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Focal loss volume best differentiates eyes with afferent pupillary defect

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Abstract

Purpose: To quantify the specificity and sensitivity of RTVue-100, Optovue parameters at determining the presence of a relative afferent pupillary defect (RAPD) by coupling their values with the instrument normative data base (NDB) and the presence of a RAPD. To generate the distribution for the focal loss volume (FLV) percentage, by coupling its value to the instrument NDB and presence of a RAPD.

Methods: Forty one subjects with a RAPD and glaucomatous or non-glaucomatous optic neuropathy participated. A neutral density filter bar was used to estimate the RAPD. The specificity and sensitivity of all parameters was analyzed using Fisher's Exact test. The distribution of the FLV percentage was analyzed using a one-way ANOVA with a Tukey HSD post hoc test.

Results: The FLV percentage was more sensitive (100%) but less specific (64%) than other parameters. Eyes of subjects with FLV percentage and NDB p-values < 1% were 33.8 times more likely to have a RAPD [95% CI: 7.2, 325.1]. Confidence limits for the distribution of FLV percentage were; 6.32/10.59 um for eyes with NDB p-values < 1% with a RAPD; 2.04/7.56 um for eyes with NDB p-values >1% with a RAPD and 1.08/6.22 um for eyes with NDB p-values > 1% without a RAPD.

Conclusion: Compared to other RTVue-100, Optovue parameters the FLV percentage is more sensitive at determining eyes with a RAPD and may significantly categorize optic neuropathy according to severity.

Keywords

Focal loss volume, spectral domain optical coherence tomography, relative afferent pupillary defect

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Focal Loss Volume Best Differentiates Eyes with Afferent Pupillary Defect

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Purpose: To quantify the specificity and sensitivity of RTVue-100, Optovue parameters at determining the presence of a relative afferent pupillary defect (RAPD) by coupling their values with the instrument normative data base (NDB) and the presence of a RAPD. To generate the distribution for the focal loss volume (FLV) percentage, by coupling its value to the instrument NDB and presence of a RAPD. Methods: Forty one subjects with a RAPD and glaucomatous or non-glaucomatous optic neuropathy participated. A neutral density filter bar was used to estimate the RAPD. The specificity and sensitivity of all parameters was analyzed using Fisher's Exact test. The distribution of the FLV percentage was analyzed using a one-way ANOVA with a Tukey HSD post hoc test. Results. The FLV percentage was more sensitive (100%) but less specific (64%) than other parameters. Eyes of subjects with FLV percentage and NDB p-values < 1% were 33.8 times more likely to have a RAPD [95% CI: 7.2, 325.1]. Confidence limits for the distribution of FLV percentage were; 6.32/10.59 um for eyes with NDB p-values < 1% with a RAPD; 2.04/7.56 um for eyes with NDB p-values >1% with a RAPD and 1.08/6.22 um for eyes with NDB p-values > 1% without a RAPD. Conclusion. Compared to other RTVue-100, Optovue parameters the FLV percentage is more sensitive at determining eyes with a RAPD and may significantly categorize optic neuropathy according to severity.

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Implications for Interprofessional Practice

1. The finding indicating that the FLV percentage is more sensitive than other SD-OCT parameters at determining eyes with a RAPD may help alert the clinician of the probable presence of a RAPD. In addition it may aid at early detection or progression of optic neuropathy. Early clinical detection or progression by focusing on the FLV percentage consequently, may influence the treatment course taken.

2. As a pattern deviation parameter, the FLV percentage higher sensitivity may be due to its ability to detect intrinsically photosensitive retinal ganglion cell (IPRGC) loss due to lesser redundancy of these cells at the assessed area. This pattern deviation parameter may be able to detect relative neural network deficits of pupillary signals that may elicit a RAPD earlier compared to cpRNFLT parameters, or even before cpRNFLT loss is detected by current technologies. The communication of this hypothesis among the Eye Care Professionals may encourage research in this area that may lead the development of more sensitive methods for the evaluation and categorization of optic neuropathy.

3. This paper covers recent developments in the understanding of the association of nerve fiber layer loss and the presence of a RAPD. This paper serves to educate Eye Care Professionals on current methodological concepts and the science behind clinical instrumentation and techniques. This in turn helps promote effective clinical applications and patient management.

