Comparison of Retinal Vessel Diameter Between Open-Angle Glaucoma Patients With Initial Parafoveal Scotoma and Peripheral Nasal Step

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• PURPOSE: To compare retinal vessel diameters (RVDs) between open-angle glaucoma (OAG) patients with initial parafoveal scotoma (PFS) and those with initial peripheral nasal step (PNS).
• DESIGN: Retrospective, cross-sectional study.
• METHODS: We enrolled 151 eyes of 151 patients with OAG (83 with normal-tension glaucoma [NTG] and 68 with primary open-angle glaucoma [POAG]). The patients were categorized into the PFS and PNS groups according to the location of the initial visual field (VF) defect. Clinical characteristics and RVD indices—central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE)—were compared between the groups. Subgroup analyses were conducted in the NTG and POAG groups.
• RESULTS: Forty-six patients had PFS and 105 had PNS. The CRAE of the PFS group was significantly lower than that of the PNS group in all glaucoma patients ($P = .001$). However, neither the mean deviation in VF nor that in the average retinal nerve fiber layer thickness showed significant intergroup differences. In the NTG subgroup analysis, the CRAE of the PFS group was significantly lower than that of the PNS group ($P = .013$). Conversely, in the POAG subgroup analysis, the CRAE in the PFS group did not differ significantly from that in the PNS group ($P = .123$).
• CONCLUSIONS: Retinal arteriolar diameter was narrower in OAG patients with initial PFS than in those with initial PNS, especially in the NTG group. This suggests that the initial location of the VF defect may be associated with the vascular mechanism in patients with glaucoma. (Am J Ophthalmol 2017;175:30–36. © 2016 Elsevier Inc. All rights reserved.)

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ALTHOUGH INTRAOCULAR PRESSURE (IOP) IS THE most important and only known modifiable risk factor for glaucoma,[1–4] not all patients with glaucoma show elevated IOP. The Collaborative Normal-Tension Glaucoma study reported that 20% of the patients with normal-tension glaucoma (NTG) show visual field (VF) deterioration, even after a 30% IOP reduction from baseline.[2] Accumulating evidence indicates that, in addition to mechanical factors, vascular pathology plays a role in open-angle glaucoma (OAG). The relationships between glaucoma and vascular factors, such as migraine,[5,6] optic disc hemorrhage,[7,8] and vasospasm,[9] are well established. Furthermore, many reports have suggested that glaucoma itself is associated with the retinal vasculature. A previous study showed that retinal vessel diameter (RVD) decreases significantly with increasing glaucoma stage, independently of the patients' age.[10] Large, population-based, cross-sectional studies have corroborated this result.[11–13]

Several reports have documented that the location of the VF defect can vary according to glaucoma type. For instance, parafoveal scotomas (PFSs) occur more frequently in patients with NTG than in those with primary open-angle glaucoma (POAG).[14–16] This higher frequency of central VF defect in patients with NTG suggests that the pathologic mechanism of PFS, unlike that of peripheral VF loss, involves vascular factors. This postulation has been supported by subsequent studies that found a significant relationship between central VF defect and vascular risk factors. Park and associates reported that the maximum untreated IOP was lower, and the frequency of disc hemorrhage detection higher, in patients with an initial PFS than in patients with an initial peripheral nasal step (PNS).[17] Furthermore, the prevalence of systemic vascular risk factors, including hypotension, migraine, and Raynaud phenomenon, was significantly higher in the PFS group than in the PNS group.[17] However, to our knowledge, RVDs have not yet been used to characterize VF defects.

Based on the possibility that vascular pathology has an influence on PFS, we hypothesized that RVDs differ according to the location of the initial VF defect in patients with glaucoma. The purpose of this study was to compare the RVD indices between patients with OAG and an initial PFS and those with OAG and an initial PNS. In addition, we assessed factors related to RVD in patients with glaucoma.

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METHODS

THIS INVESTIGATION WAS A RETROSPECTIVE ANALYSIS OF 151 patients with OAG who were enrolled from a clinical database maintained at the glaucoma clinic of the Korea University Guro Hospital, Seoul, South Korea. To identify eligible participants for the study, we reviewed the records of all patients with established glaucoma who had presented to the glaucoma clinic between January 2, 2012 and March 31, 2014. Ethical approval for this retrospective study was obtained from the hospital's Institutional Review Board, and the study adhered to the tenets of the Declaration of Helsinki.

