Retinal Blood Vessel Distribution Correlates With the Peripapillary Retinal Nerve Fiber Layer Thickness Profile as Measured With GDx VCC and ECC

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Purpose: Aim of the present study was to evaluate whether there is a correlation between retinal blood vessel density (RVD) and the peripapillary retinal nerve fiber layer (RNFL) thickness profile.

Methods: RNFL thickness of 106 healthy subjects was measured using scanning laser polarimetry, GDx variable corneal compensation (VCC), and GDx enhanced corneal compensation (ECC). A proprietary software was developed in MATLAB to measure the peripapillary retinal vessels using scanning laser ophthalmoscopy fundus images, centered on the optic disc measured by Cirrus spectral domain optical coherence tomography. The individual retinal vessel positions and thickness values were integrated in a 64-sector RVD profile and intrasubject and intersubject correlations were calculated.

Results: The mean R value $\pm$ SD for intrasubject correlation between RVD and RNFL thickness measured with GDx VCC and GDx ECC was 0.714 ± 0.157 and 0.629 ± 0.140 , with 105 of 106 subjects presenting significant correlations. In the intersubject linear regression analysis for GDx VCC, 33 of 64 (52%) sectors presented a significant Pearson correlation coefficient between RNFL thickness and RVD values, with a mean R value of 0.187 ± 0.135 ($P < 0.05$).

Conclusions: Peripapillary RNFL thickness profiles correlate with the RVD over 50% of the sectors and might explain up to 26% of the interindividual variance of the peripapillary RNFL thickness values as measured with GDx VCC. To our opinion, taking into account RVD might reduce interindividual variation in peripapillary RNFL thickness profiles measured with scanning laser polarimetry.

Key Words: peripapillary RNFL distribution, retinal blood vessel location, scanning laser polarimetry, glaucoma diagnostics

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In glaucoma, progressive loss of retinal ganglion cell axons results in peripapillary retinal nerve fiber layer (RNFL) thinning. Since the introduction of scanning laser polarimetry (SLP), which uses polarized light to measure RNFL thickness along a circular band around the optic disc (OD), it is possible to obtain in vivo measurements of the RNFL thickness. This measurement technique discriminates well between normal subjects and glaucoma patients by comparing the resulting RNFL thickness profiles to normative data.^{1,2} In several studies conducted by SLP, some overlap in thickness values between normal subjects and glaucoma patients have been reported.^{1–4}

Early diagnosis and treatment reduce the risk of visual loss due to glaucoma. RNFL thinning may be measurable even before morphologic changes of the OD become visible and visual field defects occur. However, interindividual variability increases the number of false-positive and/or false-negative results and thus hampers the use of RNFL measurement for early diagnosis. It appears logical that normative values will be more specific when normal physiological differences are taken into account. Hence, understanding the sources of the intersubject variability is central for the improvement of RNFL thickness measurement as a test for early glaucomatous damage.

Hood et al⁵ have demonstrated that the shape of the SLP RNFL profiles varied systematically with the location of the superior and inferior temporal veins and arteries. Furthermore, we were recently able to show that a more oblique retinal vessel course of the major temporal blood vessels is associated with a more oblique location of the arcuate bundles of retinal nerve fibers.⁶

Following the above idea, in the present study we expanded the model to measure all retinal blood vessels around the OD. We created the peripapillary retinal blood vessel density profile (RVD), which is a function of density and thickness of all measurable peripapillary retinal vessels.⁷

It was the aim of the present study to examine whether there is an association between the RVD profile and the peripapillary RNFL distribution in healthy subjects measured with GDx variable corneal compensation (VCC) and GDx enhanced corneal compensation (ECC).

SUBJECTS AND METHODS

Subjects

The study protocol was approved by the Ethics Committee of the Medical University of Vienna and followed the guidelines of Good Clinical Practice and the Declaration of Helsinki. The nature of the study was explained to all subjects and they gave written consent to participate.

Inclusion and Exclusion Criteria

Inclusion criteria were normal ophthalmic findings, especially normal appearance of the OD, normal visual fields, and intraocular pressure (IOP) and lack of significant retinal disorder. An abnormal visual field was defined as a glaucoma hemifield test outside normal limits and/or a corrected pattern SD with $P < 0.05$.⁸ A normal IOP was defined as ≤ 21 mm Hg. Any of the following excluded a subject from participation in the trial: evidence of any eye disease except refractive error, astigmatism $> +2.0$ D, and ametropia of $> \pm 5.0$ D.

