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Positional Independence of Optic Nerve Head and Retinal Nerve Fiber Layer Thickness Measurements with Spectral-Domain Optical Coherence Tomography

Kaweh Mansouri, **John H. K. Liu**, **Ali Tafreshi**, **Felipe A. Medeiros**, and **Robert N. Weinreb** From the Hamilton Glaucoma Center and Department of Ophthalmology, University of California, San Diego, La Jolla, California

> Primary open-angle glaucoma (POAG) is a chronic neurodegenerative disease characterized by progressive thinning of the retinal nerve fiber layer (RNFL) and of the neuroretinal rim within the optic nerve head (ONH) .¹ Assessment of the ONH and the RNFL plays an essential role in the diagnosis and follow-up of glaucomatous patients. However, the clinical examination of these structures is often difficult, qualitative, and subjective.² Several imaging technologies, such as optical coherence tomography (OCT), allow for quantitative measurements of ONH topography and RNFL thickness in a noninvasive and objective manner.³

> OCT technology has changed considerably in recent years with the incorporation of spectral-domain (SD) imaging that offers significant advantages over the time-domain (TD) OCT techniques.⁴ Several SD-OCT instruments have been commercialized in recent years. The working principles are similar for all these devices and involve a superluminescent diode scan that collects 3-dimensional images of the peripapillary region from which information about the RNFL thickness can be obtained. Despite differences in acquisition time and resolution, these instruments have been shown to have similar diagnostic abilities to detect glaucoma.⁵

> Until very recently, ophthalmic applications of OCT technology could be performed exclusively in the sitting position, limiting its use in non-compliant patients due to physical disabilities. The newly introduced iVue (Optovue Inc, Fremont, CA) is a portable SD-OCT device that enables imaging in different body positions. OCT imaging in the supine body position may induce new methodological errors that can influence measurements. IOP changes in the magnitude of 7 mmHg or greater, as a result of medical or surgical IOPlowering, have been shown to affect measurements of the RNFL and ONH using confocal

Corresponding author: Kaweh Mansouri, MD MPH, Hamilton Glaucoma Center, University of California, San Diego, Department of Ophthalmology, 9500 Gilman Drive, La Jolla, CA 92093-0946. Phone: +1 (858) 534-5334. Fax: +1 (858) 534-7014. kawehm@yahoo.com.

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scanning laser ophthalmoloscopy (CLSO). $6-8$ This has been explained by the effect of IOP reduction causing a significant reversal of ONH cupping, interpreted as an increase in rim area by the CLSO. In contrast, posture-induced changes in IOP are generally in the order of 4–5 mmHg in healthy subjects^{9, 10} and glaucoma patients^{11, 12} over a 24-hour period. Therefore, it is important to understand whether small to moderate postural IOP variations affect OCT readings of ONH and RNFL parameters dynamically when measured by sensitive instruments for assessing these changes over time. Currently, it is not known whether these IOP changes might affect OCT topographic measurements.

Before a new device can be widely accepted for use in clinical practice, its repeatability and diagnostic accuracy should be validated. Estimating instrument repeatability is essential for quantifying small changes detectable for identifying and monitoring glaucomatous progression. The current study seeks to evaluate the short-term repeatability and the correlation between supine and sitting measurements of ONH and RNFL parameters obtained with a portable OCT in healthy participants and glaucoma patients.

METHODS

Participants

Three groups of 10 individuals were included in this cross-sectional, observational study. Younger healthy subjects (age, 22.9 ± 2.6 years) (mean \pm standard deviation) and older healthy subjects (53.9 ± 5.0 years) were recruited from university employees and their families. A group of patients with POAG (61.3 \pm 11.9 years) was recruited from a university-based glaucoma clinic at the Shiley Eye Center, University of California San Diego. Exclusion criteria included myopia -5 diopters¹³ and presence of ocular disease other than glaucoma. Eyes were classified as glaucomatous if they had repeatable (2 consecutive) abnormal SAP test results on the 24-2 program of the Humphrey visual field analyzer (Carl Zeiss Meditec, Inc., Dublin, CA). An abnormal SAP result was defined as having a pattern standard deviation outside the 95% confidence limits or a glaucoma hemifield test result outside the reference range, regardless of the appearance of the optic disc. Healthy subjects had a normal visual field test (using Statpac II, Swedish interactive thresholding algorithm 24-2, Zeiss-Humphrey Field Analyzer, Carl Zeiss Meditec, Inc., Dublin, CA), an IOP 21 mmHg, and no clinical signs of glaucomatous optic neuropathy on dilated slit lamp fundus exmaination. Written informed consent was obtained from all subjects. The study adhered to the tenets of the Declaration of Helsinki, was compliant with HIPAA regulations, and was approved by the Institutional Review Board of the University of California, San Diego.

