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In Vivo 3-Dimensional Strain Mapping of the Optic Nerve Head Following Intraocular Pressure Lowering by Trabeculectomy

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Purpose: To map the 3-dimensional (3D) strain of the optic nerve head (ONH) in vivo after intraocular pressure (IOP) lowering by trabeculectomy (TE) and to establish associations between ONH strain and retinal sensitivity.

Design: Observational case series.

Participants: Nine patients with primary open-angle glaucoma (POAG) and 3 normal controls.

Methods: The ONHs of 9 subjects with POAG (pre-TE IOP: 25.3±13.9 mmHg; post-TE IOP: 11.8±8.6 mmHg) were imaged (1 eye per subject) using optical coherence tomography (OCT) (Heidelberg Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany) before (<21 days) and after (<50 days) TE. The imaging protocol was repeated for 3 controls in whom IOP was not altered. In each post-TE OCT volume, 4 tissues were manually segmented (prelamina, choroid, sclera, and lamina cribrosa [LC]). For each ONH, a 3D tracking algorithm was applied to both post- and pre-TE OCT volumes to extract IOP-induced 3D displacements at segmented nodes. Displacements were filtered, smoothed, and processed to extract 3D strain relief (the amount of tissue deformation relieved after TE). Strain relief was compared with measures of retinal sensitivity from visual field testing.

Main Outcome Measures: Three-dimensional ONH displacements and strain relief.

Results: On average, strain relief (averaged or effective component) in the glaucoma ONHs (8.6%) due to TE was higher than that measured in the normal controls (1.07%). We found no associations between the magnitude of IOP decrease and the LC strain relief ($P > 0.05$), suggesting biomechanical variability across subjects. The LC displaced posteriorly, anteriorly, or not at all. Furthermore, we found linear associations between retinal sensitivity and LC effective strain relief ($P < 0.001$; high strain relief associated with low retinal sensitivity).

Conclusions: We demonstrate that ONH displacements and strains can be measured in vivo and that TE can relieve ONH strains. Our data suggest a wide variability in ONH biomechanics in the subjects examined in this study. We further demonstrate associations between LC effective strain relief and retinal sensitivity. *Ophthalmology 2016;■:1–11 © 2016 by the American Academy of Ophthalmology.*

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Elevated intraocular pressure (IOP) is associated with increased prevalence[1] and incidence[2] of glaucoma. However, some patients with elevated IOP never develop glaucoma. Furthermore, glaucoma occurs nearly as often in patients with normal levels of IOP as in those with elevated levels[3] and does so without a distinctly different etiology.[4] In brief, our current understanding of glaucoma is insufficient: We know that IOP is an important, albeit not the only, predisposing risk factor in the development and progression of this pathology.[2]

Our previous research[5,6] and that of other investigators[7,8] have set out to provide explanations for these clinical observations and suggested that the biomechanics of an individual's optic nerve head (ONH) dictate the IOP level it can sustain without inducing glaucomatous damage. Above an individual specific threshold level of IOP, a series of cellular events could be initiated at the level of the lamina cribrosa (LC)—a putative major site of damage in glaucoma—and eventually lead to glaucomatous damage. Unfortunately, no studies have been able to test such biomechanical hypotheses directly because most were limited to postmortem experiments[5,9–12] or computational modeling.[13–16] We believe that if it were possible to directly characterize ONH biomechanics in the living human eye, this may represent an accurate predictor for future glaucoma progression.[17]

Several studies have claimed measurements of IOP-induced ONH "deformations" in vivo using optical coherence tomography (OCT), especially at the site of the LC. Agoumi et al[18] were the first to use OCT to investigate LC displacements in patients with glaucoma after changes in IOP through ophthalmodynamometry, but they found

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inconclusive evidence for LC movements after an acute IOP elevation of approximately 12 mmHg.[18] Further studies in both monkeys and humans reported changes in anterior LC surface configurations (LC depth) with IOP increases[19] or IOP lowering after trabeculectomy (TE).[20–25] However, LC depth is a poor surrogate for LC deformations, and none of the aforementioned studies have been able to map in vivo IOP-induced 3-dimensional (3D) displacements and strains (the engineering definition for deformation) that could indicate local compression, shear, or stretch of the axons passing through the LC. Such information is of critical value if we want to understand how local ONH deformations could lead to RGC damage and apoptosis. All prior studies also have been hampered by restricted LC visibility in OCT.[26,27]

The aim of this study was to establish a foundation for mapping ONH biomechanical characteristics in patients. In our previous work, we proposed and verified (but not validated) an OCT-based 3D tracking algorithm that could extract IOP-induced ONH displacements and strains after a change in IOP.[28] By using this novel technique, we report here in vivo local displacement/strain mapping of ONH tissues after IOP lowering by TE in subjects with glaucoma and establish associations with visual field loss.

