Optical Coherence Tomography of the Swollen Optic Nerve Head: Deformation of the Peripapillary Retinal Pigment Epithelium Layer in Papilledema

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PURPOSE. To examine the biomechanical deformation of load bearing structures of the optic nerve head (ONH) resulting from raised intracranial pressure, using high definition optical coherence tomography (HD-OCT). The authors postulate that elevated intracranial pressure induces forces in the retrolaminar subarachnoid space that can deform ONH structures, particularly the peripapillary Bruch’s membrane (BM) and RPE layers.

METHODS. The authors compared HD-OCT optic nerve and peripapillary retinal nerve fiber layer (RNFL) findings in eyes with papilledema caused by raised intracranial pressure to findings in eyes with optic disc swelling caused by optic neuritis and nonarteritic anterior ischemic optic neuropathy (NAION), conditions without intracranial hypertension. The authors measured average thickness of the RNFL and the angle of the RPE/BM at the temporal and nasal borders of the neural canal opening. The angle was measured as positive with inward (toward the vitreous) angulation and as negative with outward angulation.

RESULTS. Of 30 eyes with papilledema, 20 eyes (67%) had positive RPE/BM rim angles. One of eight optic neuritis (12%) eyes and 1 of 12 NAION (8%) eyes had positive angulation. In five eyes with papilledema, RNFL thickening increased, three of which developed positive RPE/BM angles. On follow-up, 22 papilledema eyes had a reduction of RNFL swelling, and 17 of these eyes had less positive RPE/BM angulation.

CONCLUSIONS. In papilledema, the RPE/BM is commonly deflected inward, in contrast to eyes with NAION or optic neuritis. The RPE/BM angulation is presumed to be caused by elevated pressure in the subarachnoid space, does not correlate with the amount of RNFL swelling, and resolves as papilledema subsides. (Invest Ophthalmol Vis Sci. 2011;52: 6558 – 6564) DOI:10.1167/iovs.10-6782

Papilledema is caused by increased intracranial pressure. Histopathologic studies in animal models have shown that elevated pressure within the optic nerve sheath causes stasis of axoplasmic flow and decreased blood flow to axons in the neural canal.1–3 The ensuing optic disc swelling (papilledema) is a consequence of axonal distension of the prelaminar and peripapillary nerve fibers. Vascular congestion, leakage, and ischemia follow the acute axoplasmic flow stasis and are associated with interstitial edema. Although the proximate cause of early edema is stagnant axonal transport, there still remains some uncertainty about the relative effects of compression and ischemia.1–5

Burgoyne et al.4 and others5–11 have proposed a conceptual approach that analyzes the optic nerve head (ONH) as a biomechanical structure. They hypothesize that stress (force/cross-sectional area) and strain (local deformation) on the ONH may be key determinants of axonal, glial, and vascular dysfunction in the pathogenesis and progression of glaucoma. Although the forces acting on the nerve head in papilledema differ from those in glaucoma, the application of biomechanical principles may provide insights about the clinical effects of intracranial pressure on the ONH with respect to pathophysiology, etiology, treatment, and monitoring.

The connective tissues of the peripapillary sclera, the lamina cribrosa, the sclera neural canal, vessels with adventitia, Bruch’s membrane (BM), RPE, and the optic nerve sheath can be considered load-bearing structures of the ONH.11,12 Precisely how intracranial hypertension affects these structures is unknown; however, there is clinical and experimental evidence that biomechanical forces play an important role in the genesis of papilledema including posterior scleral flattening, distension of the nerve sheath,13,14 resolution of papilledema after optic nerve sheath fenestration,15–17 and the occurrence of choroidal and circumpapillary folds.18

Time domain optical coherence tomography (OCT) has been shown to be a clinically useful method of monitoring the severity of optic disc edema by quantifying the thickness of the peripapillary retinal nerve fiber layer (RNFL).19–23 Scott et al.20 has validated OCT methodology by correlating RNFL thickness with corresponding fundus photos using a modified Frisén grading scale. To our knowledge, high speed, high-resolution, spectral-domain OCT (HD-OCT) investigation of the effects of papilledema and intracranial hypertension on subsurface structures of the ONH and peripapillary region has not been reported.

