In Vivo Evaluation of Focal Lamina Cribrosa Defects in Glaucoma

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Objectives: To assess focal lamina cribrosa (LC) defects in glaucoma using enhanced depth imaging optical coherence tomography and to investigate their spatial relationships with neuroretinal rim and visual field loss.

Methods: Serial horizontal and vertical enhanced depth imaging optical coherence tomographic images of the optic nerve head were obtained from healthy subjects and those with glaucoma. Focal LC defects defined as anterior laminar surface irregularity (diameter, >100 µm; depth, >30 µm) that violates the normal smooth curvilinear contour were investigated regarding their configurations and locations. Spatial consistency was evaluated among focal LC defects, neuroretinal rim thinning/notching, and visual field defects.

Results: Forty-six healthy subjects (92 eyes) and 31 subjects with glaucoma (45 eyes) were included. Ninety-eight focal LC defects representing various patterns and severity of laminar tissue loss were found in 34 eyes with glaucoma vs none in the healthy eyes. Seven of 11 eyes with glaucoma with no visible focal LC defect had a deeply excavated optic disc with poor LC visibility. Eleven focal LC defects presented clinically as an acquired pit of the optic nerve, and the others as neuroretinal rim thinning/notching. Focal LC defects preferably occurred in the inferior/inferotemporal far periphery of the LC including its insertion. Eyes with focal LC defects limited to the inferior half of the optic disc had greater sensitivity loss in the superior visual hemifield and vice versa.

Conclusions: Mechanisms of LC deformation in glaucoma include focal loss of laminar beams, which may cause an acquired pit of the optic nerve in extreme cases. Focal LC defects occur in tandem with neuroretinal rim and visual field loss.


The lamina cribrosa (LC) is a meshlike structure in the scleral canal of the optic nerve head composed of overlapping and branching collagenous beams. These collagen beams form pores through which bundles of retinal ganglion cell (RGC) axons and the retinal blood vessels pass. It has been implicated as the principal site of damage to the RGC axons in glaucoma. Histologic studies using animal, cadaver, or enucleated eyes have provided a bulk description of the deformations and displacement of the LC in eyes with glaucoma. However, the biologic effects on the cellular and connective tissue components of the LC are likely to be more strongly dependent on the local levels of stress and strain than on bulk levels. Additionally, studies of histologic specimens may not accurately reflect in vivo observations owing to postmortem or postnucleation damage, swelling, or shrinkage of tissue associated with fixation, preparation, or changes in intraocular pressure (IOP). Considering inhomogeneity and anisotropy of the LC connective tissue structure, localized structural changes of the LC should be investigated to reveal more precise pathogenic mechanisms of glaucomatous damage.

A variety of imaging devices including spectral-domain optical coherence tomography (OCT) have recently been used to evaluate the LC in vivo. These studies also described general morphologic changes of the LC such as laminar thinning and posterior laminar displacement in glaucoma, not focal defects or deformation of the LC. In addition, all previous in vivo investigations using OCT reported an inability to visualize the anterior laminar surface beneath the neuroretinal rim, vascular structures, or scleral rim.
Enhanced depth imaging (EDI) OCT was developed to improve image quality of the deep posterior segment structures.\textsuperscript{26-28} Using this imaging method, we have shown that EDI OCT is able to provide detailed high-resolution cross-sectional images of the LC including the anterior laminar surface and laminar pores in glaucoma.\textsuperscript{29} Our hypothesis was that the LC may undergo localized deformation in glaucoma in addition to the general morphologic changes. To test this hypothesis, we evaluated focal defects of the LC in healthy subjects and patients with glaucoma using EDI OCT and assessed their spatial relationship with localized neuroretinal rim loss and visual field (VF) defects.

**METHODS**

This is a cross-sectional analysis of data obtained from an ongoing, prospective, longitudinal study approved by the New York Eye and Ear Infirmary institutional review board. Written informed consent was obtained from all subjects, and the study adhered to the tenets of the Declaration of Helsinki.