Introduction

Retinal nerve fiber layer thickness (RNFLT) loss has been documented to correlate with the relative afferent pupillary defect (RAPD). Using the spectral domain optical coherence tomography (SD-OCT) circumpapillary parameters and automated pupilometer, Tatham et al. (2014) estimated an inter-eye difference of 6 um for every 0.3 log unit change in RAPD score. Similarly, Chang et al. (2013) reported a 3.2 um RNFLT difference for every 0.3 log unit increment with SD-OCT and automated pupilometer. In our previous study, using neural density (ND) filters and the RTVue-100, Optovue® SD-OCT, we observed a more sensitive RNFLT loss with ganglion cell complex (GCC) compared to circumpapillary parameters. Analogous to the results of Tatham et al. (2014) and Chang et al. (2013), we observed approximately 8.5 um RNFLT change or 9.4% inter-eye difference for every 0.3 log unit increment for the GCC average. For the focal loss volume (FLV) percentage, the inter-eye difference was lower, approximately 4.3% for every 0.3 log unit increment (Besada et al., 2017).

In this study, we compared the specificity and sensitivity of the RTVue-100, Optovue® parameters at determining the presence of a relative afferent pupillary defect (RAPD) by coupling their values with the instrument normative data base (NDB) and the presence of a RAPD (Huang & Tan, 2009). Since in our initial study we observed that the FLV percentage correlated more sensitively with a RAPD, we analyzed the distribution of FLV percentage values of subjects' eyes (Besada et al., 2017). We determined confidence limits to establish a criterion that may help categorize according to severity eyes that may have a RAPD and thus optic neuropathy. To our knowledge this type of analysis has not been previously documented. This paper covers recent developments that help to understand the association of nerve fiber layer loss and the presence of a RAPD. Similarly it serves to educate eye care professionals on current methodological concepts and the science behind clinical instrumentation and techniques. This in turn helps promote effective clinical applications and patient management. Ultimately, this paper also serves to inform neurologists, cardiologists, internists, and primary care physicians about how the SD-OCT can assist with the diagnosis and monitoring for possible progression and about systemic conditions, such as multiple sclerosis, cerebrovascular accidents, and cardiovascular disease that may cause optic neuropathy.

Methods

Informed consent (via an institutional-derived, review-board-approved protocol) was obtained for all recruited subjects attending the Nova Southeastern University Eye Care Institute. The inclusion criteria for the forty-one subjects enrolled in the study included: a diagnosis of asymmetric or unilateral optic neuropathy, presence of a RAPD, absence of retinopathy, and absence of significant asymmetric cataracts. Subjects with pupil anomalies other than RAPD or those using

ocular medications that may affect pupil reaction were also excluded. All participants had a comprehensive eye exam that included review of medical history and blood pressure measurement within one year prior to the study. Subjects with glaucoma, previously diagnosed in our clinic, had either glaucomatous visual field loss, SD-OCT RNFLT loss indicative of glaucoma, or glaucomatous optic nerve cupping. The glaucoma subjects were managed medically. Non-glaucomatous optic neuropathy subjects had optic nerve pallor and a past diagnosis of non-arteritic ischemic optic neuropathy (NAION,) traumatic optic neuropathy, multiple sclerosis, benign intracranial tumor, and undefined optic neuropathy. The study data was collected during a single visit.

A neutral density (ND) filter bar (Richmond Products) and SD-OCT (RTVue-100, Optovue) were used to quantify the RAPD. Pupil examination was performed following swinging flashlight test protocols (Brown, Zilis, Lynch, & Sanborn, 1987; Bell, Waggoner, Boyd, Akers, & Yee, 1993; Levin, Newman, Quigley, & Miller, 1983; Lagreze & Kardon, 1998; Kardon, Haupert, & Thompson, 1993; Rosenberg & Olivia, 1990; McCormick et al., 2002). A binocular indirect ophthalmoscope set at maximum intensity was used as the light source, and the room illumination was kept at a mesopic level. An adaptation period of approximately 60 seconds at mesopic illumination was used before commencing testing. The RAPD ND log unit was recorded when a stall or weak constriction was observed in the affected eye. Two independent trained observers each masked to the results of the other obtained the measurements. Approximately, a 60 second resting time was observed between examiners' measurements. In cases were the RAPD ND log unit among the two observers did not coincide the lower of the value was used in the study.