The purpose of this study was to determine how increased intracranial pressure affects the peripapillary subsurface structures of the neural canal opening (NCO) of the ONH at the level of the RPE and basement membrane (RPE/BM) layer using HD-OCT.22 We hypothesize that alterations (both worsening and improvement) in the degree of RNFL thickening associated with intracranial hypertension correlates with the angulation...
of the RPE/BM at the NCO and that inward angulation of the RPE/BM borders (toward the vitreous) is specific to papilledema with intracranial hypertension but should be unaffected in patients with other forms of disc edema (e.g., optic neuritis and nonarteritic anterior ischemic optic neuropathy [NAION]), where intracranial pressure is normal.

**METHODS AND SUBJECTS**

**Methods**

HD-OCT scans were performed using a Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA). Sharply focused, uniformly illuminated images obtained at baseline and, where possible, at subsequent visits, included optic disc cube $200 \times 200$ ($\times 2$) where the laser scanned a $6 \times 6$-mm area, capturing of a cube of data consisting of 200 A-scans from 200 linear B-scans of 2 mm per A-scan (40,000 A-scans) and average thickness for the entire circumference of the RNFL was calculated using software provided with the HD-OCT, and the HD 5 Line Raster scan consisting of five speckle-reduced B-scans of 9 mm long, each consisting of 1024 A-scans (each with an axial depth of 2 mm and 1024 pixels per A-scan). Only scans centered on the optic disc with a signal strength of six or higher were analyzed.

Axial views were evaluated from the individual B-scan (horizontal image) through the center of each optic disc. The horizontal image was 9 mm long for the five-line raster scan and 6 mm long for the optic disc cube scan. The axial image was used to identify the temporal and nasal RPE/BM borders of the neural canal. The angle formed between a line drawn tangential to the curve of the unaltered RPE/BM in the peripapillary retina furthest from the ONH and the altered border adjacent to the NCO was measured on the nasal and temporal sides of the optic nerve (Fig. 1). We evaluated the direction of the RPE/BM angle measured with the image centered on the center of the optic disc and for all horizontal images above and below the midline. Because the angle direction was the same for all images at each NCO border in individual eyes, we analyzed on the image positioned in the middle of the optic disc. The angle was measured along the NCO relative to the RPE/BM, increasing further away from the NCO. We realize that a limitation of our study was that given our 9-mm image use, we did not always reach a nondeformed region of the RPE/BM, but the direction of the angle measured and the changes over time were consistent. The expected position of the RPE/BM was based on the fellow eye for nonpapilledema eyes and based on an interpolated line from the observed outer RPE/BM position in eyes with papilledema. We recognized a limitation in current clinically available methodology related to degradation of signal intensity in deeper layers of the nerve by optic disc edema. This can make evaluation of the architecture of the sclera directly underlying the most edematous portion of the nerve difficult.

The relative RPE/BM angulation inward or toward the vitreous was measured as a positive angle and outward was measured as a negative angle. For each eye, the angulation was considered positive if there was $5^\circ$ or greater inward angulation of unadjusted images (measured with Adobe Photoshop [Adobe, San Jose, CA]) of either the temporal or nasal border of the RPE/BM immediately around the ONH. The angle was measured and the changes over time were consistent. The expected position of the RPE/BM was considered negative if it was less than or equal to $5^\circ$ and neutral if it fell between the two. The angle was relative and not absolute because the HD-OCT images used for the determinations are scaled differently for the vertical and horizontal dimensions. For a 9-mm HD 5 Line Raster scan, the horizontal dimension is decreased by a factor of three relative to the vertical dimension, because the aspect ratio presented is 2:3, while the true acquired aspect ratio is 2:9. Although this introduces some error—because the conversion for aspect ratio depends on the proportion of horizontal and vertical components—for angles $20^\circ$ or smaller, the conversion is nearly linear, and the true angle is approximately one-third of the measured angle. For the cube scans, with a 6-mm horizontal extent, the converted angle will be roughly half of the relative angle. To show this mathematically the conversion is expressed as:

