·Clinical Research·

Helvacioglu reproducibility index: a new algorithm to evaluate the effects of misalignments on the measurements of retinal nerve fiber layer by spectral-domain OCT

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Abstract

• **AIM: To evaluate the effect of misalignment on the measurements of retinal nerve fiber layer (RNFL) by spectral-domain optical coherence tomography (OCT).**

• **METHODS: A total of 42 eyes from 21 healthy young subjects underwent RNFL measurements with RTVue spectral-domain OCT (Optovue Inc., Fremont, California, USA). Two baseline measurements with perfectly aligned central circle to the borders of the optic nerve and four misaligned measurements which were misaligned towards to four quadrants were taken. The differences in RNFL between the baseline and misaligned measurements were analyzed with a new algorithm called Helvacioglu reproducibility index (HRI) which is designed to measure the reproducibility of the scans by evaluating the RNFL changes in the four main quadrants.**

• **RESULTS: The average RNFL scores of the first two baseline measurements have good correlation (c=0.930) and good reproducibility scores (0.15 ±0.07). Superior misaligned measurements had significantly lower superior quadrant score and higher inferior quadrant score, similar nasal and little higher temporal scores (*P*1, *P* 2 <0.001, *P* 3 =0.553, *P* 4 =0.001). Inferior misaligned measurements had significantly higher superior quadrant score and lower inferior quadrant score with similar temporal and little lower nasal scores (*P*1, *P*2<0.001, *P*3= 0.315, *P* 4 =0.016). Nasal misaligned measurements had significantly higher temporal quadrant score and lower nasal quadrant score with little lower superior and inferior scores (*P*1, *P*2, *P*4<0.001, *P*3=0.005). Temporal misaligned measurements had significantly higher nasal quadrant score and lower temporal quadrant score with similar superior and little higher inferior scores (*P*1, *P*2< 0.001, *P*3=0.943, *P*4=0.001).**

• **CONCLUSION: Good alignment of the central circle to the borders of optic nerve is crucial to have correct and repeatable RNFL measurements. Misalignment to a quadrant resulted in falsely low readings at that quadrant and falsely high readings at the opposite quadrant.**

• **KEYWORDS:** optical coherence tomography; retinal nerve fiber layer; repeatability; reproducibility; misalignment

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INTRODUCTION

The high-tech ophthalmic imaging devices such as optical coherence tomography (OCT) have allowed the ophthalmologist to measure the peripapillary retinal nerve fiber layer (RNFL) thickness [1]. Glaucoma detection and analyses of its progression can be performed by repeated RNFL thickness measurements[2-4].

Accurate assessment of the RNFL is an important component in the diagnosis and management of glaucoma[4]. The current clinical standard for obtaining RNFL thickness measurements is obtaining data with OCT systems that use spectral and Fourier domain detection. The sensitivity and scanning speed is increased compared with conventional OCT with time domain detection[5,6].

A circular scan centered on the optic nerve head (ONH) with a diameter of 3.4 mm which has been shown to be the most reproducible compared with scan circles of different diameters has been used for RNFL measurements[7-9]. Overall mean and sectoral (clock-hour and quadrants) RNFL thickness measurements are obtained from these images.

For the accurate evaluation of RNFL, proper alignment of the OCT scan to the ONH is important. There might be alignment artefacts during measurements with the OCT by 1) horizontal/vertical scan circle shift, 2) scan angle (obliquity) and/or 3) rotation of the object due to head tilt [10]. Well positioning of the patient is an important step to avoid misalignments. Well centralization of the RNFL measuring circle is also a crucial step to have accurate scans especially if the software does not support auto-alignment and centralization process is performed by users.

This study was performed to evaluate the effects misalignment on RNFL thickness obtained with the RTVue spectral-domain OCT (Optovue Inc., Fremont, California, USA) in healthy young subjects.

