Relationship Between Central Retinal Vessel Trunk Location and Visual Field Loss in Glaucoma

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• PURPOSE: To study the relationship between horizontal central retinal vessel trunk location (CRVTL) on glaucomatous optic discs and sector-specific visual field (VF) loss.
• DESIGN: Retrospective cross-sectional study.
• METHODS: CRVTL of 421 eyes from 421 patients was manually tracked on the horizontal optic disc axis on fundus images. Focal circumpapillary retinal nerve fiber layer thickness (cpRNFLT) measurements were extracted from optical coherence tomography (OCT). The relationship between focal visual field (VF) loss and CRVTL and focal cpRNFLT was studied by linear regression models. Furthermore, we related central VF loss to CRVTL and focal cpRNFLT separately for mild (VF mean deviation [MD] ≥ -6 dB), moderate (-12 dB $\leq$ MD < -6 dB), and severe (MD < -12 dB) glaucoma.
• RESULTS: CRVTL nasalization was significantly correlated only to central VF loss (Garway-Heath scheme [central 6 locations, C6]: correlation: $r = -0.16$, $P < .001$; macular vulnerability zone [central 2 locations, C2]: $r = -0.14$, $P = .003$; central 4 locations [C4]: $r = -0.17$, $P < .001$). While focal cpRNFLT at the sectors corresponding to C2 and C6 was significantly correlated to the respective VF sectors as well (C2: $r = 0.15$, $P = .002$; C6: $r = 0.10$, $P = .03$), multivariate models combining cpRNFLT and CRVTL substantially improved structure-function models compared with cpRNFLT alone (likelihood ratio tests, C2 and C6: $P < .001$). The correlations between CRVTL and central VF loss of C4 were -0.11 ($P = .04$), -0.39 ($P = .01$), and -0.63 ($P = .002$) for mild, moderate, and severe glaucoma, respectively.
• CONCLUSIONS: CRVTL nasalization is significantly and exclusively correlated to central VF loss for all glaucoma severities independent of cpRNFLT, and thus might be a structural biomarker of central VF loss. (Am J Ophthalmol 2017;176:53–60. © 2017 Elsevier Inc. All rights reserved.)

GLAUCOMA IS CHARACTERIZED BY OPTIC NERVE damage that leads to structural change with accompanying visual field (VF) loss.[1,2] Structure-function modeling provides a construct to understand the onset and progression of glaucoma and has therefore been extensively investigated in previous research.[3–7] For example, retinal nerve fiber layer thickness has been shown to be related to vision loss in glaucoma,[8] and disc tilt has been associated with the location of initial glaucomatous damage.[5]

The relationship between retinal structure and sector-specific VF loss is of particular clinical relevance. The most well-known sectoring scheme for the purpose of mapping retinal damage to sector-specific VF loss was proposed by Garway-Heath and associates.[9] Aside from retinal nerve fiber layer thickness changes, blood vessel positional shift outside the optic nerve head (ONH) has been shown to be associated with glaucoma functional progression.[4] Furthermore, central retinal vessel trunk (ie, the vessel cluster within the ONH) location (CRVTL), which marks the exit position of the retinal vessels on the optic disc, was shown to be associated with spatial patterns of VF loss. In particular, 1 previous study related CRVTL to central VF loss in end-stage glaucoma,[10] while a recent conference abstract reported a higher incidence of temporal VF defects for more temporal CRVTL.[11]

In this work, we quantitatively and systematically study the relationship between sector-specific VF loss and the horizontal CRVTL on the optic disc across the spectrum of glaucoma disease severity.

METHODS

THIS RETROSPECTIVE CROSS-SECTIONAL STUDY WAS approved by the institutional review board (IRB) of Massachusetts Eye and Ear (MEE). The IRB waived the need for

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informed consent because of the retrospective nature of the study. The study adheres to the Declaration of Helsinki and all federal and state laws.

• **PARTICIPANTS AND DATA:** Circumpapillary ONH optical coherence tomography (OCT) scans and accompanying VFs (SITA Standard 24-2 protocol) of all patients who presented at MEE glaucoma service between January 2011 and 2014 were initially selected and electronically transferred from the machines (Humphrey Field Analyzer HFA-II and Cirrus HD-OCT, Software version 6.5; Carl Zeiss Meditec AG, Jena, Germany). The initial data selection criteria for VF were fixation loss ≤33%, false-negative rates ≤20%, and false-positive rates ≤20%. The data selection criteria for Cirrus OCT scan (Optic Disc Cube protocol with pixel resolution 200 × 200 within an area of 6 mm × 6 mm) were signal strength ≥6 and within 1 year from the VF measurement. If more than 1 measurement per eye met the criteria, the most recent measurement was selected. If both eyes of a patient met the selection criteria, only 1 eye was included randomly to avoid potential bias of data samples. As such, we had 2161 pairs of OCT and VF measurement of 2161 eyes from 2161 patients, which satisfied the criteria of the initial data reliability check.