We prospectively included healthy subjects and patients with glaucoma with a range of optic disc and VF abnormalities representing various stages of glaucomatous damage. All participants had a detailed medical history and underwent slitlamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, and stereoscopic optic disc examination. For both eyes of each participant, serial horizontal and vertical B-scan images (interval between images, approximately 30 µm) of the optic nerve head were obtained using EDI OCT (Spectralis; Heidelberg Engineering GmbH). Patients with glaucoma had simultaneous color optic disc stereophotographs (Stereo Camera Model 3-DX; Nidek Inc) and standard automated perimetry (Humphrey Visual Field Analyzer, 24-2 Swedish interparietal nerve threshold algorithm standard strategy; Carl Zeiss Meditec Inc) within 6 months from the date of EDI OCT. Age at the time of EDI OCT, IOP reading, VF mean deviation (MD) value, and glaucoma diagnosis were recorded. We excluded individuals with previous posterior segment intraocular surgery, systemic or ocular diseases other than glaucoma known to affect at least 2 consecutive VF tests or the presence of at least 3 consecutive OCT scans and vice versa. Also, a focal LC defect detected in 1 OCT scan required at least 1 additional adjacent OCT scan with a similar finding. The observer was masked to the clinical information, including the presence and severity of glaucoma, optic disc appearance, and age.

Focal LC defects were categorized based on their shapes and locations. Spatial consistency was evaluated among focal LC defects, neuroretinal rim abnormalities, and VF defects. The correlation between VF MD and the number of focal LC defects in the glaucoma group was expressed in terms of the Spearman rank correlation coefficient (p) and P value. P values <.05 were considered significant.

A total of 46 healthy subjects (21 women, 92 eyes) and 31 patients with glaucoma (16 women, 45 eyes) were included for analysis. The mean (SD) age was 45 (18) years (range, 21-80 years) and 67 (14) years (range, 41-84 years) in the healthy and glaucoma groups, respectively. Mean (SD) IOPs were 14.8 (2.5) mm Hg and 15.3 (2.3) mm Hg in the healthy and glaucoma groups, respectively. Mean (SD) VF MD of eyes with glaucoma was −16.6 (7.9) dB (range, −32.97 to −1.70 dB). There were 31 eyes with primary open-angle glaucoma (8 with known untreated IOP ≤ 21 mm Hg at all times), 7 with exfoliative glaucoma, 4 with pigmentary glaucoma, 2 with chronic angle-closure glaucoma, and 1 with traumatic glaucoma.

No focal LC defect was detected in the healthy group (Figure 1), while a total of 98 focal LC defects of various sizes, shapes, and depths were found in 34 eyes (76%) in the glaucoma group. Among the 11 eyes with glaucoma (24%) with no visible focal LC defect, 7 (16%) had advanced glaucomatous VF defects (MD, < −20 dB) and deeply excavated optic discs, which resulted in reduced penetration of the OCT beam and poor visibility of the LC beneath the scleral rim. The mean (SD) number of focal LC defects per eye was 2.9 (1.6) (range, 1-6) in the 34 eyes with focal LC defects.

All focal LC defects corresponded well to glaucomatous optic disc changes such as neuroretinal rim thinning/notching or an acquired pit of the optic nerve (APON). We classified the identified focal LC defects based on their shapes: 6 smooth indentations (Figure 2A-C), 14 moth-eaten-appearance defects (Figure 2D-F), 10 steplike depressions (Figure 2G-I), 10 holelike defects (Figure 2J-R), and 38 altered laminar insertions (Figure 3). Hololeike defects had discontinuous anterior laminar surfaces and appeared to be full-thickness defects. Compared with the healthy eyes, in which the anterior laminar surface generally assumed a U or W shape with an upward sloping at the far periphery of the LC toward its insertion, the LC with altered insertion had a downwardly sloped periphery toward its insertion. The angle of this down-
ward sloping, which can be interpreted as the severity of laminar deformation, varied among eyes. Smooth indentations, moth-eaten appearance defects, and steplike depressions occurred in the midperiphery or far periphery of the LC. Holelike defects and altered laminar insertion exclusively occurred in the far periphery of the LC. Five holelike defects and 6 altered laminar insertions presented clinically as an APON (Figure 2J, M, and P and Figure 3G), which exclusively occurred in the inferotemporal area. No APON was detected in the optic disc photographs other than these 11 cases. The other focal LC defects presented clinically as a localized neuroretinal rim thinning/notching with or without acute angulation/bayoneting of retinal vessels.

