Retinal Nerve Fiber Layer Thickness Is Decreased in the Fellow Eyes of Patients with Unilateral Retinal Vein Occlusion

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Objective: To investigate whether retinal nerve fiber layer (RNFL) thickness is decreased in the fellow eyes of patients with unilateral retinal vein occlusion (RVO).

Design: Observational cross-sectional study.

Participants: Seventy-nine patients with unilateral RVO and 71 age-matched control subjects.

Methods: Optical coherence tomography (OCT)-measured RNFL thickness parameters (average, 4 quadrant, and 12 clock-hour thicknesses) were compared between unaffected eyes of patients with unilateral RVO and single randomly selected eyes of control subjects.

Main Outcome Measures: Optical coherence tomography-measured RNFL thickness.

Results: In the fellow eyes of patients with unilateral RVO, the mean intraocular pressure was 13.7±2.5 mmHg and the RNFL thickness was significantly thinner than in controls in the 10 and 11 o'clock sectors. In a subgroup analysis, which only included subjects aged more than 60 years, the global average and 7 and 11 o'clock sector thicknesses were significantly thinner than in controls. Glaucomatous visual field damage corresponding to RNFL defects was found in 15 unaffected eyes (19.0%) of subjects with RVO and 2 control subjects (2.8%) ($P = 0.004$).

Conclusions: In the fellow eyes of patients with unilateral RVO, RNFL thickness was decreased, especially in the inferior- and superior-temporal sectors, compared with that of control eyes. Difference between the groups also was noticeable on the visual field testing. These results suggest that RVO and glaucoma may share systemic risk factors reflecting a common pathogenic mechanism.

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An association between glaucoma or elevated intraocular pressure (IOP) and retinal vein occlusion (RVO) has been found in many studies.[1–10] It has been hypothesized that elevated IOP may compress blood vessels and induce subsequent intimal proliferation, thereby leading to collapse of retinal vessel walls.[5,6] Other authors have suggested that optic disc cupping may be associated with distortion of retinal vessels at the disk, predisposing the veins to occlusion.[8]

However, results from other studies suggest that the association between open-angle glaucoma and RVO may be, at least in part, a manifestation of a common underlying vascular abnormality, such as systemic hypertension,[2,7,11,12] diabetes mellitus,[2,13] or insulin-resistance,[14] rather than a reflection of cause and effect. Stewart and Clearkin[15] recently proposed that insulin resistance and the resultant vascular dysregulation and autoregulatory dysfunction may play pivotal roles in the cause of both RVO and glaucoma. We hypothesized that if RVO and glaucoma share systemic risk factors reflecting a common pathogenic mechanism, glaucomatous change may be present in the contralateral eyes of patients with RVO, regardless of IOP level. Thus, we measured retinal nerve fiber layer (RNFL) thickness, which may reflect the earliest glaucomatous change, in the contralateral eyes of patients with RVO using optical coherence tomography (OCT).

Materials and Methods

Subjects with unilateral RVO meeting eligibility criteria were consecutively enrolled from the retina clinic of Seoul National University Bundang Hospital. An age-matched control group was consecutively enrolled from subjects who had first visited the general ophthalmology clinic of the same hospital for dry eye syndrome. In the control group, if both eyes were eligible for the study, only 1 eye was randomly selected for inclusion. The procedures used conformed to the guidelines of the Declaration of Helsinki, and written informed consent was obtained from each subject. The study protocol was approved by the institutional review board of the Seoul National University Bundang Hospital.

Retinal specialists (WSJ and PKH) diagnosed RVO using dilated fundus examination, fundus photography, and fluorescein angiography. For subgroup analysis, the cases were classified into 4 groups according to the sites of venous occlusion using a modified classification of Beaumont and Kang.[3,8] They originally classified the RVO into 5 categories; arteriovenous crossing RVO (AV-RVO), the optic cup sited RVO, and optic nerve sited RVO

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with optical nerve head swelling (ONHS) or without optic nerve head swelling (NONHS) and no site RVO. In our modified classification, the optic cup and NONHS RVO were classified as 1 category: optic nerve sited RVO (ON-RVO). The rationale for this modification was that differentiation between optic cup sited occlusion and optic nerve sited occlusion without swelling is often ambiguous, as noted by Beaumont and Kang, and more important, optic cup sited occlusion and ONH sited occlusion without swelling share an important clinical feature (relation to IOP and primary open-angle glaucoma), suggesting that both types have similar pathogenesis.[3,8] Only patients with newly diagnosed RVO were included in the present study.

A detailed history, which included preexisting medical, ocular, and family history, was taken from all patients. Patients also underwent a full ophthalmic examination, including visual acuity measurement, a refraction test, Goldmann applanation tonometry, slit-lamp examination, dilated fundus examination, gonioscopy, stereo disc photography (using the EOS D60 instrument; Canon, Tochigiken, Japan), red-free RNFL photography (EOS D60), standard automated perimetry (Humphrey Field Analyzer II 750 instrument; Swedish Interactive Threshold Algorithm standard; Carl Zeiss Meditec, Dublin, CA), and OCT (Stratus OCT, Carl Zeiss Meditec).

