Optic Nerve Head Topographic Measurements and Retinal Nerve Fiber Layer Thickness in Physiologic Large Cups

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Purpose: To evaluate the parameters of optic nerve head (ONH) and retinal nerve fiber layer (RNFL) in patients with large cup/disc ratio (CDR) and normal neuroretinal rim configuration who have normal perimetry (physiologic large cups, LC) and to compare these parameters with those of the normal and early glaucoma patients.
Methods: Using Heidelberg retinal tomography (HRT) and optical coherence tomography (OCT), 30 patients with LC, 29 normal subjects, and 31 early glaucoma patients were examined. One eye from each subject was randomly selected.
Results: Significant differences between LC and glaucomatous eyes (GE) were found in parameters indicating loss of nerve fibers, such as rim area, rim volume, and mean RNFL thickness. However, there was no difference between LC and normal eyes (NE) in RNFL thickness, rim area, and rim volume. LC was able to be defined as a normal central excavation with a large disc and large CDR with a normal rim area.
Conclusions: HRT ONH parameters and RNFL thickness obtained with OCT may be useful for differentiating between glaucoma and LC eyes. *Korean Journal of Ophthalmology 19(3):189-194, 2005*

Key Words: HRT, OCT, Optic nerve head, Physiologic large cups, Retinal nerve fiber layer, Rim area, Rim volume

Glaucoma is an optic neuropathy characterized by a specific and progressive injury to the optic nerve and retinal nerve fiber layer (RNFL).[1] Because injury due to glaucoma is largely irreversible, early detection of glaucomatous structural changes of the optic nerve head (ONH) and prevention of progression are mandatory. The vertical cup/disc ratio (CDR) has long been used in the assessment of the glaucoma suspect, though the wide range of CDR values in the normal population, from 0.00 to 0.87, limits its use.[2-5]

The term pseudoglaucomatous physiologic large cups (LC) was introduced by Jonas et al.[6] The morphologic characteristics of LC are: (1) abnormally large optic disc area, (2) large CDR, (3) normal neuroretinal rim area and configuration, (4) normal form of zone alpha, (5) no zone beta, and (6) normal parapapillary RNFL.

Examination of ONH and its surrounding RNFL is considered essential in both detecting and monitoring glaucoma.[7] Damage to RNFL has been shown to precede visual field (VF) loss.[8] Hence, objective methods of measuring these structures may aid physicians in making accurate diagnoses. Recent advances in ocular imaging technology utilizing the optical properties of RNFL provide a potential means of obtaining quantitative RNFL thickness measurements. Furthermore, these techniques offer objectivity, rapidity, and reproducibility of measurements.[9]

Confocal scanning laser ophthalmoscopy (CSLO), a technology embodied in Heidelberg Retinal Tomography (HRT, Heidelberg Engineering, Heidelberg, Germany), enables the operator to evaluate three-dimensional characteristics of ONH topography quantitatively.[10-13] Stereometric parameters of ONH topography are generated relative to the reference plane, including rim area and volume, cup area and volume, cup-disc area ratio, mean RNFL thickness, and retinal nerve fiber cross-sectional area. Parameters independent of the reference plane include mean and maximum cup depth, height variation contour, and cup shape measure. A normal retinal height variation diagram demonstrates a “double-hump” pattern corresponding to the

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thicker retinal ganglion cell axons along the superior and inferior portions of ONH.

Optical coherence tomography (OCT, Zeiss-Humphrey Systems, Dublin, CA) is a noninvasive, noncontact, transpupillary imaging technology that can image retinal structures *in vivo* with a resolution of 10 to 17 µm.[14,15] Cross-sectional images of the retina are produced using the optical backscattering of light in a fashion analogous to B-scan ultrasonography. The anatomic layers within the retina can be differentiated and retinal thickness can be measured.[16]

The purpose of this study is to evaluate the ONH and RNFL parameters with HRT and OCT in patients with LC who have normal VF and to compare these parameters with those of the normal population and early glaucoma patients.

Materials and Methods

Thirty patients with a vertical CDR greater than 0.65 on photographs, 29 normal subjects, and 31 early glaucoma patients were included. One eye from each subject was randomly selected for study.

All subjects underwent a complete ophthalmic evaluation, including medical history, intraocular pressure (IOP) measurement, ONH photography (Canon CR - 45VAF), VF testing, and undilated and dilated biomicroscopy. The perimetry, HRT ONH scanning, and OCT examinations were performed within 3 months.