Most focal LC defects occurred in the inferior or inferotemporal far periphery of the LC. Seventeen focal LC defects (17%) were found in the midperiphery of the LC. These consisted of 5 smooth indentations, 9 moth-eaten appearance defects, and 3 steplike depressions. The remaining 81 focal LC defects (83%) were detected in the far periphery of the LC including its insertion area. All 98 focal LC defects were detected in the inferior (n=67) or superior (n=31) areas of the LC, sparing the temporal and nasal 45° sectors.

Focal LC defects had a good structure-function relationship with VF defects. Focal LC defects were limited to either the superior or inferior half of the LC in 14 eyes, and they were detected in both halves of the LC in 20 eyes. In each of the 14 eyes with either superior or inferior LC defects, the location of focal LC defects (superior or inferior) corresponded to the VF hemifield with greater mean loss of sensitivity in the pattern deviation plot. That is, an eye with focal LC defects limited to the inferior half of the LC had greater loss of sensitivity in the superior hemifield and vice versa (Figure 4). However, glaucomatous VF defects occurred not only in the field corresponding to the focal LC defects, but also in the field corresponding to the LC area with no visible focal LC defects. The number of focal LC defects was significantly correlated with the VF MD before \( P = .003; \) \( \rho = -0.498 \) and after \( P = .002; \rho = -0.529 \) controlling for age (Figure 5). The mean VF MD and the number of focal LC defects were similar among the 8 eyes with primary open-angle glaucoma with known untreated IOP of 21 mm Hg or less all the time and the other 26 eyes with higher untreated IOP (mean [SD], −14.0 [7.4] dB vs −16.4 [7.2] dB, \( P = .42; 2.6 [1.6] \) dB vs 3.0 [1.6] dB, \( P = .60 \); both by independent-samples t test).

**COMMENT**

We evaluated the configuration and location of focal LC defects in healthy subjects and those with glaucoma using EDI OCT. Excluding the eyes with poor visibility of the peripheral LC due to deeply excavated optic discs and highly advanced glaucoma, focal LC defects of various shapes and depths were found in 34 of 38 eyes with glaucoma (89%) with a wide range of VF defects. In the area with focal LC defects, the LC appeared to have focal loss of laminar beams, probably as a result of physical collapse/disruption or remodeling, and the anterior laminar surface had irregularity violating the smooth curvilinear U- or W-shaped contour observed in healthy eyes. Among the 5 categories of focal LC defects identified in this study, altered laminar insertion was the most common type, composing 59% of all focal LC defects. Focal LC defects mostly occurred in the far periphery of the LC and presented clinically as neuroretinal rim thinning/notching or, in extreme cases, as an APON. Only 11 focal LC defects were clinically shown as an APON, probably because the peripheral LC is obscured by the scleral rim, prelaminar neural tissue, and/or retinal vessels. There was a good structure-function correlation between focal LC and VF defects. These findings demonstrate that mechanisms of LC deformation in glaucoma include focal loss of laminar beams in addition to the general changes in its thickness or position.

The LC is implicated as the main site of damage to the RGC axons in glaucoma. It was suggested that com-
pression, extension, or shearing of axons within the LC leads to the axonal damage in the optic nerve head and loss of RGCs. High IOP plays an important role in laminar damage by generating mechanical stress (force/cross-sectional area) and strain (physical deformation of the tissue) within the LC, leading to changes of its microarchitecture and progressive damage to the adjacent axons. Intraocular pressure exerts a uniform load on the inner eye wall but because of regional variation in the LC microarchitecture, local mechanical stress and strain within the LC are inhomogeneous and correlated with local laminar density. Strain is likely to be the most relevant mechanical factor for predicting tissue-level insult and has an inverse relationship with the laminar density. The superior and inferior parts of the LC tend to contain larger pores and thinner connective tissue, and especially inferior and inferotemporal regions of the LC have considerably lower collagen density compared with the other

