Development of Computerized Densitometry for the Quantitative Analysis of Diffuse Retinal Nerve Fiber Layer Atrophy

이재성, *박광석, **이가영, **김동명
서울대학교 대학원 협동과정 의용생체공학 전공, 서울대학교 의과대학 *의공학교실, **안과학교실

J. S. Lee, *K. S. Park, **K. Yi, and **D. M. Kim
Interdisciplinary Program in Medical and Biological Engineering Major, *Department of Biomedical Engineering, **Department of Ophthalmology, Seoul National University

Abstract

Computerized densitometry was developed for the quantitative measurement of diffuse retinal nerve fiber layer (RNFL) atrophy and intra- and inter-operator reliability and clinical validity of this system were evaluated.

Vertical diameter, center of the optic disc, and peripapillary circles which had radii of 1.5 and 2.5 times that of the optic disc were user-interactively determined in digitized RNFL photograph and density profile along each circle was measured and normalized. The areas under the normalized density profiles of the superior and the inferior segments in both circle were used for the study of RNFL. To determine the variability and correspondence in the measurements of density variations, 21 RNFL photographs of glaucoma patients which showed varying degrees of atrophy underwent computerized densitometry by two operators on two separate occasions.

Coefficient of variation in the densitometric measurements was 1.2~5.4%. Intra- and inter-operator reliabilities were excellent. The correlations between the densitometric values and mean deviations of Humphrey C30-2 visual field showed statistical significance.

Computerized densitometry of RNFL photographs was useful in the objective and quantitative assessment of diffuse RNFL atrophy.

Introduction

Observable retinal nerve fiber layer (RNFL) loss occurred several years before measurable glaucomatous visual field (VF) damage in glaucoma patient. RNFL photography has been used to detect and monitor this glaucomatous damage.

Visual interpretation of RNFL photograph seems to be somewhat subjective and qualitative method. Some instruments based on optic tomographic method have been developed to measure the thickness of RNFL. However, they are expensive and not sufficient in clinical validation. So, semi-quantitative studies using RNFL photographs have been investigated.

Because the decrease of RNFL reflections and simultaneous increase of retinal mottling appear in monochrome RNFL photographs during the evolution of RNFL atrophy, density profile of the retinal regions was thought to be useful for the quantification of atrophy of RNFL.

So, we developed computerized densitometry of RNFL photographs for the objective and quantitative measurement of diffuse atrophy of RNFL and evaluated intra- and inter-operator reliability and clinical validity of this method.

We also attempted some processing to compensate the intensity decrease due to the vessels in retina which could undermine the reliability of the densitometry.

Method

RNFL photograph

Three RNFL photographs were taken from each eye with the Canon CF60U fundus camera, with a blue filter and TMX 100 Kodak film. We selected photographs that have well-focused vessels and width of peripapillary atrophy not larger than one-third of the vertical diameter of the optic disc. Photographs with wedge-shaped defect and reflection from internal limiting membrane were excluded.

Computerized densitometry

RNFL photographs were digitized using a scanner (ScanJet 4C/T, Hewlett-Packard Co.) and saved as monochrome GIF format. A semi-automatic image analysis program was developed using MATLAB 4.2b (MathWorks Inc., Natick, USA). Procedure of analysis is as follows:

1. User clicks two points on the vertical ends of the optic disc and one point on the darkest area in the fovea. The vertical diameter and center of the optic disc are calculated using two points which have been determined previously.
2. Two peripapillary circles of which the centers are same as that of the optic disc are drawn. The diameters of the circles are 1.5 and 2.5 times that of optic disc, respectively (Fig 1). With 0 degree defined as temporal, the following four segments were defined: superior (20~120°), nasal (120~240°), inferior (240~340°) and temporal (340~20°).
3. Density profiles (gray level variations) along both circle were measured with one degree interval three times. They were normalized from 0 to 1. We defined maximum (brightest) value in the center of optic disc as 1 and minimum (darkest) in the area of fovea as 0.
4. The area under the normalized density profile in each segment was defined as total density variation of that segment. Total density variation of each photograph was obtained by averaging the results of three measurements. Those of the superior and the inferior segments of the 1.5 times circle (SNF 1.5 and INF 1.5) and 2.5 times circle (SNF 2.5 and INF 2.5) were used for the study of RNFL.

Validation of the performance and the measurement correspondence

Thirty-nine photographs of 39 patients (mean age: 45.2, range: 19~71, M/F = 15/24) were selected randomly from RNFL photograph file. The diagnoses were primary open-angle glaucoma (9 patients), normal-tension glaucoma (11), glaucoma suspect (9), glaucoma-like disc (9), and glaucomatocyclitic crisis (1). Twenty eyes were right and 19 were left.