All tested eyes had a best corrected visual acuity of 20/40 or better. Refractive error was between +3.00 and -6.00 diopters. Eyes were excluded if they exhibited signs of posterior pole pathology other than those attributed to glaucoma or significant media opacity.

Inclusion criteria for LC were patients with CDR greater than 0.65. All tests to exclude glaucoma, including a complete eye examination, VF, diurnal IOP, and more than one follow up ocular examinations after 6 months or later, were performed.

Normal eyes (NE) were defined as those with CDR lower than 0.6, healthy neuroretinal rim, normal VF, no familiar history of glaucoma, and no other sign of glaucoma. Twenty-nine cases were included in this category.

Exclusion criteria for the two groups included IOP higher than 20mmHg at the time of testing, history of elevated IOP, poor quality photographs, unreliable results or generalized depression on VF testing, factors other than glaucoma affecting color vision, and the presence of other significant ocular disease.

Glaucomatous eyes (GE) had glaucomatous optic neuropathy (GON) and associated VF loss in the corresponding hemifield location. GON was defined as one of the following: cup/disc asymmetry between fellow eyes of greater than 0.2, or findings of rim thinning, notching, or RNFL defect. The glaucomatous VF defects were evaluated based on the following liberal criteria: two or more contiguous points with a pattern deviation sensitivity loss of $P<.01$, or three or more contiguous points with sensitivity loss of $P<.05$ in the superior or inferior arcuate areas, or a 10dB difference across the nasal horizontal midline at two or more adjacent locations and an abnormal result in glaucoma hemifield test.[17] Early glaucomatous VF loss was defined as mean deviation (MD) >-6 dB in HFA.

Achromatic automated perimetry was performed with the Humphrey field analyzer (HFA; Humphrey-Zeiss Instruments, Dublin, California, USA) using the central full-threshold program 30-2. VF reliability criteria included fixation losses and false-positive and false-negative rates of less than 25%.

In all subjects, confocal optic nerve analysis scans were done with HRT (software version 2.01; Heidelberg Engineering GmbH, Heidelberg, Germany). This device has been shown to provide reproducible results.[18-23] HRT scanned a continuous grid of 256×256 measuring points with an image field of 15 degrees×15 degrees along the ONH region and the operator was required to draw a contour line along the disc margin. The standard reference plane was used, and the following parameters were analyzed: optic disc area, cup area, cup volume, cup/disc area ratio, rim area, rim volume, mean cup depth, maximum cup depth, and cup shape measure.

OCT scanning (version 1; Humphrey-Zeiss Instruments) was the optical equivalent of B-scan ultrasonography where the light echo from the scanned area was detected. Because OCT is based on near infrared interferometry, images and measurements are not affected by the refractive status or axial length of the eye. RNFL thickness was defined as the number of pixels between the anterior and posterior edges of RNFL. Each scan consisted of 100 individual A-scan samples (1 thickness value per 3.6 degrees) evenly distributed along a circle circumference. These 3.4-mm-diameter circular scans, centered on the optic disc and of good quality (as judged by an experienced observer), were obtained from each test eye after pupillary dilation (minimum diameter, 5 mm). For each subject, RNFL thickness was assessed in four retinal regions: temporal (316°-45° on unit circle), superior (46°-135°), nasal (136°-225°), and inferior (226°-315°). Average RNFL thickness (0°-359°) was also assessed.

Results

The mean values of the NE group parameters were similar to those of normal Koreans in the literature.[24,25]

The three groups showed significant differences in all mean parameters by ANOVA. The GE group had MD and corrected pattern standard deviation (CPSD) on HFA that were significantly different from those of the other groups ($P<.01$). Significant differences existed between the NE and LC eyes in disc area, cup area, cup/disc area ratio, cup volume, mean and maximum cup depth, and cup shape measure (all, $P\leq.01$) (Table 1). There were no differences in rim area (P=

Table 1. Comparison of optic nerve head parameters between normal eyes (NE) and physiologic large cups (LC)

	NE (n=29)	LC (n=30)	P value
Age (years)	24.73±4.27	25.60±14.42	0.75
HRT parameters			
Disc Area (mm^2)	2.28±0.33	2.65±0.35	<0.01
Cup Area (mm^2)	0.75±0.39	1.22±0.28	<0.01
Cup/Disc Area Ratio	0.31±0.13	0.46±0.07	<0.01
Rim Area (mm^2)	1.53±0.32	1.43±0.18	0.14
Cup Volume (mm^3)	0.17±0.17	0.54±0.22	<0.01
Rim Volume (mm^3)	0.43±0.09	0.39±0.09	0.10
Mean Cup Depth (mm)	0.24±0.10	0.42±0.09	<0.01
Maximum Cup Depth (mm)	0.60±0.20	0.89±0.14	<0.01
Cup Shape Measure	-0.16±0.07	-0.09±0.06	0.01
MD (dB)	-1.81±1.42	-2.43±1.44	0.97
CPSD (dB)	1.02±0.99	1.30±0.66	0.19

NE: normal eyes, LC: physiologic large cups, HRT: Heidelberg retinal tomography, MD: mean deviation in Humphrey field analyzer (HFA), CPSD: corrected pattern standard deviation in HFA.