Experimental Paradigm

Initially, a prestudy screening was carried out, where the medical and ocular history was taken. A complete ophthalmological examination was performed, including fundoscopy, visual acuity, measurement of IOP by Goldmann applanation tonometry, and standard automated perimetry.

Subjects eligible for participating in the study according to the inclusion/exclusion criteria were included. If both eyes were includable, 1 eye was selected randomly.

The study was performed at the Department of Ophthalmology, Allgemeines Krankenhaus, Medical University of Vienna, Austria.

METHODS

Automated visual field testing was performed with the Humphrey field analyzer II (program 30-2). Visual field eligibility criteria were $<33\%$ false-positive responses, $<33\%$ false-negative responses, and $<33\%$ fixation losses.

SLP measurements were performed using a commercial GDx VCC system, version 5.5.0 (NDB version 1.05.00; Carl Zeiss Meditec, Dublin, CA). In addition, we used the GDx ECC method, which provides individualized corneal compensation with enhanced SLP measurement sensitivity. Details of set-up are described elsewhere.^{9–11} Briefly, SLP assesses RNFL thickness in the peripapillary retina by measuring the RNFL retardation with a near-infrared diode laser.

In our study, each subject with pupils undilated had scans on the same day performed by an experienced operator. The spherical equivalent refractive error was tested subjectively and entered into the software to allow the GDx VCC and ECC to focus on the retina. All selected images were of high quality (quality scan score of ≥ 8) with a centered OD, were well focused and illuminated throughout the image, and were without motion artefacts. A fixed concentric measurement band with 27 pixels (approximately 2.4 mm) inner and 35 pixels (approximately 3.2 mm) outer diameter was centered on the OD, after which the measurements of peripapillary retardation were conducted. Areas of blood vessels are a source of noise¹² and are therefore automatically excluded for analysis by the GDx software. Retardation was converted to an estimate of RNFL thickness by the software. The GDx data were exported to a personal computer for data analysis. All analyses were done for GDx VCC and ECC. The parameters investigated in this study were RNFL thickness values of 64 sectors (plots) on the measurement band around the OD.

In addition, spectral domain optical coherence tomography (Cirrus Carl Zeiss Meditec) measurements were conducted using the OD cube protocol. The scanning

laser ophthalmoscopy images were exported into a personal computer. To assess the peripapillary retinal vessel thickness and position, a proprietary software was developed in Matlab (Matlab R2009b; Mathworks Inc., MA). With this tool, a trained grader (S.W.) manually determined the OD border and the limits of all measurable retinal vessels at the OD vicinity on each scanning laser ophthalmoscopy image. The centers of the vessels were automatically determined. To assess the position, for each vessel we determined the angle of the intersection between a horizontal line passing through the OD center and a line between OD center and the center point of the vessel measured at the OD border. The OD border was divided into 64 sectors, to enable a correlation with the 64 RNFL thickness plots measured with GDx VCC and ECC. For each of those sectors, the software algorithm looked for vessels with appropriate angles and summed up the thickness values of all measured vessels contained in each sector. Data were convoluted with a Gaussian-shaped function to generate a peripapillary RVD profile. The RVD profile is thus a function of density and thickness of all measurable peripapillary retinal vessels.

Statistical Methods

All statistical analyses were performed using the SPSS software package (SPSS Inc.) release no. 17.0.1.

A $P < 0.05$ was considered the level of significance.

We calculated the intersubject correlation between the RVD profile and the RNFL thickness profile for different bandwidths that define the Gaussian shape. The Gaussian function is defined as:

$$(n) = e^{-\frac{1}{2} \left(\frac{x - \mu}{\sigma} \right)^2}$$

We used a grid search method, calculating the median value (for the 64 sectors) for intersubject correlation for every set combination of N ranging from 2 until 64 and α ranging from 2.5 until 10, with a step size of 0.1. From all combinations, the one with the maximum median value of intersubject correlation was considered the optimum set for the Gaussian curve description. These parameters were determined separately for GDx VCC and ECC and were used for the analyses presented in this manuscript. Figure 1 shows an example of the individual retinal vessels' positions and thicknesses (vertical dashed lines), as well as the RVD profiles (solid line) for GDx VCC and ECC.

Pearson correlation coefficient of each individual RVD profile with the respective RNFL thickness profile was calculated to assess the strength of intrasubject correlation.