Optical Coherence Tomography

Images of the optic nerve and adjacent retina were obtained using a portable spectral-domain OCT (SD-OCT) system (iVue SD-OCT; Optovue Inc, Fremont, CA). The iVue SD-OCT uses a superluminescent diode scan with a center wavelength of 840 ± 10 nm to provide high-resolution images. The manufacturer's 3D Disk protocol was used to collect data. A 6 \times 6-mm raster scan centered on the optic disc and composed of 101 B scans each composed of 512 A-scans (acquisition time, 2.2 seconds). The resulting scan provides a 3D image of the optic disc and surrounding area. The analysis points are derived from a 3.45 mm diameter area. The iVue SD-OCT is delivered on a slit-lamp style base but can be mounted on multi-directional rolling floor stand (iStand, Optovue) for universal positioning of the device. The stand's articulating arm is designed to facilitate scanning in the supine and other positions. All SD-OCT scans were obtained through undilated pupils. Quality assurance checks were done and images that had RNFL segmentation algorithm failures, motion

artifacts, were poorly focused, were not centered, or had a scan score index (SSI) of less than 40 were excluded.

Two experienced examiners scanned all participants. Measurements of both eyes of each study participant were taken in the supine followed by the sitting position. Participants were instructed to lie flat on a bed looking up for 5 minutes. For this position, the scan head was attached to the arm of the iStand, facing downward and placed directly over the subject's eye. Five scans were taken of the right eye followed by the left eye. After having assumed the sitting position for 5 minutes, another set of 5 scans of each eye was taken in the same order using the iVue-table and mount.

Outcome measures were repeatability within the same body position and correlation between both body positions for 4 ONH parameters (optic disc area, cup area, rim area, and rim volume) and 3 RNFL parameters (overall average RNFL thickness, inferior, and superior). All RNFL values were sampled from a 3.45 mm diameter circle centered on the optic disc. The optic cup was defined automatically by the iVue software as the intersection points of the nerve head inner boundary and a parallel line that is 150 μm above the connecting line of the RPE tips. All other parameters were defined automatically by the iVue software.

Statistical Analysis

Paired t test, one-way analysis of variance (ANOVA) with Scheffé's test for multiple comparisons, and chi-square test were used to compare different measures between subject groups. Repeatability was defined as the variation of repeat measurements in the same body position. Intraclass correlation coefficients (ICC) were used to test repeatability of 5 measurements per eye in each body position. Concordance correlation coefficients (CCC) were calculated to test the strength of the relationship between body position and each of the ONH and RNFL parameters. CCCs are based on the differences between the observations made on the same subject in different positions and thus evaluate the agreement between two readings by measuring the variation from the 45° line through the origin.¹⁴ For this reason, CCC analysis was preferred to other reported statistical methods for evaluating correlation, such as intraclass correlation coefficients and linear regression.¹⁴ A correlation between 0.4 and 0.75 is considered fair to good, whereas higher correlations are qualified as excellent agreement.¹⁵ The agreement between measurements in the sitting and supine positions was further graphically evaluated using Bland-Altman plots and the difference in slopes was analyzed using Pitcairn's test of difference in variance.16 Finally, Pearson correlation coefficients were used to determine the association between image quality and ONH and RNFL measurements.