Table 2. Comparison of optic nerve head parameters between physiologic large cups (LC) and early glaucomatous eyes (GE)

	LC (n=30)	GE (n=31)	P value
Age (years)	25.60±14.42	49.63±10.84	<0.01
HRT parameters			
Disc Area (mm^2)	2.65±0.35	2.44±0.32	0.02
Cup Area (mm^2)	1.22±0.28	1.16±0.41	0.40
Cup/Disc Area Ratio	0.46±0.07	0.47±0.13	0.87
Rim Area (mm^2)	1.43±0.18	1.27±0.29	0.02
Cup Volume (mm^3)	0.54±0.22	0.39±0.26	0.03
Rim Volume (mm^3)	0.39±0.09	0.27±0.11	<0.01
Mean Cup Depth (mm)	0.42±0.09	0.34±0.11	0.01
Maximum Cup Depth (mm)	0.89±0.14	0.73±0.16	<0.01
Cup Shape Measure	-0.09±0.06	-0.08±0.08	0.68
MD (dB)	-2.43±1.44	-3.74±1.31	<0.01
CPSD (dB)	1.30±0.66	2.36±1.61	<0.01

LC: physiologic large cups, GE: early glaucomatous eyes, HRT: Heidelberg retinal tomography, MD: mean deviation in Humphrey field analyzer (HFA), CPSD: corrected pattern standard deviation in HFA.

Table 3. Comparison of RNFL thickness between normal eyes (NE) and physiologic large cups (LC)

	NE (n=29)	LC (n=30)	P value
Thickness in OCT (μm)			
Mean RNFL	103.6±14.6	109.3±19.0	0.20
Superior RNFL	141.5±16.6	140.3±22.5	0.82
Nasal RNFL	59.7±22.8	66.0±25.6	0.32
Inferior RNFL	134.6±15.7	142.8±25.6	0.14
Temporal RNFL	83.4±21.3	85.8±21.2	0.66

RNFL: retinal nerve fiber layer, NE: normal eyes, LC: physiologic large cups, OCT: optical coherence tomography.

Table 4. Comparison of RNFL thickness between physiologic large cups (LC) and early glaucomatous eyes (GE)

	LC (n=30)	GE (n=31)	P value
Thickness in OCT (μm)			
Mean RNFL	109.3±19.0	91.6±22.9	<0.01
Superior RNFL	140.3±22.5	119.0±32.4	<0.01
Nasal RNFL	66.0±25.6	66.7±27.7	0.92
Inferior RNFL	142.8±25.6	107.9±31.3	<0.01
Temporal RNFL	85.8±21.2	72.2±20.8	0.15

RNFL: retinal nerve fiber layer, LC: physiologic large cups, GE: early glaucomatous eyes, OCT: optical coherence tomography.

.14) and rim volume (P=.10). However, significant differences existed between GE and LC eyes in disc area (P =.02), rim area (P=.02), cup volume (P=.03), rim volume (P <.01), mean cup depth (P=.01), and maximum cup depth (P <.01) (Table 2).

Tables 3 and 4 summarize RNFL thickness values in the three groups. Mean RNFL thickness was significantly lower in GE than in LC eyes (P<.01). Analysis of RNFL thickness in NE, GE, and LC eyes revealed a characteristic, double-hump pattern with RNFL thickness peaks in the superior and inferior quadrants and troughs in the temporal and nasal quadrants. The peaks in this pattern were more flattened in GE. In the superior and inferior quadrants, RNFL was significantly thinner in GE (mean, 119.0 μm and 107.9 μm; range, 86.6-151.4 μm and 76.6-139.2 μm, respectively) than in NE (141.5 μm and 134.6 μm; 124.9-158.1 μm and 118.9-150.3 μm, respectively) and LC eyes (140.3 μm and 142.8 μm; 117.8-162.8 μm and 117.2-168.4 μm, respectively).