Intersubject correlation was calculated by a linear regression analysis, using each RVD sector of all subjects as independent variable and each sector of the RNFL thickness profile as dependent variable. To depict the slopes of the regression lines of the 64 sectors according to the formula ($y = Kx + d$) and their significances we plotted a modified temporal-superior-nasal-inferior-temporal (TSNIT) graph using K values (slopes) and the upper and lower limits of the 95% confidence interval (CI) of the K values. Statistical significance of the slope was reached when the 95% CI did not include zero and if both limits of the 95% CI are positive or negative ($P < 0.05$). In addition, the Pearson correlation coefficient was calculated for the intersubject correlation between each RNFL sector and the corresponding RVD sector.

FIGURE 1. A, Example of an individual retinal vessel thickness assessment at the optic disc border in a healthy subject, performed by a trained grader (numbered). B, Example of peripapillary distribution of individual retinal vessel thickness values (vertical dashed lines) with the corresponding vessel number and the respective results of the convolution with a Gaussian shaped function (solid line).

To test the linearity of regression, we performed a stepwise multiple linear regression analysis using the RVD and its square as independent variables.

In addition, the coefficients of variance (CV) of 12 clock-hour sectors for both, the measured RNFL thickness and for the compensated RNFL thickness according to our model were calculated. The compensated RNFL thickness was calculated according to the formula:

$$RNFL_{comp} = RNFL_{mean} - (RVD_i - RVD_{mean}) \times \text{slope},$$

where RVD_i is the individual RVD.

RESULTS

From 127 screened subjects, 8 subjects had to be excluded because of bad image quality and/or RNFL measurement errors and 13 due to errors of the exact determination of vessel borders. Hence, all data are from 106 subjects, both sexes aged between 20 and 76 years. Subjects' baseline characteristics, IOP, and visual field MD are given in Table 1.

GDx VCC

The maximum median R value of intersubject correlation between RVD and RNFL thickness measurements obtained with GDx VCC was 0.202, with $N = 31$ and $\alpha = 2.6$.

Using these settings as optimal parameters, the mean R value $\pm$ SD for intrasubject correlation between RVD and RNFL thickness measured with GDx VCC was 0.714 ± 0.157 , with a statistically significant positive correlation in 105 of 106 cases.

Intersubject linear regression analysis was performed for each sector. In this analysis, 33 of 64 (52%) sectors presented a significant Pearson correlation coefficient between RNFL thickness and RVD values, with a mean R value $\pm$ SD of 0.187 ± 0.135 (Table 2).

GDx ECC

The maximum median R value of intersubject correlation between RVD and RNFL thickness measurements

obtained with GDx ECC was 0.185 ($N = 43$, $\alpha = 2.5$), whereas the mean R value $\pm$ SD for intrasubject correlation was 0.629 ± 0.140 , in this case, with 105 of 106 cases presenting statistically significant positive correlations.

For the intersubject linear regression analysis between RNFL thickness measured with GDx ECC and RVD values, 29 of 64 (45%) sectors presented a significant Pearson correlation coefficient, with a mean R value $\pm$ SD of 0.191 ± 0.116 (Table 2). The sectors that did not present a significant correlation correspond to nasal areas.

Both, average TSNIT profiles of RNFL, as measured with GDx VCC and ECC and the average RVD profiles are presented in Figure 2. The similarity of each of the 2 TSNIT profiles with the RVD profiles is easily recognized. The difference between the 2 average RVD profiles is explained by the different settings of the Gaussian function as obtained by the optimization processes.

Figure 3A displays a modified TSNIT graph, measured with GDx VCC and ECC, based on the intersubject linear regression analysis. The slopes of the 64 sectors (solid line) are plotted together with their 95% CIs (dashed lines). The slopes reach their maximum at the temporal superior and temporal inferior areas.

To estimate the impact of the RVD profile variation on the RNFL thickness, we calculated the difference between the 10th and the 90th percentile of the RVD profile

TABLE 1. Subjects Baseline Characteristics, IOP, and Visual Field MD

Age (y)	36.9 $\pm$ 16.9*
Sex (female/male)	57/49
Refractive error (D)	+ 0.05 $\pm$ 1.46*
IOP (mm Hg)	14.8 $\pm$ 2.4*
MD (dB)	-0.13 $\pm$ 1.04*

*Results are presented as means $\pm$ SD ($n = 106$).
IOP indicates intraocular pressure.