Based on a significance level of 5%, a type II error rate () of 10%, our study had an 82% power to detect a difference of 0.3 mm² between disc area (for a mean area of 1.5 mm² and a mean standard deviation of 0.4 mm²) and a 96% power to detect a difference of 10 μ m between the RNFL measurements obtained in each position (for a mean RNFL thickness of 100 μm and a mean standard deviation of 10 μm). The 10 μm difference was based on the minimum significant difference required to exceed the intramachine variability.17 All tests were two-tailed and a P-value less than 0.05 was considered statistically significant. All statistical analyses were performed with commercially available software (Stata version 10; StataCorp, College Station, TX).

RESULTS

This study included 60 eyes (40 healthy, 20 glaucomatous) from 30 individuals (20 healthy, 10 glaucomatous). Mean age was 22.9 ± 2.6 years (mean \pm standard deviation) for the

younger healthy subjects, 53.9 ± 5.0 years for the older healthy subjects and 61.3 ± 11.9 years for the glaucomatous patients. The older subjects had a similar age-range to the glaucoma patients ($P = 0.09$). Glaucomatous eyes had a mean IOP of 16.9 ± 3.8 mmHg under ocular hypotensive treatment and a mean visual field mean deviation (MD) of $-1.6 \pm$ 2.0 dB and a mean pattern standard deviation (PSD) of 4.0 ± 3.7 dB at the time of iVue SD-OCT examination compared to 15.3 ± 2.3 mmHg ($P = 0.09$), 0.6 ± 1.1 dB ($P < 0.001$), and 1.6 ± 0.4 dB ($P < 0.001$), respectively, in the older group. Table 1 demonstrates demographic characteristics of the study population. All participants in the older healthy group were female and the difference to the other two groups was statistically significant (P) < 0.001). There was no difference in ancestry between the groups. Five RNFL scans of five different eyes had to be excluded from the analysis because of motion artifacts despite adequate quality scores and valid ONH readings.

Variation of repeat measurements in the same body position

Tables 2 and 3 show the repeatability of iVue SD-OCT ONH and RNFL thickness measurements for each body position. The ICCs for ONH parameters ranged from 86% (rim volume) to 99% (cup area) for the younger healthy group, 77% (rim area) to 99% (cup area) for the older healthy group, and 73% (rim area) to 99% (cup volume) for the glaucoma group. The ICCs for RNFL thickness parameters ranged from 72% (inferior RNFL thickness) to 99% (superior RNFL thickness) for the younger healthy group, 72% (inferior RNFL thickness) to 97% (superior RNFL thickness) for the older healthy group, and 92% (inferior RNFL thickness) to 99% (overall RNFL thickness) for the glaucoma group.

Variation of measurements between the supine and sitting position

Table 4 shows the different ONH parameters of each group for the two body positions. Statistical comparison of mean values and standard deviations among groups did not show significant posture-related differences for any of the studied parameters. Table 6 shows concordance correlation coefficients (CCC) and their 95% limits of agreement for ONH measurements in healthy subjects and glaucoma patients. Overall, CCC values were high, ranging from 98% to 99% for all parameters. Table 5 shows the different RNFL thickness parameters of each group for the two body positions. The correlation between RNFL thickness measurements for supine vs. sitting positions was also very strong. Overall, CCC values varied from 96% (inferior RNFL thickness) to 99% (overall average RNFL thickness). (Table 7)

Bland-Altman plots were used to evaluate the agreement between supine and sitting measurements. Values for all three groups were combined to assess the agreement between different ranges of ONH parameters using Bland-Altman plots (Figure 1). The slopes calculated were similar for disc area (r = -0.12 ; P = 0.38), cup area (r = 0.12; P = 0.37), and rim volume (r = −0.11; P = 0.43) but not rim area (r = −0.34; P = 0.01), indicating that sitting measurements are similar to supine measurements, with the exception of rim area. Bland-Altman plots were also constructed for the average overall RNFL thickness and average inferior and superior RNFL thickness (Figure 2) for healthy and glaucomatous eyes combined. The slopes were similar in both body positions for overall RNFL thickness ($r =$ 0.09; $P = 0.50$), inferior RNFL thickness ($r = 0.17$; $P = 0.20$), and superior RNFL thickness $(r = 0.05; P = 0.70)$. For ONH and RNFL parameters, there was no statistically significant difference in agreement within individual subject groups when this analysis was performed separately (Data not shown).