SUBJECTS AND METHODS

Healthy young patients were recruited in January 2014 at the Maltepe University School of Medicine, Department of Ophthalmology. The study was in adherence with the tenets of the Declaration of Helsinki, and the Institutional Review Board approved this prospectively designed study. Each subject underwent a full ophthalmology examination, including the assessment of visual acuity, refractive error and intraocular pressure with a tono-autorefractokeratometer (Topcon TRK 1P; Topcon, Tokyo, Japan), ONH evaluation and fundus examination with a 90 D lens, and fundus photography with non-mydriatic fundus camera (VK-2, Kowa Optimed, Tokyo, Japan) as well as peripapillary RNFL thickness measurement with RTVue spectral-domain OCT (Optovue Inc., Fremont, California, USA). All images were acquired by a single, well-trained examiner (Helvacioglu F) at one session without pupillary dilatation, in a dimly lit room. Only good-quality images, as defined by a signal strength index of $\geqslant 30$, were used for analysis. Patients younger than 40 years of age and who had best corrected visual acuity of 20/20 or better, spherical equivalent of refractive errors less than ±3.00 D, normal intraocular pressure (<21 mm Hg), normal ONH without glaucomatous changes or other disc pathologies (*i.e.* increased cup-disc ratio more than 0.4, narrowing of neuroretinal rim, optic disc druzen) and no macular pathology were included. Both eyes of each subject were examined. Subjects with a history of systemic diseases including hypertension and diabetes, previous ocular trauma or surgery, vestibular disease or any large peripapillary atrophy extending more than 1.7 mm from the centre of the optic disc were excluded.

RTVue software version 2.0.4.0 (Model RT 100; Optovue Inc.) uses a scanning laser diode to emit a scan beam with a wavelength of 840 ±10 nm to provide images of ocular microstructures. OCT measurements were performed by fast RNFL scan, which measures RNFL thickness at 3.45 mm from the center of the optic disk. In the fast RNFL protocol, a total of 3 scans, each composed of 256 A scans, are acquired consecutively using a circle with a diameter of 3.45 mm. An automated computer algorithm delineates the anterior and posterior margins of the RNFL. The RNFL thickness parameters are measured by assessing 2325 data points between the anterior and posterior RNFL borders. Centralization of the circle was performed by the operator. Two baseline measurements with perfectly aligned central circle to the borders of the optic nerve and four misaligned measurements which were misaligned towards to four quadrants were taken. While having a fast RNFL scan the operator uses a central circle landmark to locate the borders of the optic disk. The distance between the borders of the central circle and the peripheral circle which actually locates the RNFL scan at 3.45 mm is about 1.15 mm. While performing misaligned scans the operator shifts the circles to a quadrant about half of the distance between the inner and outer circles which resulted in approximately 0.5 mm shifts towards that quadrant. The differences in RNFL between the baseline and misaligned measurements were analyzed. A new algorithm which was named as Helvacioglu reproducibility index (HRI) was developed to show the repeatability of two consecutive measurements. The formula is basically related to the mean overall and four quadrant RNFL thickness measurements (Figure 1). The formula was composed of 3 parts. In the first part the average measurements of two scans were compared. If both scans have same average RNFL measurements the ratio of the measurements would be one and the result of this part would be zero. The other parts of the formula were designed with the same principle. In the second part superior and inferior RNFL measurement ratios of the scans were compared. And in the last part of the formula nasal and temporal measurements of the scans were compared. Similarly, the result of these parts would also be zero for two scans with exactly same opposing quadrants RNFL measurements. When the result of HRI is zero or close to zero, it explains that two consecutive measurements have good correlation. HRI of first two baseline measurements were compared with the mean overall and quadrant RNFL thickness of these measurements. Also HRI of the misaligned scans were compared with the baseline scans in the same manner.

$$\left|1-\frac{Average1}{Average2}\right|+\left|1-\frac{\frac{Superior1}{Inferior1}}{\frac{Superior2}{Inferior2}}\right|+\left|1-\frac{\frac{Nasal1}{Temporal1}}{\frac{Nasal2}{Temporal2}}\right|$$

Figure 1 The formula of HRI.

Statistical Analysis Statistical analysis was performed using SPSS software (version 12.0, SPSS, Inc.). Paired samples and independent sample *t*-tests were used to test the difference in mean overall and quadrant RNFL thickness measurements and HRI scores. A *P* value less than 0.05 was considered statistically significant. Pearson's correlation analyses were also performed to analyze the capability of HRI in discriminating the differences between two consecutive measurements.

RESULTS

Twenty-one healthy subjects were enrolled in the study. The mean age of the participants was 27.4±8.3y and there were fourteen women, seven men. The mean spherical equivalent of the 21 subjects was -0.57±1.16 D (range -2.63 to 2.50 D).