The RTVue-100, Optovue® SD-OCT was used to obtain RNFLT measurements. A trained technician or an optometric physician obtained the measurements. The RTVue-100, Optovue® SD-OCT optic nerve head (ONH) pattern retinal nerve fiber layer (RNFL) parameters were identified for the purpose of this study as circumpapillary RNFLT (cpRNFLT). The average cpRNFLT (cpRNFLTA), superior cpRNFLT (cpNFLTS) and inferior cpRNFLT (cpNFLTI) parameters were examined. Likewise, the RTVue-100, Optovue® SD-OCT GCC average (GCCA), GCC superior (GCCS), GCC inferior (GCCI), FLV percentage and global loss volume (GLV) percentage parameters were analyzed. The RTVue-100, Optovue® SD-OCT parameters values were coupled with their respective allocation on the RTVue-100, Optovue® SD-OCT NDB and the presence of a RAPD in order to quantify the specificity and sensitivity of the parameters at determining the presence of a RAPD. The categories included, eyes having parameter values: with NDB p-values < 1% with a RAPD, with NDB p-values < 1% without a RAPD, with NDB p-values > 1% with a RAPD and with NDB p-values > 1% without a RAPD. The Chi Square and Fisher's Exact test were used to analyze the specificity and sensitivity. In the cases where some categories had no quantities, we followed the work of Parzne et al. (2002) and added 0.5 to each cell of the table to calculate the odds ratios and their respective 95% confidence intervals. A distribution of the FLV percentage, along with its respective allocation on the RTVue-100, Optovue® SD-OCT, and presence of a RAPD, was further generated and analyzed using a one-way ANOVA with a Tukey HSD post hoc test.

Results

Forty-one subjects (18 females and 23 males) participated in the study. The average age was 58 (7.52) with range of 41 to 71. The self-reported ethnicities of the subjects included: 20 Afro-Caribbean, 13 African Americans, 5 Hispanics, 2 Whites, and 1 Asian. Overall 33 of the 41 subjects were of African descent. Eight subjects had non-glaucomatous optic neuropathy other than glaucoma while thirty-three had glaucoma. The non-glaucomatous optic neuropathy categories included NAION, traumatic optic neuropathy, multiple sclerosis, benign intracranial tumor, and undefined optic neuropathy.

The inter-observer's estimation of the RAPD varied by one log unit in 15% of the measurements. In such cases the lower RAPD value was used in the analysis. Although using the lower of the two inter-observer's RAPD measurements may lead to a skewed value, it was considered to have a random distributed effect. In addition, since the discrepancy occurred in 15% of measurements and was of only a 1 log unit magnitude, its overall influence was considered minimal.The GLV and FLV percentage were more sensitive but less specific than other parameters at determining the RAPD. The FLV percentage was more sensitive (100%) but was less specific (64%). Other GCC and cpRNFLT parameters were less sensitive but more specific than the GLV and FLV percentage, at determining eyes with a RAPD (table 1). The eyes of subjects with FLV percentage values exhibiting NDB p-values < 1% were approximately 34 times more likely to have a RAPD than eyes of subjects which had a NDB above p-values > 1% [95% CI: 7.2, 325.1] (table 2).

FLV%	***NDB <1% Eye***	***NDB > 1% Eye***
APD Yes	41 (100.0%)	0 (0.0%)
APD No	15 (36.5%)	26 (63.5%)
GLV%	***NDB <1% Eye***	***NDB >1% Eye***
APD Yes	38 (92.7%)	3 (7.3%)
APD No	18 (43.9%)	23 (56.1%)
GCCA	***NDB <1% Eye***	***NDB >1% Eye***
APD Yes	31 (75.6%)	10 (24.3%)
APD No	9 (21.9%)	32 (78.0%)
GCCS	***NDB <1% Eye***	***NDB >1% Eye***
APD Yes	32 (78.0%)	9 (22.0%)
APD No	11 (26.8%)	30 (73.2%)
GCCI	***NDB <1% Eye***	***NDB >1% Eye***
APD Yes	29 (70.7%)	12 (29.3%)
APD No	9 (22.0%)	32 (78.0%)
cpRNFLTA	***NDB <1% Eye***	***NDB >1% Eye***
APD Yes	33 (80.4%)	8 (19.6%)
APD No	10 (24.4%)	31 (75.6%)
cpRNFLTS	***NDB <1% Eye***	***NDB >1% Eye***
APD Yes	32 (78.0%)	9 (22.0%)
APD No	10 (24.4%)	31 (75.6%)
cpRNFLTI	***NDB <1% Eye***	***NDB >1% Eye***
APD Yes	30 (73.2%)	11 (26.8%)
APD No	9 (21.9%)	32 (78.1%)

Table 1. Chi Square of circumpapillary retinal nerve fiber layer thickness average (cpRNFLTA), superior (cpRNFLTS), inferior (cpRNFLTI), ganglion cell count (GCC) average (GCCA), superior (GCCS), inferior (GCCI), focal loss volume percentage (FLV%), and global loss volume percentage (GLV%).