At the initial evaluation, each participant underwent a comprehensive ophthalmologic examination, including a detailed review of medical and ocular histories, measurement of best-corrected visual acuity, slit-lamp biomicroscopy, autorefraction, Goldmann applanation tonometry, axial length measurement, central corneal thickness measurement using a specular microscope, gonioscopic examination, and automated perimetry using the 30-2 Swedish Interactive Threshold Algorithm standard program (Zeiss-Humphrey, San Leandro, California, USA). The peripapillary retinal nerve fiber layer (RNFL) thickness was measured using spectral-domain optical coherence tomography (3D OCT-1000 Mark II, software version 3.20; Topcon Corp, Tokyo, Japan). Dilated 30-degree stereoscopic photography and 50-degree red-free photography (model FF450 Plus; Carl Zeiss Meditec AG, Jena, Germany) were also conducted.

The inclusion criteria were as follows: age >18 years, best-corrected visual acuity >20/30, spherical equivalent between −6.0 and +4.0 diopters, cylinder correction within ±3.0 diopters, and at least 2 reliable VF results. The exclusion criteria were as follows: (1) history of ocular trauma or surgery including trabeculectomy or Ahmed valve implantation, but with the exception of uncomplicated cataract surgery; (2) any medial opacity that prevented good-quality optic disc photography or other imaging tests; (3) history of any retinal disease, such as diabetic retinopathy, retinal vessel occlusion, or epiretinal membrane; (4) optic nerve disease other than glaucoma; and (5) history of a cerebrovascular event that could have affected the VF.

OAG was diagnosed on the basis of the presence of glaucomatous VF loss together with corresponding glaucomatous optic disc changes (neuroretinal rim thinning, notching, and excavation). Gonioscopy was used to exclude angle closure, rubeosis, and secondary glaucoma. A glaucomatous VF change was defined as (1) the consistent presence of a cluster of 3 points with $P < 5\%$ on the pattern-deviation map in at least 1 hemifield, including at least 1 point with $P < 1\%$; (2) glaucoma hemifield test results outside of the normal limits; or (3) a pattern standard deviation (PSD) beyond 95% of the normal limits, as confirmed by at least 2 reliable VF test results and with a false-positive error <15%, a false-negative error <15%, and a fixation loss <20%. On the basis of the data from the Namil study,[18] the patients with OAG were categorized into 2 subgroups—NTG and POAG—depending on the level of untreated IOP. POAG was defined as OAG with a baseline IOP of ≥20 mm Hg, whereas NTG was defined as an IOP of <20 mm Hg throughout the follow-up period.

• **VISUAL FIELD CRITERIA FOR PERIPHERAL NASAL STEP AND PARAFOVEAL SCOTOMA:** In the glaucoma group, only patients with an initial PFS or PNS in 1 hemifield, as defined below, were enrolled. Based on a previous study,[17] PFS was defined as a glaucomatous VF defect with (1) ≥3 adjacent points with $P < 5\%$ within the central 10 degrees of fixation, (2) ≥1 point with $P < 1\%$ at the innermost paracentral point, and (3) no VF abnormality outside the central 10 degrees. In contrast, PNS was defined as a glaucomatous VF defect with (1) ≥3 adjacent points with $P < 5\%$ in the nasal periphery outside the central 10 degrees of fixation, (2) a nasal-most point with $P < 1\%$, and (3) no VF abnormality within the central 10 degrees. In patients in whom both eyes were eligible for the study, 1 eye was randomly chosen for inclusion.

• **MEASUREMENT OF RETINAL VESSEL DIAMETER:** Using a fundus camera (model FF450 Plus; Carl Zeiss Meditec AG), we obtained dilated 30-degree stereoscopic optic disc photographs centered on the disc. The methodology used for the measurement of RVD has been described elsewhere.[19–22] We used IVAN software version 1.3 (Department of Ophthalmology and Visual Science, University of Wisconsin, Madison, Wisconsin, USA) to obtain the RVD indices. This is a semiautomated software system that can measure the RVD on a digitized retinal image. The IVAN program automatically identified the optic disc and measured the diameter of the individual vessels; it then automatically calculated 2 variables—the central retinal arteriolar equivalent (CRAE) and the central retinal venular equivalent (CRVE)—by using the revised Parr-Hubbard formula. The vessel equivalents were designed to represent the average vessel diameter of the eye. Briefly, the 6 largest arterioles and venules, passing completely through a circumferential zone 0.5 to 1 disc diameter from the optic disc margin, were identified. Then, the vessel equivalents were approximated by using the following formulas:

$$\text{Arterioles} : W = 0.88\left(w_1^2 + w_2^2\right)^{1/2}$$

$$\text{Venules} : W = 0.95\left(w_1^2 + w_2^2\right)^{1/2}$$

where w_1, w_2, and W are, respectively, the widths of the narrower branch, the wider branch, and the parent trunk.