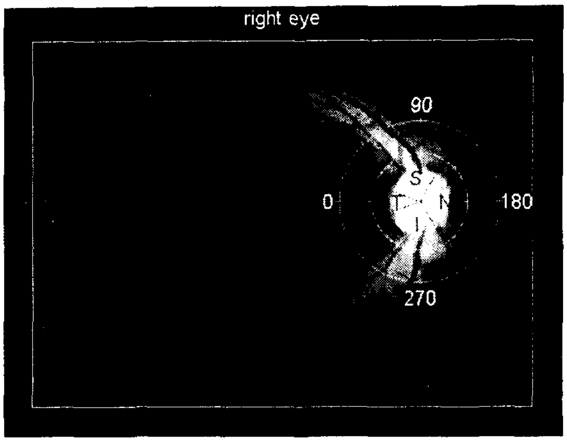

Fig 1. Two peripapillary circles on the nerve fiber layer photograph. With 0 degree defined as temporal, four segments were defined.

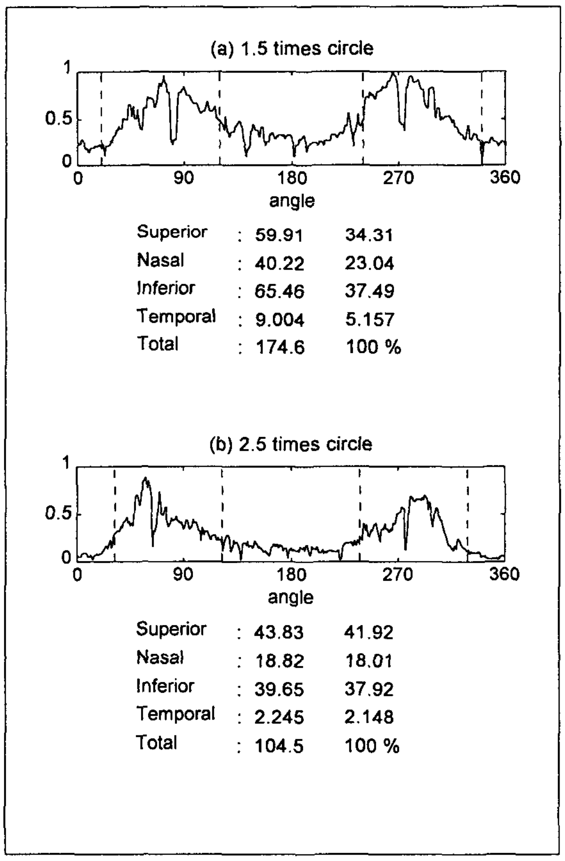

Fig 2. Density profiles and total density variations in the four segments along 1.5 and 2.5 times peripapillary circle.

To determine the variability and correspondence in the measurements of density variations, two operators performed computerized densitometry of the first 21 RNFL photographs on two separate occasions, independently.

Coefficient of variation was used to determine the variability of measurements in each session. Pearson's correlation coefficient was used to determine the correspondence of measurements between two sessions within and between two operators.

Clinical validity of densitometry was tested by comparing total density variations in the superior and the inferior segments with the mean sensitivity of corresponding VF region from age-matched normal eyes. Spearman's correlation coefficient was used for this analysis. The visual field was divided into ten sectors on the basis of glaucoma hemifield test sector definitions. The superior visual field (SVF) region was defined as sectors 2 through 5 and the inferior (IVF) as sectors 7 through 10. Additionally, the difference of INF 1.5 from SNF 1.5 (or INF 2.5 from SNF 2.5) was compared with the difference in mean sensitivity of SVF region from IVF region.

Signal processing on density profile

Intensity decrease due to the vessels in retina could cause the under-estimation of total density variation and undermine the reliability of the densitometry. So, processing to compensate this effect was independently attempted as follows.

1. Each profile was smoothed to remove the high frequency components including the abrupt changes of intensity caused by the existence of vessels.
2. Difference of the original profile and the smoothed one was calculated and used as the criteria for the segmentation of vessels.
3. Mean value of the range, difference of the maximum and minimum value in difference profile, was determined as a threshold and the periods higher than the threshold was considered as the vessel segments in difference profile.
4. Final compensated profile was consisted with the smoothed one in vessel segments and the original one in other areas.