The iVue SD-OCT instrument measures a total of 11 ONH and 15 RNFL thickness parameters. All of these parameters were analyzed but only the most relevant are reported in

Relationship Between Image Quality and Agreement

The mean signal strengths of scans for younger healthy eyes in the sitting and supine positions were 79.01 (95% confidence interval [CI], 76.55 to 81.46) and 75.84 (95% CI, 73.52 to 78.16), 75.44 (95% CI, 73.24 to 77.63) and 70.10 (95% CI, 66.21 to 73.98) in older healthy eyes, and 62.58 (95% CI, 58.45 to 66.70) and 59.90 (95% CI, 56.42 to 63.39) in glaucoma eyes, respectively. Positive correlations were found between signal strength and decreasing age in the sitting ($t^2 = 0.45$; 95% CI, 0.62 to 0.25; P < 0.001) and the supine ($t^2 =$ 0.46; 95% CI, 0.63 to 0.24, $P \le 0.001$) position for the combined group. The signal strength was significantly higher in the healthy vs. the glaucoma group in the sitting $(P = 0.01)$ but not the supine position ($P = 0.09$). There were no statistically significant correlations with other studied variables, such as gender ($r^2 = 0.09$; $P = 0.16$), ancestry ($r^2 = 0.16$; $P = 0.82$), CCT ($t^2 = 0.05$; $P = 0.09$), and IOP ($t^2 = 0.19$; $P = 1.80$).

DISCUSSION

The iVue SD-OCT is one of only two commercially available portable OCT instruments. The first of these, the handheld-OCT (Bioptigen, Durham, NC), has been demonstrated to have utility in children^{18, 19} and for intraoperative imaging.²⁰ Their repeatability and positional dependence of measurements has not been reported. In this study, we investigated cross-sectional ONH and RNFL thickness measurements obtained with the iVue SD-OCT. Our results show that these measurements do not change significantly between the supine and sitting positions in healthy and glaucoma eyes.

The repeatability of all ONH parameters in the same body position was good to excellent. The ONH parameter with the lowest repeatability (although not statistically significant) was rim area. Rim area and rim volume are of particular interest because, like the RNFL thickness, they reflect the number of axons converging to leave the eye. The ICC of rim area measurements varied between 93% to 95% (younger healthy), 77% to 96% (older healthy), and 73% to 82% (glaucoma). These results are in the lower range of reported average ICC values of 96% with the Cirrus HD-OCT²¹ and 96% (glaucoma eyes) and 97% (healthy eyes) with the RTVue SD-OCT.²² With an average 0.73 mm², the rim area was smaller in our glaucoma patients than in previous studies, suggesting more advanced disease.^{21, 22} Several earlier studies have shown that OCT measurements in glaucomatous eyes are slightly more variable than in normal eyes.^{22, 23, 24} It is possible that repeatability of ONH parameters decreases with more severe disease, $2³$ particularly in the absence of an eye-tracking system. This study, however, was not designed to answer this particular question.

Repeatability for overall average RNFL thickness was also good to excellent with values ranging from 93% to 98% (younger healthy), 87% to 96% (older healthy), and 98% to 99% (glaucoma). These results are comparable to reported ICC values with different OCT instruments, ranging from 79% (Stratus TD-OCT)²⁵ to 99% (Spectralis SD-OCT).²⁶ There was no statistically significant difference in variability between different RNFL thickness parameters. The current results showed somewhat lower ICCs with the iVue SD-OCT than previous studies. The RTVue SD-OCT analyzes RNFL thickness using the ONH scan pattern and sampling from a 3.45 mm diameter circle centered on the optic disc (TSNIT circle). This circle is sampled after the scan is complete and is adjusted to be centered on the optic disc in every scan. In addition, the ONH scan is registered to the 3-D Disc scan using an algorithm that matches the scans based on blood vessel patterns, allowing for more precise registration of scans. This study used iVue SD-OCT beta software, in which RNFL thickness measurements were derived from the TSNIT circle centered on the optic disc from

the 3-D Disc scans but blood vessel registration was not available and was not used. This may have reduced the repeatability of RNFL measurements. In addition, the 3-D disc scans take longer to acquire than the ONH scans, and are more susceptible to eye motion artifacts potentially adding further to the variability.