\[
\text{Measured angle} = \alpha_{\text{meas}} = \tan(H_{\text{true}}/V_{\text{true}}) \quad \text{for a cube scan}
\]

\[
\text{True angle} = \alpha_{\text{true}} = \tan(H_{\text{true}}/V_{\text{true}}) = \tan(H_{\text{true}}/f \cdot V_{\text{true}})
\]

where $H_{\text{true}}$ is the true horizontal extent of the right triangle that defines the angle, $V_{\text{true}}$ is the vertical extent, $H_{\text{true}}$, is the horizontal extent of the right triangle that defines the measured angle, $V_{\text{true}}$, is the vertical extent, and $f$ is the ratio of the aspect ratios, equal to 3 for a 9-mm long B-scan and 2 for a 6-mm long B-scan. Solving for the relationship of the measured angle to the true angle gives:

\[
\tan(\alpha_{\text{true}}) = H_{\text{true}}/V_{\text{true}}
\]

\[
\tan(\alpha_{\text{true}}) = H_{\text{true}}/f \cdot V_{\text{true}} = > H_{\text{true}}/V_{\text{true}} = \tan(\alpha_{\text{meas}})/f
\]

\[
\tan(\alpha_{\text{true}}) = \tan(\alpha_{\text{meas}})/f
\]

For small angles, this implies that the true angle is proportional to the measured angle, so the sign of the angle will be correct. Therefore, in no case should the direction of the angular deviation be affected by this aspect ratio conversion. Because we used unaltered exported images to derive the angle, we adjusted the angle sizes after measurements were obtained from the unaltered images accordingly and used the term relative angle with respect to the plane of the peripheral peripapillary retina away from the nerve head in reporting angle measurements for the study findings. We determined whether the angle was positive, negative, or at neutral (called zero).
A review of 246 subjects (491 eyes with images that could be evaluated) in the INN Neuro-Ophthalmology Cirrus database, who at the time of imaging had no clinically swollen optic nerves or chronic open angle glaucoma (mean age, 53 years [SD, 17]), revealed only nine eyes in five subjects who met our criteria for having positive RPE/BM angulation. Out of one image for each of 491 eyes, the median relative angle for the temporal and nasal borders was -1.0 (SD, 1.7) and -1.0 (SD, 1.6) degrees, respectively, and six eyes (1%) had an angle of 5°. In the 491 eyes and patients in this study, on the unadjusted images, the RPE/BM temporal and nasal angles on repeat scans at each visit were within 5°, and none were positive on one side and negative on the other, nor positive on one and negative on the repeat scan. In addition, we prospectively performed five-line HD scans horizontally through the middle of the optic disc in the right eye of 50 subjects without optic nerve disease. Without correction for the aspect ratio, for the temporal and nasal neural canal angles the mean was -7.2° (SD, 6.6; range, 0 to -22) and -3.8° (SD, 3.7; range, 0 to -15), respectively. No eyes had a positive angle or inward deflection. We used this information to require on unadjusted images at least 5° change for eyes with more than one examination visit over time to determine that the angle was altered. In addition, because the variability for at least two optic cube images per eye at the same examination was <10 µm (data not shown) and the reproducibility of OCT RNFL measurements (shown in many previous peer reviewed journals) is within 10 µm, we required the average RNFL to differ by >10 µm (increase for thickening and decrease for thinning) between visits to determine that the RNFL was changed.

### Subjects

This study was conducted with New York Eye and Ear Infirmary Institutional Review Board approval. As part of an exploratory project to develop a protocol for an HD-OCT substudy as part of the National Eye Institute–supported “Idiopathic Intracranial Treatment Trial” conducted by the Neuro-Ophthalmology Research Disease Investigator Consortium, we prospectively evaluated patients with active idiopathic intracranial hypertension ([IIH] modified Dandy criteria) with clinically apparent papilledema (some treated and some at baseline).