Figure 2. Localized defects of the lamina cribrosa in glaucoma with various shapes, depths, and sizes identified in enhanced-depth imaging optical coherence tomographic (OCT) scans (B, E, H, K, N, and Q; arrows) and the same images without the labels (C, F, I, L, O, and R). The inferotemporal acquired pit of the optic nerve (J, M, and P) in the optic disc photographs corresponds to the focal laminar defects in the OCT scans. The dotted lines with arrows indicate the locations of the cross-sectional OCT scans (A, D, G, J, M, and P). The anterior laminar surface and focal laminar defect are indicated by the solid lines (B, E, H, K, N, and Q).
Figure 3. Localized alterations of the lamina cribrosa insertion in glaucoma with varying degrees of downward sloping of the anterior laminar surface toward its insertion identified in enhanced depth imaging optical coherence tomographic (OCT) scans (B, E, and H; arrows) and the same images without the labels (C, F, and I). The inferotemporal acquired pit of the optic nerve (G) in the optic disc photographs corresponds to the focal laminar disinsertion in the OCT scans. The locations of the cross-sectional OCT scans are indicated by the dotted lines with arrows (A, D, and G). Anterior laminar surfaces and focal laminar defects are indicated by the solid lines, and the downward sloping of the anterior laminar surfaces toward the laminar insertion are indicated by the dotted lines with arrows (B, E, and H).

Figure 4. A case showing a good structure-function relationship among localized neuroretinal rim notching (A), focal lamina cribrosa defect (a holelike defect) (B, arrow), visual field defect (C), and retinal nerve fiber layer defect (D, arrow). The location of the cross-sectional optical coherence tomographic scan is indicated by the dotted line with an arrow (A). The lamina cribrosa is indicated by the asterisk (B). INF indicates inferior; NAS, nasal; SUP, superior; and TMP, temporal.
regions.20 These findings are consistent with our results that all focal LC defects in our study were detected in the inferior or superior areas of the LC, sparing the temporal and nasal 45° sectors. Additionally, disruption of both collagen and elastin at the laminar insertion sites was demonstrated in human and monkey optic nerve heads with early glaucomatous damage,26 and all mathematical models of the optic nerve head consistently predicted regions of relatively large mechanical strain in the peripheral LC.31 This explains our result that 83% of the focal LC defects were found in the far periphery of the LC. Once an area of the LC is focally damaged and deformed because of locally greater intrinsic susceptibility, that area with focal LC defect may be more vulnerable to glaucomatous damage and enter a vicious cycle. Therefore, an initially small focal LC defect may evolve to a larger and deeper defect, clinically presenting as an APON.

Impaired blood supply to the laminar region either associated with or independent of increased IOP may be another factor that can lead to structural changes of the LC, weakening the laminar beams and making them prone to collapse even within a statistically normal range of IOP.37,38 It has also been proposed that mechanical stresses and strains result in activation of LC astrocytes, which may initiate an immunogenic cascade characterized by production of cytokines, antigen presentation, and activation of neuronal cytotoxicity, leading to neural and laminar tissue degeneration.30,32,39,40 Additionally, cyclic mechanical stretch of LC cells induces increased matrix metalloproteinase activity and changes in the transcription of extracellular matrix genes in vitro.41,42 Therefore, although it remains speculative, there may be a regional predisposition to focal LC defects associated with locally decreased blood perfusion, increased astrocyte or enzymatic activities, and/or increased immunologic reaction, especially in the inferotemporal far periphery of the LC. Further investigations are needed to address and clarify this issue.

A good structure-function relationship was revealed between the focal LC and VF defects. For the eyes with focal LC defects limited to either the superior or inferior area, the visual hemifield corresponding to the area with focal LC defects had greater loss of sensitivity than the other hemifield. Also, approximately two-thirds of focal LC defects (68%) were found in the inferior area, which is consistent with the observation that superior VF defects are more common than inferior VF defects in glaucoma.43,44 These findings as well as the spatial consistency between focal LC defects and neuroretinal rim thinning/notching found in this study demonstrate that the focal LC defects occur with localized RGC axonal damage, consequently leading to corresponding VF defects. This is supported by our finding that eyes with a greater number of focal LC defects had more advanced glaucomatous VF defects. Further investigation is required on the more sophisticated relationship between focal LC and VF defects.