Beyond the good repeatability of measurements, the iVue SD-OCT can image the eye in different body positions. OCT imaging has been problematic in certain population groups, such as pediatric patients and patients with chronic or acute physical disabilities precluding examination in the vertical position. Therefore, the correlation between measurements taken in the two body positions is of particular interest. This correlation was very strong for both ONH (CCC, 98% to 99%) and RNFL parameters (CCC, 96% to 99%). The standard deviation measurements were similar between the two body positions, with a statistically non-significant tendency for lower variability in the supine position (for average overall RNFL thickness, SD range was 6.8–14.2μm in sitting vs. 3.9–13.4μm in supine), despite the more challenging manipulation of the instrument in the latter. This could be due to a more stable head position or less displacement of the head with breathing, as the subject lies flat. Although the correlation between supine and sitting measurements was very strong, postural effects of IOP may have induced some changes in the studied parameters, which cannot be detected using the current technology of SD-OCT.

IOP generally increases when individuals change from the sitting to the supine. $27-30$ The magnitude of this postural effect on IOP has been reported to be generally between 4 to 5 mmHg in normals and higher in glaucoma patients.^{11, 29} Previous studies have looked at the impact of acute IOP increases on ONH topographic parameters in non-human primates.^{6, 31} Using CSLO imaging of enucleated human eyes, Yan et al., 32 demonstrated progressive increase in cup depth with increasing IOP from 5 to 50 mmHg. More recently, Fatehee et al., 33 evaluated the effects of acute IOP increase from 0 to 49 mmHg in ex vivo porcine eyes using SD-OCT technology and demonstrated a posterior displacement of the ONH and lamina cribrosa. In this previous study, cup area increased by 28%, while lamina cribrosa area and prelaminar tissue area decreased by 18% and 5.5%, respectively.

In vivo observations in human eyes have shown that smaller changes in IOP can also affect ONH measurements. Agoumi et al.,³⁴ used ophthalmodynamometry to raise IOP in a group of glaucoma patients, age-matched normal subjects, and young healthy subjects. Using SD-OCT imaging, they found increased cupping with a mean IOP elevation of 12.4 mmHg and suggested that this was directly linked to prelaminar tissue compression. Of interest, the percentage of the prelaminar compression was 4 times higher in young subjects and 2 times higher in old controls compared to glaucoma patients. Ophthalmodynamometry, however, may itself lead to non-physiological ONH changes by altering the intraorbital and optic nerve tissue pressures. A case report showed significant changes in CLSO-ONH parameters in a glaucoma patient with a particularly large diurnal intraocular pressure fluctuation of 42 mmHg.³⁵ Other studies have shown that medical and surgical lowering of IOP by as little as 7.2 mmHg could lead to changes in CLSO-ONH topography in glaucoma patients.^{7, 36, 37} It can reasonably be expected that most individuals in our group would present a significantly smaller IOP change between the two body positions than the above-mentioned reports.³⁸ It is, therefore, unlikely, that physiological postural IOP changes would have affected the iVue SD-OCT readings significantly.

It is possible that differences in signal strength between images taken in the 2 positions may have influenced the correlation between the measurements. Previous studies have shown a significant association between the magnitude of signal strength and SD-OCT values.^{39, 40} To minimize this effect, all images were reviewed for quality and only images with good signal strength were included. A post-hoc analysis did not show any significant association

between signal strength and iVue SD-OCT values in our study. Although glaucomatous patients had, in the sitting position only, lower signal strength compared with healthy eyes, this was most likely the result of a significant relationship between older age and signal strength. No significant effect of signal strength was found on other studied parameters after adjusting for age.