If glaucoma was suspected in a patient or control subject on the basis of the above examination (i.e., with a cup-to-disc ratio ≥ 0.6, thinning or notching of the neuroretinal rim, localized pallor or RNFL defect with or without a glaucomatous visual field defect), diurnal IOP variation was measured between 9 AM and 5 PM on a single day, or at separate visits, to rule out unexpected IOP spikes. The medical records were sought of the 3 patients in the RVO group who had glaucoma treatment history outside of our clinic, and their baseline IOPs before glaucoma treatment were recorded.

Exclusion criteria for both patients and control subjects were a known history of uveitis, retinal disease (in the fellow eyes for patients with RVO), previous intraocular surgery other than cataract extraction, a neurologic disease such as migraine, or prior cerebrovascular accident. Subjects were also excluded if they had a best-corrected visual acuity <20/40 (in the fellow eyes for patients with RVO), a spherical refraction greater than ±5.0 diopter (D), cylinder correction greater than ±3.0 D, closed angles, or a disease that might affect the peripapillary area (where OCT measurements are obtained).

Optical Coherence Tomography

Optical coherence tomography was performed by a single examiner. All measurements were taken after pupillary dilation to a minimum diameter of 5 mm using the peripapillary Fast RNFL program. The operator centered the circular scan on the optic nerve head while the studied eye was fixated (internal fixation technique). With the Fast RNFL program, RNFL thickness is determined 3 times during a single scan at 256 points covering a set diameter (3.4 mm) around the center of the optic disc. These values are then averaged to yield 12 clock-hour thicknesses, 4 quadrant thicknesses, and a global average thickness (360-degree measure). We excluded all poor-quality scans, defined as those with signal strength <7, or overt decentration of the measurement circle location, assessed subjectively. All OCT data were aligned according to the orientation of the right eye. Thus, clock-hour 9 of the circumpapillary scan represented the temporal side of the optic disc in both eyes. The following OCT parameters were used in analysis: average RNFL thickness, mean RNFL thickness in each quadrant, and mean RNFL thickness in each of 12 clock-hour segments.

Visual Field Testing

Visual field analysis was performed using the Swedish Interactive Threshold Algorithm standard of the Humphrey Field Analyzer II 750 instrument and the central full-threshold program 24-2. Glaucomatous visual field loss was defined as the presence of a cluster of 3 or more non-edge points on the pattern deviation plot with a probability of occurrence in less than 5% of the normal population ($P<5\%$), and where one of the points had a probability of occurrence in <1% of the normal population ($P<1\%$), a pattern standard deviation with $P<5\%$, or a glaucoma hemifield test result outside normal limits. Only reliable visual fields (fixation losses, false-positives, and false-negatives all ≤20%) were included in the analysis.

Data Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (version 13.0; SPSS Inc., Chicago, IL). Student *t* test and Bonferroni correction for multiple comparisons were used to compare the unaffected eyes of subjects with RVO and randomly selected single eyes of control subjects. Categoric variables were compared using the chi-square test. The RNFL parameters and other variables were compared between subgroups divided by occlusion site, and in the control group by analysis of variance (ANOVA). Follow-up pairwise intergroup comparisons were performed using the Tukey test.

Results

Ninety-two patients were diagnosed with unilateral RVO during the enrollment period. Of these, 13 were excluded from further analysis: 3 as a result of poor visual acuity, 3 because the spherical refraction was <−5.00 D, and 7 because the OCT scan was unacceptable. In the control group, 82 subjects were enrolled. Of these, 11 were excluded: 1 as a result of poor visual acuity, 2 because the spherical refraction was <−5.00 D, 1 because of a history of retinal detachment surgery, and 7 because of the unacceptable OCT scan, leaving a final control sample of 71.

Table 1 presents the characteristics of the unilateral RVO and control groups. Subjects with RVO had a significantly higher rate of hypertension than did controls, and the contralateral eyes of unilateral RVO subjects showed significantly poorer visual field pattern standard deviation index (all $P<0.05$). There was no significant difference in age, gender, refraction, IOP, visual field mean deviation, or presence of diabetes mellitus between the RVO and control groups.

The OCT-measured RNFL thicknesses in unaffected eyes of the RVO group and the control group are presented in Table 2. In clock-hour sector measurement, the RVO group showed significantly thinner RNFL thicknesses in the 10- and 11-o'clock sectors (all $P<0.001$, Table 2). The 7 o'clock sector thickness was marginally thinner in the RVO group ($P = 0.003$).

Retinal Nerve Fiber Layer Thickness in Subgroups Divided by Age

A subset of subjects aged more than 60 years (42 in the RVO group; 38 controls) showed thinner average OCT-measured RNFL thickness compared with that of control eyes ($P = 0.001$; Table 3 [available at http://aaojournal.org]). In clock-hour sector measurement, RNFL thickness was significantly thinner than that of control eyes in the 7 and 11-o'clock sectors (all $P<0.001$). The inferior quadrant and 10-o'clock sector thicknesses were margin-

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