Methods

Patient Recruitment and Trabeculectomy

This study was approved by the Bloomsbury Research Ethics Committee, United Kingdom, and adhered to the ethical principles outlined in the Declaration of Helsinki. All recruited subjects gave written informed consent. Inclusion criteria for healthy controls ($n = 3$) were IOP $\leq$21 mm Hg, healthy ONHs with vertical cup-to-disc ratio $\leq$0.5, and normal visual fields. These subjects were not attending the hospital eye service for any clinical reason and had no other relevant pathology. In addition, 9 subjects with primary open-angle glaucoma (POAG) who were to undergo TE as part of their standard clinical care were recruited.

Primary open-angle glaucoma was defined as glaucomatous optic neuropathy, characterized as loss of neuroretinal rim with vertical cup-to-disc ratio >0.7 or focal notching with nerve fiber layer defect attributable to glaucoma and/or asymmetry of cup-to-disc ratio between eyes >0.2, with repeatable glaucomatous visual field defects (independent of the IOP value) in at least 1 eye.

The decision to perform TE was not made on the basis of participation in the study but after detection of visual field progression despite the use of 3 or more topical IOP-lowering agents as per UK National Institute of Clinical Excellence guidance.[29] All surgery was undertaken by 1 of 3 glaucoma fellowship–trained consultant surgeons (D.S.K., M.P., N.G.S.). The surgical method in all cases adhered to the technique described as the Moorfields Safer Surgery Technique.[30] In all cases, mitomycin C 0.2 mg/ml was used. Postoperative management involved a gradual reduction of IOP through adjustment and removal of sutures in the first 4 weeks after the surgery. One subject with POAG was excluded from analysis, because IOP lowering was not achieved by the time of postoperative imaging. Demographics and clinical data for all included subjects are listed in Table 1.

Optical Coherence Tomography Imaging

After pupillary dilatation (1% tropicamide), each glaucoma subject's ONH was imaged twice using enhanced-depth imaging spectral-domain OCT (Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany). The first acquisition was performed before TE (within 21 days) when IOP was medically treated but inadequately controlled. The second acquisition was performed after TE when target IOP had been achieved without medication (within 50 days) (Table 1). Each OCT volume (horizontal raster) comprised 145 horizontal B-scans (each composed of 384 A-scans) covering a rectangular region of 15°×15° centered on the ONH. The average distance between 2 consecutive B-scans was 30.59 μm, and the axial and lateral B-scan pixel resolutions were 3.87 μm and 11.49 μm, respectively. Note that all A-scans were averaged 10 times during acquisition to reduce speckle noise. The OCT imaging protocol was repeated for the 3 normal controls except that both OCT volumes were acquired consecutively at the same visit with no IOP manipulation.

Visual Field Testing

All subjects with POAG underwent static automated perimetry using the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA), 24-2 SITA Standard test protocol. Each subject was an experienced visual field witness (>7 previous tests), and all tests included in this study were reliable (<20% fixation losses, <33% false-positives, <33% false-negatives). All visual fields were undertaken within 12 weeks before TE surgery and processed to extract "raw" retinal sensitivity values (in decibels).

Light Attenuation Correction Using Adaptive Compensation

To remove light-attenuation artefacts, all OCT volumes were postprocessed using adaptive compensation (AC).[27,31] In OCT images, AC has been shown to improve tissue visibility below blood vessel shadows and to improve the visibility/contrast of the LC/choroid/scleral boundaries and of the LC insertions into the sclera.[26,32] In addition, our previous work has indicated that AC can improve the accuracy of 3D displacement tracking when 10× signal averaging was used[28] (as performed in this article).

Optic Nerve Head Reconstruction through Manual Segmentation

In this study, we aim to establish the characteristic deformation pattern of each major ONH tissue after a change in IOP. To this end, each compensated post-TE (lower-IOP) OCT volume was manually segmented (i.e., digitally partitioned) using Amira (version 5.4, FEI, Hillsboro, OR) to identify the following tissue groups: (1) choroid, Bruch's membrane, and retinal pigment epithelium; (2) peripapillary sclera; (3) LC; and (4) prelaminar tissues (Fig 1). Note that all segmentations were cropped (Fig 1) to ensure that only overlapping ONH image regions (pre- and post-TE) were used for 3D tracking. Note also that segmentations were conducted only when tissue was visible as detected from the compensated OCT signal. In most cases, full-thickness segmentation of the LC and sclera could not be achieved because of poor or absent visibility of the posterior LC/scleral boundaries.[26] On average, the en face sectoral visibility of the anterior LC in the post-TE volumes (after compensation) was 58.6% (inferonasal), 57.4% (nasal), 59.9% (superonasal), 81.0% (superotemporal), 73.2% (temporal), and 68.1% (inferotemporal). Note that for the purpose of this study, only a single ONH geometry per eye needs to be reconstructed (pre-TE or post-TE) because the second can be "morphed" from such segmented reconstruction using the 3D displacements derived from 3D tracking.