All subjects were women with a mean age of 34 years. Once we began to explore the data from the patients with IIH, we prospectively evaluated patients with acute (evaluated within 14 days of vision loss) NAION (using accepted diagnostic criteria) and clinically apparent optic disc swelling (Table 1). We also retrospectively evaluated patients with acute (evaluated within 14 days of vision loss) optic neuritis (meeting accepted clinical criteria, all with magnetic resonance imaging verification), and clinically apparent optic disc swelling. No patient in any group had an IOP >20 mm Hg, and none had signs of glaucoma in either eye.

### RESULTS

We found a positive angulation of the RPE/BM borders in 20 of 30 eyes (67%) among 10 of the 15 patients with papilledema (Fig. 1). The mean inward RPE/BM angle was +1.5° (SD, 1.5°) temporally and +2.5° (SD, 1.8°) nasally. Among the remaining 10 eyes, the mean inward angle was -1.06° (SD, 2.6°) temporally and -0.92° (SD, 1.6°) nasally. For the 20 eyes with positive angles, the larger angle was nasal in nine eyes (Figs. 2A, 3) and was temporal in four eyes and equal in seven eyes. Temporal and nasal border angles were moderately correlated (r ≥ 0.63; P = 0.01) for each eye and between eyes in each papiledema subject. No patient had positive angulation in one eye and negative angulation in the other. Two patients had a positive angle in one eye and a zero angle in the contralateral eye, despite slightly more RNFL swelling in the zero angle eyes (average RNFL 350 µm and 242 µm vs. 401 µm and 263 µm, respectively).

There were two patterns of inward angulation. Twelve eyes had a positive RPE/BM angle with mild deformation of the RPE/BM and choroid (Fig. 1) confined to the NCO margin. The second pattern observed in six of the eyes showed a large

### Table 1. Patients with Acute NAION and Clinically Apparent Optic Disc Swelling

<table>
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<th>Papilledema</th>
<th>NAION</th>
<th>Optic Neuritis</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>38</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>Sex</td>
<td>15 women</td>
<td>8 women</td>
<td>5 women</td>
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<tr>
<td>Mean RNFL thickness at presentation, µm</td>
<td>221 (SD, 102)</td>
<td>260 (SD, 82)</td>
<td>176 (SD, 59)</td>
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There were two patterns of inward angulation. Twelve eyes had a positive RPE/BM angle with mild deformation of the RPE/BM and choroid (Fig. 1) confined to the NCO margin. The second pattern observed in six of the eyes showed a large
inward bowing of the RPE/BM and choroid (Figs. 2A, 3) that extended well into the surrounding peripapillary region.

We explored the relationship between changes in the average RNFL thickness and RPE/BM angulation over multiple visits in 13 patients with papilledema. In five eyes, the average RNFL thickness increased (Table 2) and at least one of the RPE/BM angles increased in the inward direction for three of these eyes (Fig. 4). The average RNFL decreased or was less thick (including two eyes that had previously had increasing thickness) in 22 eyes (Table 2) and the RPE/BM angle of at least one border was less positive or became negative in 17 of these eyes (Figs. 2 and 4). For all 30 papilledema eyes, the amount of change in the nasal RPE/BM angle (Spearman \( r = 0.63; P = 0.01 \)) but not the temporal angle (\( r = 0.13; P = 0.51 \)) correlated with the change in average RNFL (examples in Figs. 2 and 4). Our prototypical case in Figure 4 for our prototypical case. Another example of normalization of optic disc swelling and RPE/BM angulation is seen in Figures 2B, 2C after dramatic weight reduction.

For papilledema patients, there was no correlation of having positive (inward) with the lumbar puncture opening cerebrospinal fluid (CSF) pressure (mean, 35 cm H2O [SD, 8]) but the CSF pressure determination was frequently remote in time from the first HD-OCT measurements.

One eye out of eight (12%) with optic neuritis had positive angulation (5° for both temporal and nasal borders) and this optic nerve had magnetic resonance imaging evidence of retrolubar inflammation up to and including the sclera and an average RNFL thickness of 294 \( \mu m \). The opposite eye did not have a positive angle. Within 2 weeks of the first examination, the average RNFL was 138 \( \mu m \) and both angles were zero.