TABLE 2. Statistical Analysis for Intrасubject and Intersubject Pearson Correlation Coefficients Measured With GDx VCC and GDx ECC

	GDx VCC Intrасubject Correlation Coefficients	GDx VCC Intersubject Correlation Coefficients	GDx ECC Intrасubject Correlation Coefficients	GDx ECC Intersubject Correlation Coefficients
Significance	105 (106) subjects	33 (64) sectors	105 (106) subjects	29 (64) sectors
Maximum	0.951	0.507	0.888	0.463
Minimum	0.225	0.005	0.217	0.003
Mean	0.714	0.187	0.628	0.191
Median	0.753	0.202	0.636	0.185
SD	0.157	0.135	0.141	0.116
25 percentile	0.630	0.040	0.527	0.087
75 percentile	0.830	0.297	0.740	0.268
90 percentile	0.885	0.356	0.799	0.342

ECC indicates enhanced corneal compensation; VCC, variable corneal compensation.

at each of the 64 locations. We multiplied these values by the slopes of intersubject regression analysis (Fig. 3B). For each location, this calculation gives the expected difference in RNFL thickness between subjects with thin versus thick (or few vs. many) retinal vessels. This difference reached its maximum in the temporal inferior region and amounted to 20 μ m for GDx VCC and 15 μ m for GDx ECC.

Table 3 presents the interindividual CV for the TSNIT profile of RNFL, divided into 12 clock-hour sectors, starting from temporal. The variances of the measured data are compared to those of the compensated values (according to the model). For the clock-hour sectors, our model

reduced the CV up to 2.0 percentage points, which is a relative reduction of 10% in the GDx VCC, whereas the maximum relative reduction was 8.8% in GDx ECC.

DISCUSSION

Peripapillary RNFL thickness profiles vary considerably among the healthy population. We have previously suggested that taking into account the location of major temporal blood vessels may decrease the interindividual variability of RNFL measurement by SLP.⁶

FIGURE 2. Average temporal-superior-nasal-inferior-temporal (TSNIT) profiles based on 106 healthy subjects. A, Retinal nerve fiber layer (RNFL) average TSNIT profile for GDx variable corneal compensation (VCC) and enhanced corneal compensation (ECC). B, average profile of Gaussian-shaped functions of retinal vessel density (RVD) for GDx VCC and GDx ECC. Solid lines represent the average values; dashed lines represent average values $\pm$ SD.

FIGURE 3. A, Modified temporal-superior-nasal-inferior-temporal (TSNIT) graph, based on the slopes of the regression lines of all sectors (solid line) and 95% confidence interval (CI) (dashed lines) for GDx variable corneal compensation (VCC) and enhanced corneal compensation (ECC). B, Modified TSNIT graph, for the expected difference in retinal nerve fibre layer thickness (RNFL) thickness between 2 subjects at the 10th and the 90th percentile of retinal vessel density (RVD) for GDx VCC and ECC. Solid line represents the differences. Dashed lines represent the 95% confidence interval (CI). One pixel corresponds to 10.845 μm .

It has been established that there is an association of retinal blood vessels and the formation of thicker branches of RNFL. The development of blood vessels is influenced by the axonal distribution, as axons offer guidance for sprouting and developing vasculature in the retina and may share common guidance signals.^{13,14} Considering these findings one should expect some correlation between the location of retinal arteries and veins, for example and the distribution of retinal ganglion cell axons. As a consequence, the location of the blood vessels may help to predict the variation of RNFL thickness profiles because they indicate regions of increased axonal density.

In the present study, we included into the analysis all measurable retinal blood vessels around the OD, the RVD profile (relying on an average of 9.97 vessels with a range from 6 to 15 vessels) of 106 healthy eyes. The RVD profile is a function of density and thickness of retinal vessels. On the basis of the assumption that the particular locations of vessels do not mark the RNFL thickness at those specific locations, but rather reflect their vicinity, we did not take the retinal blood vessel position value itself, but convoluted the specific values with a Gaussian function, obtaining a density profile (RVD). This RVD profile was equally distributed into 64 sectors corresponding to the RNFL plots measured with GDx. As expected, there was considerable interindividual variation of the RVD profiles. Our data indicate that about 50% of the TSNIT profile of RNFL, as

measured with GDx VCC and ECC is influenced by vessel location and thickness. Intraindividually, 99% of the subjects presented a significant correlation between RVD profile and the TSNIT profile of RNFL. Measured with GDx VCC, for some sectors up to 26% of the inter-individual variance of the RNFL thickness can be explained by distribution of retinal vessels around the OD. We furthermore were able to show that especially for the temporal inferior areas, the expected difference in RNFL between healthy subjects with relatively thin and thick RVD at these locations may be 20 μm , which is clinically relevant.