Parameter	Two-tailed Fisher's exact test, Cramer's *V* value, $p <$ 0.001,confidence interval CI	Likelihood of eyes with NDB <1% having RAPD vs. eyes with NDB >1%
FLV%	V= 0.68, 95% CI: 7.2, 325.1	34 times more likely
GLV%	*V* = 0.52, 95% CI: 3.9, 91.6	16 times more likely
GCCA	*V* = 0.53, 95% CI: 3.5, 35.1	11 times more likely
GCCS	*V* = 0.51, 95% CI: 3.1, 30.3	9 times more likely
GCCI	*V* = 0.49, 95% CI: 2.8, 26.5	8 times more likely
cpRNFLTA	*V* = 0.56, 95% CI: 4.0, 42.1	12 times more likely
cpRNFLTS	*V* = 0.53, 95% CI: 3.6, 35.2	11 times more likely
cpRNFLTI	*V* = 0.51, 95% CI: 3.2, 30.3	9 times more likely

Table 2. Fisher's Exact test results of circumpapillary retinal nerve fiber layer thickness average (cpRNFLTA), superior (cpRNFLTS), inferior (cpRNFLTI), ganglion cell complex (GCC) average (GCCA), superior (GCCS), inferior (GCCI), focal loss volume percentage (FLV%), and global loss volume percentage (GLV%).

Category	X (um)	Diff (um)	LCI (um)	UCI (um)	P
FLV%: - RAPD/ NDB <1% vs. FLV%: - RAPD/NDB >1%	6.03	4.80	2.04	7.56	0.000
FLV%: + RAPD/NDB <1% vs. FLV%: - RAPD/NDB >1%	9.69	8.46	6.32	10.59	0.000
FLV%: + RAPD/NDB <1% vs. FLV%: - RAPD/NDB <1%	1.23	3.66	1.08	6.22	0.003

Table 3. Mean (X) of category focal loss volume percentage (FLV%), FLV%: negative (-) RAPD/ NDB <1% in first row; of FLV%: positive (+) RAPD/NDB <1% in second row; and of FLV%: negative (-) RAPD/NDB >1% in third row. Difference between means (Diff) and p value of each respective statistically compared category in row. Lower confidence limits (LCI) and upper confidence limits (UPL) in first row relates to category FLV%: negative (-) RAPD/ NDB <1%; in second row to FLV%: positive (+) RAPD/NDB <1%; and in the third row to FLV%: negative (-) RAPD/NDB >1%.

The confidence limits of the distribution for the FLV percentage, along with its respective allocation on the RTVue-100, Optovue® SD-OCT, and presence of a RAPD, were 6.32/10.59 um for eyes having parameters with NDB p-values < 1% with a RAPD, 2.04/7.56 um for eyes having parameters with NDB p-values >1% with a RAPD and 1.08/6.22 um for eyes having parameters with NDB p-values > 1% without a RAPD. There was a significant difference by measurement, F (2, 79) = 44.75, p < 0.001, η^2=0.53 (table 3).

Discussion

To our knowledge, this type of comparative analysis of the different SD-OCT parameters has never been documented. Previously, we have observed that, compared to cpRNFLT, the GCC parameters correlated more sensitively with the RAPD. However, the cpRNFLT, demonstrated a stronger and consequently more specific correlation with the RAPD than the GCC parameters. In this study, the GLV and FLV percentage demonstrated a higher sensitivity at identifying an eye with a RAPD compared to cpRNFLT and other GCC parameters. Both the GLV and FLV percentages, however, were also less specific. The FLV percentage was the most sensitive value. Eyes of subjects with FLV percentage estimates falling within NDB p-values < 1% were approximately 34 times more likely to have a RAPD than eyes with FLV percentage values allocated to NDB p-values > 1%. The specificity would possibly be higher, approximately 74%, if we consider that the FLV percentage value of the contralateral eye without a RAPD of six subjects had nonetheless lower values that fell within the 95% confidence limit for RAPD eyes with FLP percentage values with NDB p-values < 1%.