The average RNFL scores of the first two baseline measurements had good correlation (c=0.930). The results of the pair-wise comparison of RNFL thickness between the two baseline positions and correlation of the mean overall and quadrant measurements were listed in Table 1. The mean

HRI score of first two baseline measurements was 0.15±0.07. Misalignment to a quadrant resulted in falsely low readings at that quadrant and falsely high readings at the opposite quadrant. Superior misaligned measurements had significantly lower superior quadrant score and higher inferior quadrant score with similar nasal scores and little higher temporal scores ($P1$, $P2<0.001$, $P3=0.553$, $P4=0.001$). Inferior misaligned measurements had significantly higher superior quadrant score and lower inferior quadrant score with similar temporal and little lower nasal scores ($P1$, $P2<0.001$, $P3=0.315$, $P4=0.016$). Nasal misaligned measurements had significantly higher temporal quadrant score and lower nasal quadrant score with little lower superior and inferior scores ($P1$, $P2$, $P4<0.001$, $P3=0.005$). Temporal misaligned measurements had significantly higher nasal quadrant score and lower temporal quadrant score with similar superior score and little higher inferior scores ($P1$, $P2<0.001$, $P3=0.943$, $P4=0.001$). The effect of horizontal and vertical circle displacements on RNFL thickness and HRI scores that compared the misaligned and baseline measurements were summarized in Tables 2, 3 and 4.

DISCUSSION

OCT is one of the rapidly evolving technologies of the ophthalmology. The quality of the scans gets better and time to obtain these scans gets less and less with new innovations. Early detection of glaucoma has focused on evaluation of the ONH and the RNFL which can be imaged and have been shown to undergo structural changes prior to clinically detectable visual field loss. In theory, RNFL analysis may be more sensitive than ONH evaluation, because OCT has shown thinning of the nerve fiber layer due to aging without detectable changes in the ONH appearance [11]. Nerve fiber layer thinning is seen in glaucoma, because it is directly correlated with loss of ganglion cells, which is assumed to be a primary event in glaucomatous damage [12]. Therefore, RNFL thickness scans are one of the important measurements which are used to evaluate the progression of glaucoma or to assess the risk of glaucoma in healthy subjects[13,14]. In order to detect progression in glaucoma, the following three criteria must be met: 1) the measurements must be reproducible; 2) the images must be accurately registered to each other; 3) a statistical test must be performed to differentiate true biological change from normal measurement variability.

Several studies have shown the RTVue to have excellent reproducibility. Tan *et al* [15] found the coefficient of variance (CV) of the RTVue was 1.6% for normals, 1.7% for pre-perimetric glaucoma patients, and 2.1% for perimetric glaucoma patients. Gonzalez-Garcia *et al* [16] reported the excellent reproducibility of RTVue with the CV of the RTVue for average RNFL thickness to be 2.1%, and the intraclass correlation coefficient was 0.97, they also found the RTVue had better reproducibility than the Stratus (lower CV). One likely explanation for the improved reproducibility compared to the Stratus comes from the fact that the Stratus takes a single circular scan around the ONH. The exact position of this circle can affect the RNFL results. The software support of this imaging device helps us to have correctly aligned and repeatable measurements of the inner retinal layers. The RTVue spectral-domain OCT was used in the study. Actually it has a software tool to analyze the changes in ONH parameters and RNFL thickness with good followability. To use this support, two different scan protocols should be taken. The 3-dimensional (3D) disc and nerve head map 4-mm diameter (NHM4) RTVue protocols are used for this purpose. The 3D disc protocol is a 4×4-mm^2 raster scan centered on the optic disc and composed of 101 B scans each composed of 512 A scans (acquisition time, 2.2s). The resulting scan provides a 3D image of the optic disc and surrounding area. The en-face image generated by this scanning protocol was used to draw the contour line describing the disc margin that is required to generate optic disc parameters from the NHM4 protocol. The NHM4 protocol is composed of 12 radial scans 3.4 mm in length (452 A scans each) and 6 concentric ring scans ranging from 2.5 to 4.0 mm in diameter (587 or 775 A scans each) all centered on the optic disc (using the previously drawn contour line to ensure scan registration). This scan configuration provides 9510 A scans in 0.39s. Areas between A scans are interpolated. A polar RNFL thickness map and various parameters that describe the optic disc are provided. To compare measurements between the RTVue and Stratus OCT, RNFL thickness measurements were obtained for the 3.45-mm radius ring only, and measurements were described as average RNFL and RNFL in the inferior, temporal, superior, and nasal quadrants. The RNFL thickness parameters were measured by assessing a total of 2325 data points between the anterior and posterior RNFL borders [16]. With these protocols the borders of ONH was drawn by the software and existing 3D image and generated en-face images from this protocol are used to position ONH and circular scans that measure RNFL thickness at 3.45 mm in following scans or visits. The software minimizes the operator dependence and corrects misaligned scans up to 4 mm RNFL scan radius by automatically centralization of the ONH. In our study, the software support of RTVue was not used on purpose to analyze the changes seen in fast RNFL thickness measurements that resulted in quadrant misalignments.