Recently, Hood et al⁵ demonstrated that the adjustment for temporal retinal blood vessel locations had only a little and negligible effect on the interindividual variability of RNFL thickness of quadrants and the arcuate regions, as measured with OCT and SLP. This finding might be explained by the fact that they included only 4 retinal blood vessels into their analysis. Contrary to their approach, we have developed a method that takes into account all measurable peripapillary retinal blood vessels. Furthermore, the approach to simply rotate the RNFL profile to compensate for the retinal vessel location is based on the assumption that the shape of the TSNIT curve does not change which is questionable. Finally, it is not surprising that quadrant averages are not influenced by an average rotation of possibly 10 degrees. In our study we report a reduction of only 2 percentage points of the variance of the peripapillary RNFL

TABLE 3. CV for RNFL Thickness Measured With GDx VCC and ECC Divided in Clock-Hour Sectors (Sector 1 = Temporal) and Compensated by the Model

Sectors	CV RNFL (GDx VCC)	CV RNFL (Model)	CV Differenc
Sector 1	30.999	30.209	0.789
Sector 2	30.939	29.480	1.459
Sector 3	24.883	23.376	1.507
Sector 4	15.187	15.114	0.073
Sector 5	14.594	14.526	0.068
Sector 6	20.931	20.902	0.029
Sector 7	25.125	25.114	0.011
Sector 8	26.117	25.081	1.036
Sector 9	17.937	17.712	0.225
Sector 10	14.626	14.617	0.009
Sector 11	20.005	17.977	2.028
Sector 12	33.692	31.902	1.789

Sectors	CV RNFL (GDx ECC)	CV RNFL (Model)	CV Differenc
Sector 1	29.026	28.900	0.126
Sector 2	31.635	30.564	1.071
Sector 3	26.092	24.722	1.370
Sector 4	13.560	13.445	0.116
Sector 5	13.706	13.554	0.152
Sector 6	23.118	23.104	0.014
Sector 7	27.652	27.634	0.018
Sector 8	29.705	28.672	1.032
Sector 9	15.903	15.506	0.397
Sector 10	12.499	12.341	0.158
Sector 11	18.796	17.148	1.648
Sector 12	31.332	29.451	1.881

CV indicates coefficients of variance; ECC, enhanced corneal compensation; RNFL, retinal nerve fiber layer; VCC, variable corneal compensation.

thickness for some locations, which was a relative reduction of 10%. Although this may be considered as irrelevant, it possibly reflects the fact that most participants had more typical RNFL distribution in our sample (as in the average population), which reduces the average impact of our model. However, for subjects with a more atypical distribution of the RNFL our findings may be clinically relevant, especially for the temporal superior and inferior regions.

Limitations that need to be considered when discussing the results of our experiment are the assumption of a linear association between RVD and RNFL thickness. To test a possible nonlinear relationship we additionally performed a stepwise multiple regression analysis including a quadratic term of RVD. This analysis demonstrated a nonlinear relationship for 12% of those plots with significant results (measured with GDx ECC). However, the effect of nonlinearity was small and taking into account this effect, did not significantly increase the mean intersubject correlation (data not shown). Furthermore, Kim et al¹⁵ were able to show a significant association between narrowing of retinal arteries and RNFL thinning and visual field defects in patients with glaucoma. Retinal venular caliber was not significantly associated with RNFL thickness. To which extent retinal vessel attenuation secondary to glaucoma may negatively affect our approach of individualizing the RNFL profile, are subject of future investigations. However, the RVD profile in our study is a function of density and thickness of both, peripapillary

arteries and veins while apparently only the arterial diameters are significantly correlated with functional and morphologic glaucomatous damage.

In the present study we aimed to examine the physiological correlation between vessel distribution and RNFL in a healthy study population. Further studies in glaucoma patients are necessary.

In conclusion, our results may have implications for the understanding of RNFL measurement results in glaucoma diagnostics. The present model of peripapillary RVD profile might explain up to 26% of the interindividual variance for some RNFL areas, and shows a significant correlation with RNFL thickness for about 50% of the sectors. When using our model to compensate peripapillary RNFL thickness for individual RVD in clock-hour sectors, the interindividual variance was reduced by 10% (relative reduction). Although this may sound a minor reduction, our model still may be of clinical interest, because generally a reduced variability of a measurement value is expected to translate into an increase of diagnostic separation. We have demonstrated that the difference between individual RNFL thicknesses as a result of variation in the RVD profile may amount 20 μ m for clinically relevant locations. Taking into account peripapillary retinal blood vessel distribution might reduce interindividual variation in peripapillary RNFL thickness profiles using SLP.

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