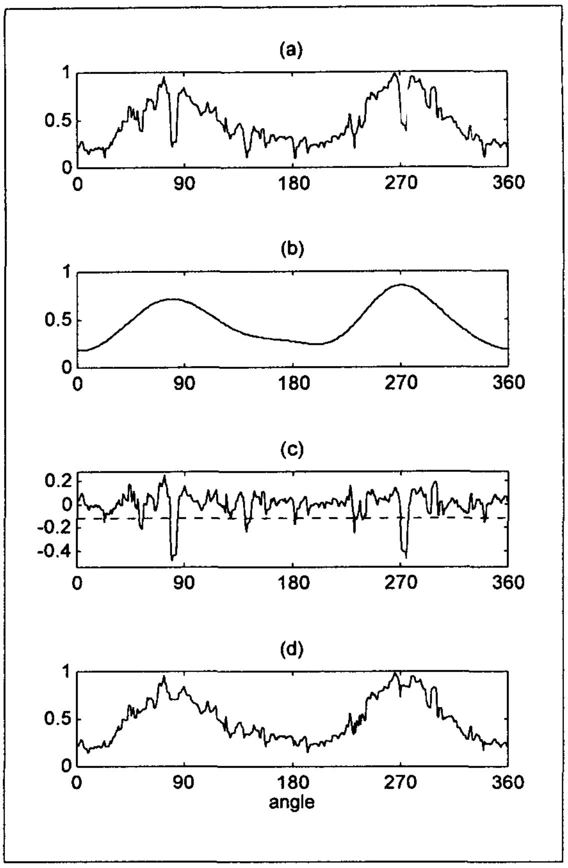

Fig 3. Processing to compensate the intensity decrease due to the vessels in retina.
(a) Original profile
(b) Smoothed profile to remove high frequency components including the abrupt changes of intensity due to the vessels
(c) Difference of the original profile and the smoothed one (dashed line: threshold to find the vessel segments)
(d) Final compensated profile consisted with the smoothed one in vessel segments and the original one in other areas

Result

Coefficients of variation in the densitometric measurements of RNFL photographs were 1.2~5.4%. The correspondence of measurements within operator was excellent (Pearsons correlation coefficients=0.98~1.00). The correspondence of measurements between two operators were also excellent (Pearsons correlation coefficients=0.96~1.00). The correlations between the densitometric values of nerve fiber layer (SNF 1.5, SNF 2.5, INF 1.5, and INF 2.5) and mean deviations of VF showed statistical significance (Spearmans correlation coefficients=0.51 ~ 0.55, p=<.001). The correlation between difference in densitometric value and deviation of Humphrey C30-2 visual field was moderated. The Spearman's correlation coefficients were 0.61 with 1.5 times circle (p=.000) and 0.43 with 2.5 times circle (p=.007).

Conclusion

Computerized densitometry was developed for the quantitative measurement of diffuse retinal nerve fiber layer (RNFL) atrophy and intra- and inter-operator reliability and clinical validity of this system were evaluated.

Computerized densitometry of RNFL photographs was useful in the objective and quantitative assessment of diffuse RNFL atrophy.

Reference

[1] W.F. Hoyt, L.L. Frisen, N.M. Newman, "Fundoscopy of nerve fiber layer defects in glaucoma", Invest Ophthalmol, Vol. 12, pp. 814-829, 1973

[2] W.F. Hoyt, N.M. Newman, "The earliest sign of glaucoma", Lancet Vol. 1, pp. 692-693, 1972

[3] A. Sommer, N.R. Miller, I. Pollack, A.E. Maumenee, T. George, "The nerve fiber layer in the diagnosis of glaucoma", Arch Ophthalmol, Vol. 95, pp. 2149-2156, 1977

[4] T. Takamoto, B. Schwartz, "Photogrammetric measurement of nerve fiber layer thickness", Ophthalmology, Vol. 96, pp. 1315-1319, 1989

[5] M. Lundstrom, J.O. Eklundh, "Computer densitometry of retinal nerve fiber atrophy : a pilot study", Vol. 58, pp. 639-644, 1980

[6] H.A. Quigley, M. Reacger, J. Katz, E. Strahlman, D. Gilbert, R. Scott, "Quantitative grading of nerve fiber layer photographs", Ophthalmology, Vol. 100, pp. 1800-1807, 1993

[7] A.G.J.E. Niessen, T.J.T.P. Berg, C.T. Langerhorst, P.M.M. Bossuyt, "Grading of retinal nerve fiber layer with a photographic reference set", Am J Ophthalmol, Vol. 120, pp. 577-586, 1995

[8] P. Asman, A. Heijl, "Glaucoma hemifield test : automated visual field evaluation", Arch Ophthalmol, Vol. 110, pp. 812-819, 1992

[9] J.S. Schuman, M.R. Hee, C.A. Puliafito, *et al.*, "Quantification of nerve fiber layer thickness in normal and glaucomatous eyes using optical coherence tomography", Arch Ophthalmol, Vol. 113, pp. 586-596, 1995

[10] M.J. Tjon-Fo-Sang, J. Varies, H.G. Lemij, "Measurement by nerve fiber analyzer of retinal nerve fiber layer thickness in normal subject and patients with ocular hypertension", Am J Ophthalmol, Vol. 122, pp.220-227, 1996