One eye of 12 (8%) with acute NAION had positive angulation (5° temporal border only) and the unaffected fellow eye also had positive angulation (5° temporal border only). The affected eye had an average RNFL of 275 \( \mu m \) at presentation and 133 \( \mu m \) at 1 month. The angulation did not change in either eye at 1 month.

Among all papilledema, optic neuritis, and NAION eyes, there was no correlation of the amount or direction of RPE/BM angulation with the amount of total RNFL thickening for all etiologies.

### Discussion

This study confirms that in addition to revealing peripapillary RNFL thickening associated with papilledema, HD-OCT is able to detect changes in the subsurface architecture of the ONH and peripapillary region\(^{23} \) (Williams GSN, et al. IOVS 2009;50:ARVO E-Abstract 2253). Papilledema with intracranial hypertension results in an inward bowing of the RPE/BM layer at the NCO not typically seen in normal eyes or other forms of disc edema. Although the sclera is not imaged clearly or completely by HD-OCT, the angulation and displacement of the RPE/BM presumably reflects deformation of the underlying peripapillary sclera and lamina cribosa in response to an elevated pressure gradient between the retrolaminar subarachnoid perioptic nerve sheath compartment and the globe. This deformation is dynamic and in the opposite direction in glaucoma. In experimental acute IOP elevation, outward bowing of the RPE/BM occurs but the amount of displacement is small.\(^{24} \) In chronic glaucoma and chronic experimentally induced elevated IOP, the IOP gradient exceeds the perioptic subarachnoid pressure more than under normal conditions. This may induce changes in load-bearing connective tissues that results in laminar thinning, peripapillary scleral bowing posteriorly, and expansion of the scleral canal.\(^{4,25-30} \)

Our findings in humans are consistent with experimental studies in dogs. Using confocal scanning laser tomography,
Morgan has shown that intracranial hypertension displaces the optic disc surface and lamina cribosa anteriorly (toward the vitreous), whereas ocular hypertension displaces the disc surface posteriorly. An increase in CSF pressure resulted in greater anterior displacement of the disc surface than the posterior displacement induced by a corresponding increase in IOP. The normal lamina cribrosa is already slightly bowed backwards (as is the RPE/BM in our controls). This makes it difficult to show an additional increase in the bowing backward until the pressure gradient increases significantly and damages support structures of the ONH, as in untreated glaucoma. However, in the case of raised intracranial pressure, a reversal in the direction of this bowing is seen and may be easier to detect. In addition, the retrolaminar tissue pressure was shown to be determined by the CSF pressure and the translaminar pressure gradient was related to the difference between IOP and CSF pressure across a wide range of both IOP and CSF pressure.

The inward angulation of the peripapillary RPE/BM cannot be explained solely by the degree of disc edema or RNFL thickening. With two exceptions (one with optic neuritis and one with NAION), the inward angulation of the peripapillary RPE/BM layer was confined to those patients with papilledema and absent among those with other forms of disc edema in the patients sampled in this study. The average RNFL thickness did not correlate with a positive RPE/BM angle or the degree of positive angulation or inward bowing of the RPE/BM across all patients with papilledema. The mean angle was greater nasally than temporally and the change in the nasal RPE/BM angle but not the temporal angle correlated with the increase in average RNFL. The difference may relate to regional variations in the compliance or elasticity of the lamina cribrosa and peripapillary sclera. Downs et al. has shown that the nasopalpebral sclera in monkeys is thinner and possibly more compliant than the temporal sclera to extraocular pressure forces. We considered whether the degree of myopia might be another factor to influence the compliance of the RPE/BM border but found no correlation with the presence or degree of positive displacement and refractive error (data not shown).