This study has some limitations. We investigated relatively short durations (5 minutes) in each body position, similar to durations used in other studies.^{9, 41} It is possible that longer durations in the supine position, 42 as in prolonged surgical interventions, may affect OCT measurements either by a sustained higher IOP or intracranial pressure,⁴³ or both. However, a probable concomitant increase of cerebrospinal fluid in the supine position could counter the biomechanical effect of rising IOP on translaminar pressure and could mitigate changes in optic nerve head parameters. Future studies with longer testing protocols could address these matters. Another limitation is that all subjects in the older healthy group were of female sex, potentially introducing a selection bias. It seems, however, unlikely that such a bias would alter the overall results of this study.

In conclusion, these results suggest that the ability of the portable iVue SD-OCT to quantify ONH and RNFL parameters is good to excellent in both body positions and comparable to reported values for stationary SD-OCT instruments in the sitting position. The iVue-SD-OCT is useful for individuals in whom imaging in body positions other than sitting is indicated.

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FIGURE 1.

Bland-Altman plots showing the agreement of optic nerve head measurements between the supine and sitting position in the combined group of young healthy subjects, older healthy subjects, and glaucoma patients.

Footnote: Cup area (Mean difference = −.005, Limits of agreement;−.13, .13) (1 Top left), disc area (Mean difference = .017, Limits of agreement; −.15, .18) (2 Top right), rim volume (Mean difference = .004, Limits of agreement;−.03,.04) (3 Bottom right), and rim area (Mean difference = .02, Limits of agreement;−.13, .18) (4 Bottom left). Variability is consistent for cup area (r = 0.12; P = 0.37), disc area (r = -0.12 ; P = 0.38), and rim volume $(r = -0.11; P = 0.43)$ but not rim area $(r = -0.34; P = 0.01)$.

Average, Superior RNFL sitting and Superior RNFL supine

FIGURE 2.

Bland-Altman plots of showing the agreement between the supine and sitting position in the combined group of young healthy subjects, older healthy subjects, and glaucoma patients. Variability is low and stable across the range of mean values.

Footnote: Overall average retinal nerve fiber layer (RNFL) thickness (Mean difference = . 10, Limits of agreement; −4.47, 4.68), superior RNFL thickness (Mean difference = .016, Limits of agreement; -8.61 , 8.64), and inferior RNFL thickness (Mean difference = 1.12, Limits of agreement; −10.12, 12.36). Variability is consistent for overall RNFL thickness (r $= 0.09$; P = 0.50), superior RNFL thickness (r = 0.05; P = 0.70), inferior RNFL thickness (r $= 0.17$; $P = 0.20$).

Demographic Characteristics of Healthy Participants and Glaucoma Patients.

 ${}^{a}P<0.001$ (analysis of variance),

 b $P < 0.001$ (Chi-square test)

SD = standard deviation

Repeatability (intraclass correlation coefficients) of optic nerve head measurements in each body position and by subject group. Repeatability (intraclass correlation coefficients) of optic nerve head measurements in each body position and by subject group.

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Values represent the mean and 95% confidence interval.

Repeatability (intraclass correlation coefficients) of retinal nerve fiber layer thickness measurements in each body position, by subject group. Repeatability (intraclass correlation coefficients) of retinal nerve fiber layer thickness measurements in each body position, by subject group.

Values represent the mean and 95% confidence interval. Values represent the mean and 95% confidence interval.

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 $\ensuremath{\mathsf{RNFL}} = \ensuremath{\mathsf{Re}}\xspace$ tinal nerve fiber layer RNFL = Retinal nerve fiber layer

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Table 4

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Values represent the mean and standard deviation.

Values represent the mean and standard deviation.

Summary statistics of retinal nerve fiber layer thickness measurements.

Values represent the mean and standard deviation.

RNFL = retinal nerve fiber layer

Correlation of supine and sitting measurements of optic nerve head parameters, assessed using concordance correlation coefficients.

Values represent the mean and 95% confidence interval.

Correlation of supine and sitting measurements of retinal nerve fiber layer thickness measurements, assessed using concordance correlation coefficients.

Values represent the mean and 95% confidence interval.

RNFL = retinal nerve fiber layer