all retinal ganglion cell axons as axons emanating from different parts of the retina converge onto the optic disc.

Interestingly, the two instruments agreed well in classifying individuals based on most parameters of macular ganglion cell analysis. This agreement likely reflects the similarity in diagnostic efficacy of ganglion cell analysis performed with these two devices, although further studies are needed to confirm or refute this assumption. The reason for this similarity may be that the RNFL in the macular region is thin and should not have a significant impact on the ganglion cell layer thickness measurement and diagnostic accuracy despite the difference in the shape and size of macular regions used to determine the thickness of GCIPL and GCC. In contrast, there was a lack of agreement based on RNFL analysis, which is probably related to differences in segmentation algorithms. We are not aware of any other study examining the agreement between Cirrus OCT and RTVue or other spectral-domain OCT devices in classifying RNFL and ganglion cell scans as positive based on RNFL or ganglion cell analysis.

Abnormal peripapillary RNFL and macular ganglion cell layer scans occur frequently on Cirrus OCT and RTVue in healthy myopic eyes. From a practical standpoint, clinicians should rely more on clinical judgment than on current imaging techniques. The RNFL and ganglion cell layer analyses may not be interchangeable on either of the two devices. Similarly, these two devices are not interchangeable for classifying healthy myopic eyes based on RNFL or ganglion cell layer analysis.

REFERENCES