Table 1 Results of the pair-wise comparison of RNFL thickness between the two baseline positions and correlation of the mean overall and quadrant measurements

RNFL thickness	Baseline 1 (μm)	Baseline 2 (μm)	Correlation	P
Average	113±8.45	112.30±8.44	0.930	0.165
Superior	139.97±14.52	139.38±14.95	0.881	0.535
Nasal	81.76±11.59	81.64±11.95	0.906	0.881
Inferior	147.28±14.71	146.54±14.82	0.893	0.488
Temporal	82.61±10.87	81.64±9.58	0.928	0.129

Table 2 The results of the pair-wise comparison of RNFL thickness between the superior and inferior misaligned scans with baseline 1 scan and correlation of the mean overall and quadrant measurements of the misaligned scans with baseline 1 scan

RNFL thickness	Superior misaligned (μm)	Correlation with B1	*P*	Inferior misaligned (μm)	Correlation with B1	*P*
Average	115.38±9.45	0.902	0.001	111.52±18.05	0.460	0.554
Superior	112.78±15.23	0.727	<0.001	172.30±20.28	0.674	<0.001
Nasal	81.16±11.07	0.839	0.553	78.83±10.22	0.768	0.016
Inferior	180.42±19.82	0.692	<0.001	120.66±14.52	0.791	<0.001
Temporal	86.45±10.54	0.780	0.001	83.59±10.81	0.836	0.315

B1: Baseline 1 scan.

Table 3 The results of the pair-wise comparison of RNFL thickness between the nasal and temporal misaligned scans with baseline 1 scan and correlation of the mean overall and quadrant measurements of the misaligned scans with baseline 1 scan

RNFL thickness	Nasal misaligned (μm)	Correlation with B1	*P*	Temporal misaligned (μm)	Correlation with B1	*P*
Average	111.59±8.32	0.728	0.09	118.64±10.50	0.793	<0.001
Superior	131.19±23.69	0.577	0.005	140.07±13.55	0.774	0.943
Nasal	62.42±7.65	0.728	<0.001	118.95±24.41	0.571	<0.001
Inferior	136.76±14.97	0.869	<0.001	151.33±12.36	0.868	0.001
Temporal	114.59±18.41	0.504	<0.001	64.71±6.50	0.786	<0.001

B1: Baseline 1 scan.

Table 4 HRI of the misaligned scans were calculated by comparison of the quadrants of the misaligned scans with the quadrants of baseline 1 scan (HRI with B1). Statistical analyses (paired sample *t* test) of the HRI of the misaligned scans with baseline 1 and two baseline scans were performed to show the effectiveness of HRI in discriminating misaligned scans

HRI of the scans	Baseline 2	Superior	Nasal	Inferior	Temporal
HRI with B1	0.15±0.07	0.69±0.26	1.19±1.70	0.70±1.39	0.56±0.13
Correlation	1	-0.021	-0.195	-0.121	-0.223
P	1	<0.001	<0.001	0.014	<0.001

B1: Baseline 1 scan.

Histomorphologic and imaging studies have shown that the maximum RNFL thickness appears in the superotemporal and inferotemporal regions[11]. Any shift in the location of the scan circle that brings a sector closer to the disc margin causes a thickness increase in this region and a decrease in the opposite region. A downward displacement of the circle brings the scan circle closer to the disc margin in the superior quadrant, with subsequent thickening of RNFL measurements in that quadrant and thinning in the inferior quadrant. Any shift in the location of the scan actually changes the RNFL thickness ratio of the opposite quadrants. Therefore we have developed a formula to show the reproducibility of two consecutive scans by comparing the ratios of superior-inferior and nasal-temporal RNFL thickness.