Our findings also suggest that there may be regional differences in the deformation of the peripapillary RPE/BM in patients with papilledema. The mean angle was greater nasally than temporally and the change in the nasal RPE/BM angle but not the temporal angle correlated with the increase in average RNFL. The difference may relate to regional variations in the compliance or elasticity of the lamina cribrosa and peripapillary sclera. Downs et al. has shown that the nasopalpebral sclera in monkeys is thinner and possibly more compliant than the temporal sclera to extraocular pressure forces. We considered whether the degree of myopia might be another factor to influence the compliance of the RPE/BM border but found no correlation with the presence or degree of positive displacement and refractive error (data not shown).

We cannot explain why 33% of the eyes with papilledema did not exhibit positive angulation or displacement of the RPE/BM. The HD-OCT and lumbar puncture in many of our patients were performed at different times and, in some cases, the HD-OCT was obtained after treatment was initiated. Presently, there are no data correlating the lumbar intracranial pressure with the retrolaminar pressure or the degree of RNFL thickening or the pattern of swelling of the optic disc. Eyes without positive RPE/BM angulation did not have less RNFL swelling. The degree of structural stiffness is a structural property that can vary among eyes and patients that can influence the deformation of the optic nerve. This is determined by a complex interaction of numerous factors, including size, shape of the scleral canal, scleral thickness, orientation and density of the lamina cribrosa, scleral insertion of the optic nerve sheath, and material properties of the lamina and peripapillary sclera. The trabecular architecture of the distal optic nerve may asymmetrically affect translamellar pressure gradients or structural stiffness. Therefore, two patients or each eye in the same patient may respond quite differently to the same periocular nerve sheath pressure. Moreover, the absence of a measurable deformation by HD-OCT does not necessarily indicate an absence of stress and strain on the load bearing structures of the optic nerve. Lastly, without knowing the premorbid position of the RPE/BM, we cannot rule out that small incremental inward deformations of the RPE/BM might have occurred.

It has been suggested that the stability of the RPE/BM position at the neural canal may serve as reference plane from...
which other structural parameters may be derived.22,37–41 While this may be correct in a slowly progressive condition like glaucoma, our findings in papilledema shows substantial deformations of the peripapillary RPE/BM, in some cases over short time intervals, relative to other surface and subsurface regions of the optic disc. There may be limits to the use of the RPE/BM as a reference plane in patients with intracranial hypertension. The inward angulation of the RPE/BM must be considered when measuring other structural parameters of the optic disc in papilledema.

This preliminary study was intended to determine whether HD-OCT was capable of analyzing additional structural parameters beyond RNFL thickness in patients with papilledema. By its very nature, there are a number of limitations. First, the sample was small and heterogeneous. Some of the patients underwent their HD-OCT assessment after treatment had been instituted, the follow-up was short, and treatment modalities varied. The depth penetration of commercially available HD-OCT is limited and, in the presence of severe disc edema, may be subject to artifacts that shadow subsurface structures. The output display image used to ascertain the angulation from the axial images from the HD-OCT on the Cirrus has an aspect ratio that differs for horizontal and vertical dimensions from the acquisition image. Although the reported angle sizes are calculated and relative, in no case was the direction of the angular deviation altered from the true direction. This study provides HD-OCT evidence that intracranial hypertension alters the biomechanical environment of the peripapillary ONH at the level of the RPE/BM. The inward angulation of the NCO and the nasal peripapillary displacement of the RPE/BM presumably reflects pressure-induced stress and strain on the surrounding choroid, sclera, and lamina cribrosa. Because papilledema resolves with treatment, we have shown an improvement of—and, in some cases, complete reversal of—this deformation that is not explained by the presence of disc edema or thickening of the RNFL alone. Previous studies have shown that intracranial hypertension impedes axonal transport, compromises blood flow, damages axons, and stimulates glial proliferation in the ONH. The extent to which these biomechanical changes in the ONH directly or indirectly affect or modulate cellular function and blood flow has yet to be established. It is also unknown if and how these structural deformations correlate with or predict a decline in vision. Nonetheless, HD-OCT may prove to be a clinically useful adjunct to the study and management of patients with papilledema that warrants further study. Additional studies with greater numbers of subjects will determine whether RPE/BM angulation will be a clinically useful finding to differentiate etiologies of ONH swelling with and without elevated intracranial pressure.

References