The RTVue-100, Optovue® SD-OCT NDB p-values < 1% indicates that subjects whose parameters values fell within <1% of the distribution were statistically different from 99% of the rest of those analyzed by the designer of the instrument database (Huang & Tan, 2009). However, it does not necessarily represent values that may be attributed to a particular ocular pathology. By coupling the FLV percentage with the instrument normative data base (NDB) and the presence of a RAPD in this study, values within a range of 6.32/10.59 um represent values of subject's eyes that have a RAPD and optic neuropathy. Since the presence of a RAPD correlates with a level of unilateral or asymmetric optic neuropathy, the distribution of FLV percentage, coupled with its respective allocation on the RTVue-100, Optovue® SD-OCT and presence of a RAPD, may secondarily permit a categorization according to the severity of optic neuropathy. Consequently, FLV percentage values within a range of 6.32/10.59 um may be expected to correspond to eyes with advanced optic neuropathy as opposed to eyes within the 1.08/6.22 um range. Although an overlap is present between both extreme categories, an intermediate category may be classified at FLV percentage values between a range of less than 6.32 um but greater that 2.04 um.

As indicated by other investigators, the stronger or more specific correlation of the cpRNFLT with a RAPD compared to that of the GCC parameters can

be attributed to the fact that although the GCC area accounts for a large fraction of retinal ganglion cells (RGC) that conveys pupillary signals, RGC all throughout the retina similarly contribute to the pupillary reflex. Thus the summation of all RGC signals of the entire retina covered by cpRNFLT yields a more specific and stronger stimuli and consequent correlation compared to GCC parameters (Gracitelli et al., 2016; Tatsumi et al., 2007; Younis & Eggenberger, 2010). Contrary, the correlation of the GCC parameters with a RAPD is more sensitive since the majority of RGC conveying the pupillary signal are located within the area assessed by the GCC (Tatsumi et al., 2007; Younis & Eggenberger, 2010). In addition, in this area anatomically, the nerve fiber layer is very thin compared to the ganglion cell layer (GCL) and the inner plexiform layer; consequently, the RNFLT loss relatively represents more GCL loss (Huang & Tan, 2009). Although less specific, the higher sensitivity identifying an eye with a RAPD by the GLV and FLV percentage values compared to other GCC and cpRNFLT parameters may be due to a superior capability at identifying the pattern of RGC loss observed in glaucoma and other optic neuropathies (Naghizadeh, Levin, Newman, Quigley, & Miller, 2014). This pattern deviation parameter may be able to detect relative neural network deficits of pupillary signals that may elicit a RAPD earlier compared to cpRNFLT parameters or even before cpRNFLT loss is detected by current technologies. Alternatively, since the distribution of intrinsically photosensitive RGC (IPRGC) that are involved in the pupillary signal is not homogeneous through the retina, the highest sensitivity of FLV percentage may reflect to the ability of this pattern deviation parameter to detect focal signal network redundancy loss involving IPRGC (Kawasaki & Kardon, 2007; Münch & Kawasaki, 2013; Galindo-Romero et al. 2013, Gracitelli, 2014). The communication of this hypothesis among the Eye Care Professionals may encourage research in this area and therefore may lead to the development of more sensitive methods for the evaluation and categorization of optic neuropathy.

It should be emphasized that although relative RNFLT loss documented by GCC has the advantage of representing an objective measurement that seems to be more sensitive than cpRNFLT parameters at detecting a RAPD, in certain instances a RAPD may be observed without the presence of relative loss of RNFL in the affected eye (Besada et al., 2017; Takizawa, et al. 2015; Noval et al., 2011). For instance, while RNFLT loss tends to occur after three to six months following an acute episode of anterior optic neuritis, during the acute phase paradoxically an increase in RNFLT has been reported. Similarly, in patients with multiple sclerosis without previous episodes of optic neuritis, the RNFLT loss is milder that in patients with optic neuritis and appears isolated to the temporal quadrant. In such cases, a RAPD may be observed without significant or even absence of RNFLT loss (Takizawa et al., 2015; Noval et al., 2011).

Conclusion

The GLV and FLV percentage were the more sensitive parameters at determining an eye with a RAPD. The FLV percentage value was the most sensitive overall. Similarly, the FLV percentage value may reflect and help categorize optic neuropathy severity more sensitively. This information may assist at alerting the clinician of the probable presence of a RAPD. In addition, it may aid at early detection and verifying progression of optic neuropathy. Further studies involving larger number of subjects across ethnic groups, using a computerized pupilometer and measurements of IPRGC activity should be conducted as it may serve to increment the sensitivity and specificity and facilitate identifying eyes at risk of optic neuropathy using SD-OCT. Other studies aiming at testing the capability of the methodology use in this study at identifying at risk populations or progression of optic neuropathy also should be promoted.

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