Our study is partly limited by the different age distribution between the healthy and glaucoma groups. Therefore, the focal LC defects found in patients with glaucoma may be related to age-related changes in the LC architecture in addition to glaucomatous damage. However, the age range of the healthy group (21-80 years) almost covers that of the glaucoma group (41-84 years). Also, the significant correlation between the number of focal LC defects and the VF MD after controlling for age suggests that the focal LC defect is more glaucoma-specific rather than age-related. Focal LC defects may have been underestimated in our study, especially in the healthy eyes. Since healthy eyes have a thicker neuroretinal rim, which causes a greater decrease in sensitivity and scattering of the OCT beam, and likely smaller focal LC defects, if any, detection of focal LC defects in EDI OCT images may be more difficult. Subtle focal anterior laminar irregularities with a diameter of 100 µm or less or a depth of 30 µm or less were not considered focal LC defects in our study, but these may nevertheless have been caused by glaucomatous processes. Although the observer was masked to the clinical information including the presence and severity of glaucoma, optic disc appearance, and age, the thickness and shape of prelaminar tissue, especially in the eyes with severe glaucoma, could possibly have given the observer some clues regarding the subjects’ disease status and affected the observer’s evaluation of the anterior laminar surface. Additionally, our findings need histologic confirmation in the future.

Our findings underscore the importance of LC evaluation in glaucoma in addition to the conventional structural assessment of the optic nerve head using ophthalmoscopy, photography, or conventional imaging methods. Mechanisms of LC deformation in glaucoma include focal loss of laminar beams, which occurs in tandem with neuroretinal rim loss and glaucomatous VF defects. Further studies are needed to demonstrate the pathophysiologic course of focal LC defects including molecular or cellular events. Also, the detailed relationship between focal LC defects and clinical parameters, especially of glaucoma progression, should be investigated in the future.

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REFERENCES


**OBITUARY**

In Memoriam: Goodwin M. Breinin, MD (1918-2011)

Goodwin M. Breinin, MD, passed away peacefully at his home on December 14, 2011, at the age of 93 years. He is best remembered as the Daniel B. Kirby Professor and Chairman of the Department of Ophthalmology, New York University (NYU) Medical Center, from 1959 to 2000, serving for 41 years.

After receiving his medical degree from Emory University in Atlanta, Georgia, Dr Breinin served in the Army for 2 years during World War II. Following residency at NYU, he became Professor of Research Ophthalmology there, specializing in clinical motility and neurophysiology of extracocular muscle. A world-renowned expert in ophthalmic electromyography, his classic monograph on the subject, published by the American Ophthalmological Society in 1960, was based on the research performed at his Bellevue laboratory. Among his feats was the insertion of a needle into his own medial rectus, monitoring its electrical patterns. Asked why he chose to study ocular motility, he mused that it was the most challenging of all the ocular subspecialties.

Dr Breinin’s mission was “bringing Helmholtz into ophthalmology” by integrating its clinical and basic science components. Under his aegis, world-class investigators produced landmark discoveries in muscle research, retinal physiology, and ophthalmic pathology. His own 129 publications include such pioneering subjects as the use of Diamox (acetazolamide) in treating glaucoma and corneal chelation for band keratopathy.

For these achievements, Goodwin Breinin received international recognition. He served on the Board of Directors of the American Board of Ophthalmology and was Chairman of the Ophthalmology section of the American Medical Association. Among his numerous lectureships and awards were the American Medical Association Knapp Medal for Contributions to Ophthalmology and the Emory Medal for lifetime achievement.

Dr Breinin was conversant with nearly every aspect of ophthalmology, a rarity in an era of superspecialization. He always concluded Grand Rounds with cogent comments on the topic of the day.

On the occasion of his retirement, Dr Breinin’s patients, friends, and faculty endowed a Visiting Professorship at NYU Medical Center. A similar program at Emory University has featured 4 Nobel laureates. In perpetuity, Goodwin Breinin’s legacy will, appropriately, be one of education.

Those who knew “Dud” Breinin experienced his wit, charm, erudition, and elegant verbiage, often peppered with Greek and Latin. A philosophy buff, he wrote several short stories that spoof Gnostic ideas. When he lost his hearing, Goodwin finished the daunting task of reading all the novels of Trollope, Elliot, Dickens, and Hardy. His illness did not rob him of his sense of humor. As he put it, “I have started chemo—which is an interesting experience, I am exchanging heated words with the Demiurge. Actually it’s one-way—he doesn’t choose to debate.”

During his final years, buffered by the love of his wife Rose-Helen, his children Bart and Constance, and his 4 multitalented grandchildren, he learned to cook. He remained active in his research laboratory, pursuing the effects of novel pharmacological agents on conductivity at the neuromuscular junction. Glancing at my own microscope, he remarked to me that “the answers are all there, staring you in the face.”

That was Goodwin. In the parlance of the theater, a hard act to follow.

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