The three dimensional anatomy of the RNFL is very important to understand the scan quality and centralization. The optic disk is the start point of the nerve fibers, but they are not radial projections. The majority of the fibers tend to join the superior and inferior temporal loops which actually thickens the RNFL in that quadrants. Therefore a nasal shift in the RNFL measurements leads to decreased nasal, superior, inferior and overall RNFL thickness. In the same manner, a temporal shift leads to decreased temporal and increased nasal, superior, inferior and overall RNFL thickness. HRI which compares the overall and opposite quadrants (superior/inferior and nasal/temporal) RNFL thickness ratio plays an important role to understand the centralization of the scans. It is important to have an algorithm like HRI to evaluate the reproducibility of two consecutive scans since a nasal shift might show glaucomatous changes in healthy subjects or a temporal shift might show good results in a glaucoma patient. Also vertical shifts could mislead to false diagnosis. Glaucomatous thinning of the superior RNFL thickness could be observed in a superiorly shifted fast RNFL scan.

In the literature, some studies examined RNFL thickness changes due to misaligned or tilted scans. Gabriele *et al*[17] investigated the effect on OCT RNF thickness measurements of varying the standard 3.4-mm-diameter circle location. A model for the distance between the two thickest measurements along the RNFL thickness circular profile (peak distance) was also calculated. The study demonstrated that any shift in the scan circle caused a thickness increase in the region that got closer to the disk margin and a decrease in the opposite region. When the scan circle was displaced horizontally, superior and inferior RNFL thicknesses remained stable. During vertical displacements, the superior and inferior RNFL thicknesses changed. The model for peak distance demonstrated that as the scan moves nasally, the RNFL peak distance increases, and as the circle moves temporally, the distance decreases. Vertical shifts had a minimal effect on peak distance. Hwang *et al*[10] investigated the effect of head tilt on the measurements of retinal nerve fibre layer and macular thickness by spectral-domain OCT. The right head tilt caused superior-temporal RNFL thickening, inferior-temporal RNFL thinning, superior outer macular thickening and inferior outer macular thinning. The left head tilt induced superior-temporal RNFL thinning,

RNFL Parameters	Baseline	Follow up 1	Change
Avg, RNFL	114.27	116.31	2.04
Sup, Avg	110.22	127.54	17.31
Inf, Avg	118.31	105.10	-13.21
TU	83.76	90.52	6.76
ST	142.31	170.28	27.97
SN	134.91	177.78	42.87
NU	79.71	71.18	-8.54
NL	72.95	69.90	-3.05
IN	146.45	119.89	-26.56
IT	171.38	150.30	-21.08
TL	82.52	80.40	-2.12

HRI = 0.45

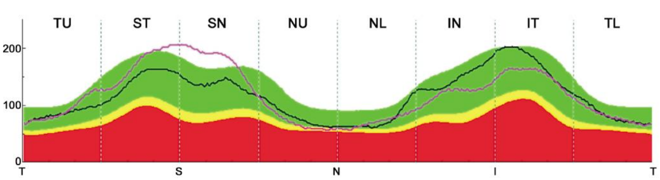

Figure 2 The comparison of baseline and inferior misaligned scan. Although average RNFL thickness values are very close (114.27 and 116.31), HRI is able to show the difference between the scans with a result of 0.45.

inferior-temporal RNFL thickening, superior outer macular thinning, nasal outer macular thickening and inferior outer macular thickening. Since the main superior and inferior nerve fibers tend to go temporally, temporal shift of the inferior peak location caused RNFL thickening whereas nasal shift of the superior peak location caused RNFL thinning.

Our results demonstrated that RNFL thickening was observed in the sector that measured near to disk margin and RNFL thinning was observed in the opposite sector. HRI was found to be great tool to understand the reproducibility of the two consecutive scans. Overall mean RNFL thickness could be found similar even significant differences were seen in the quadrant measurements therefore could not be used to analyze the reproducibility of the scans (Figure 2). Good centralization of the RNFL circle is crucial to have correctly aligned scans. Therefore a fast RNFL scan is not a good choice for the follow-up visits. Protocols that could have repeatable measurements of the exact circular RNFL thickness by using auto alignment tools for recognition of the optic disk margins and should be used for this purpose. If fast RNFL scans are taken then, two or three consecutive scans should be taken and should be analyzed by quadrant thickness ratio comparisons such as HRI which calculates the reproducibility of all of the quadrants. If HRI value of the two scans is zero or close to zero than the two scans have good reproducibility. We believe this formula could be used as a safety tool in determining the reproducibility of the scans.

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Helvacioglu reproducibility index could be used for scientific purposes with the permission of Dr. Helvacioglu. For commercial use, it is mandatory to have a contact with Dr. Helvacioglu.

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