• **DATA PROCESSING:** The ONH center is measured using a proprietary technique by the Cirrus OCT machine and then marked on the fundus image. A total of 221 eyes with decentered ONH on OCT scans, defined as OCT scans with ONH centers that deviated more than 0.3 mm in horizontal and vertical direction from the fundus image center, were excluded. OCT fundus images and thickness plots were visually examined by a trained observer for missing thickness data (black pixels on thickness plots) and motion artifacts (defined as vessel shifts of more than 1 vessel diameter or a visible shift within ONH). A total of 167 eyes were excluded because of missing data, and 1082 eyes were excluded owing to motion artifacts. One hundred twenty-two eyes were excluded for missing diagnostic data in the medical record of the respective patient. In addition, we excluded 7 eyes with unidentifiable CRVTL on fundus image owing to low image quality. As our focus was central VF loss induced by glaucoma, we excluded 124 and 17 eyes with cataract (nuclear sclerosis 3+ or worse) and age-related macular degeneration (AMD), respectively. Ultimately, 421 out of 2161 eyes were retained for data analyses.

• **CENTRAL RETINAL VESSEL TRUNK LOCATION TRACKING:** For CRVTL tracking, we developed a customized software in programming language R (version 3.2.2; R Foundation, Vienna, Austria).[12] In previous work by Huang and associates,[10] CRVTL was defined as the ratio between the distance from CRVT to temporal disc border and the horizontal disc diameter. To take disc torsion into account, we calculated the optimally fitted ellipse around the ONH border (determined by the Cirrus machine based on the OCT volume scan).[13] The fitted ellipse centered at the ONH center was parameterized by major axis, minor axis, and rotation angle. Nonlinear optimization[14] was applied to obtain the optimal fitted ellipse by minimizing the boundary discrepancy between the ellipse and ONH. A trained observer marked the CRVTL on the minor axis (temporal-nasal direction) of the ellipse on each fundus image, as shown in Figure 1. The CRVTL on minor axis was normalized into the range between 0 (temporal pole) and 1 (nasal pole) of the ellipse.

• **STATISTICAL ANALYSES:** All statistical analyses were performed using the R platform.[12] We applied 2 different VF sectoring schemes and calculated the correlation between CRVTL and average pattern deviation (PD) of each VF sector. The usage of PD was motivated by our intention to emphasize visual sensitivity within each sector relative to the general height of vision. The 2 sectoring schemes of VF encompass the well-known Garway-Heath scheme[9] and our annular scheme, as illustrated in Figure 2 (Left and Right, respectively). The motivation to use an annular scheme was to test whether CRVTL is only associated with central VF loss rather than peripheral VF loss, since temporal CRVTL has been shown to be related to the preservation of central VF loss in end-stage glaucoma.[10] The Garway-Heath scheme was additionally tested because temporal VF defects were related to temporal CRVTL,[11] suggesting that the association of CRVTL with VF loss might reach beyond pure center-periphery differences. *P* values of the correlations for each sector were corrected for multiple comparisons.[15]

For the sectors for which CRVTL was significantly correlated to the sector VF loss, we evaluated the relationship between focal circumpapillary retinal nerve fiber layer thickness (cpRNFLT), which was mapped to the specific sector of VF in established works,[16,9] and the corresponding sector VF loss. In addition, multivariate analyses were performed to assess whether focal cpRNFLT and CRVTL were independently correlated to the corresponding sector VF loss. Lastly, we performed a correlation test for mild (including suspects) (mean deviation [MD] ≥−6 dB), moderate (−12 dB ≤ MD < −6 dB), and severe (MD < −12 dB) glaucoma, respectively.[17] Our definition of mild glaucoma includes VFs with non-negative MD, as relative differences of light sensitivity between center and periphery, captured by PD values, may be present over the whole MD range, including VFs with normal and supernormal MD. Particularly the group that we called "mild glaucoma" is expected to contain a substantial number of glaucoma suspects in addition to true glaucoma patients.