Discussion

The disc area of the LC group was significantly larger than that of the other two groups in this study (P<.01, P=.02, for the NE and GE groups, respectively) (Table 1, 2). The occurrence of LC in primary large disc is explained by the correlation between optic disc and cup size: the larger the disc, the larger the cup.[5,26] Inclusion criteria for LC in this study was a CDR greater than 0.65. The proportion of normal subjects with a CDR of 0.65 or greater in previous reports ranged from 2.2% to 4%.[3,27,28]

Significant differences between GE and LC eyes were found in parameters indicating loss of nerve fibers, such as rim area, rim volume, and the superior and inferior RNFL values. RNFL loss is correlated with decreased neuroretinal rim area.[29] Despite Iester et al's[30] assertion that rim area and cup shape measure are the most important predictors of mean VF defect, this study showed that cup shape measure value of LC eyes was more similar to that of GE than NE.

The neuroretinal rim size is correlated with optic disc area: the larger the disc, the larger the rim.[5,6,31,32] The increase of rim area with enlarging disc area is marked for eyes with no disc cupping. However, the rim area value of LC eyes tended to be less than that of NE in this study, although the difference was not significant. Possible reasons for this result are a different relationship between embryologically formed and regressed retinal ganglion cell axons,[33] different density of nerve fibers within the optic disc,[34] different lamina cribrosa architecture,[35] different diameters of retinal ganglion cell axons,[34,36] different proportion of glial cells on the whole intrapapillary tissue,[37] and/or other factors. But significant difference in rim area between GE and LC eyes is due to different nerve fiber count.[34,36,38,39]

OCT has been shown to obtain accurate and reproducible RNFL and retinal thickness measurements.[40,41] VF loss correlates with RNFL thickness as determined by OCT prototype in glaucoma patients.[40,42] RNFL profile obtained with OCT demonstrates the so-called “double-hump” pattern.[43] These results are in agreement with the histologic study done by Varma et al.[44] RNFL thickness at the superior and inferior segments in GE was significantly decreased compared with LC eyes in this study. Conversely, RNFL thickness in LC eyes indicated no significant reduction compared with NE in all segments. This similarity between NE and LC eyes might correspond to the result that no difference was found in neuroretinal rim area between NE and LC eyes. However, sampling was limited to 25 A-scans per quadrants, which may have limited the ability to detect localized change.[45]

Using planimetric analysis of stereoscopic optic disc photographs, Jonas et al[6] reported the morphologic characteristics of pseudoglaucomatous LC: normal neuroretinal rim area and normal parapapillary RNFL. It was reported that megalopapilla is an entity characterized by a large ONH which may appear abnormal, with an increased cup, but which is associated with a normal rim volume, normal VF, and normal IOP.[46] Based on HRT study, Arenas et al[47] defined physiologic macro cups as an excavation with a large CDR with a tendency to be larger in the horizontal plane but usually round, and with conservation of a thick neuroretinal rim in the inferior-nasal quadrant. Our study quantified and compared RNFL thickness in LC eyes with NE and GE by using OCT. Average RNFL thickness was significantly thinner in GE than in NE and LC eyes. Conversely, it is not surprising that there was no significant difference between NE and LC eyes.

Cup shape measure indicates the indentation of the layer of optic fibers against the papillary cup. Cup shape measure or third moment has been accepted as one of the most important parameters to diagnose glaucomatous changes in optic nerve with HRT.[48-50] In another study, however, neuroretinal rim area and RNFL thickness, compared with cup shape measure, were best correlated with mean defect.[51] The sectorial and Bathija formulas tended to have higher diagnostic precision than the Mikelberg formula and cup shape measure.[52] In our study, cup shape measure of LC eyes showed an inclination more similar to that of GE than NE and was less valuable than those parameters showing loss of fibers such as RNFL values. However, caution is necessary in any generalization of these results from our study because the LC patients in our study were recruited from a university-based glaucoma practice and the subject number was small.

In summary, we have confirmed that LC can be defined as a normal central excavation with a large disc and large CDR with a normal rim area. Consequently, a large optic cup in a large optic disc should not lead to the diagnosis of glaucoma if other intrapapillary variables, particularly the configuration of neuroretinal rim, are within normal limits. OCT revealed statistically significant quantitative differences in RNFL thickness between GE and LC eyes, but not between NE and LC eyes. OCT measurement of RNFL thickness may be useful to differentiate between GE and LC eyes. Further studies with a large number of cases and longer follow-up should be done to prove the clinical usefulness in the diagnosis and monitoring of patients with LC and to determine if patients with large CDR with normal VF subsequently develop VF defect.

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