Optic Disc Diameter Increases during Acute Elevations of Intraocular Pressure

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PURPOSE. To evaluate optic nerve diameter changes in glaucomatous and nonglaucomatous eyes during transient elevation of intraocular pressure (IOP).

METHODS. This prospective experimental study included 100 subjects: 38 with glaucoma and 62 without glaucoma. Elevation of IOP to an average of 64 mm Hg for less than 30 seconds was induced in one eye of all subjects by means of a modified LASIK suction ring. The optic nerve heads were imaged before and during the elevation.

RESULTS. During IOP elevation, optic disc area and linear disc measurements increased by a small but significant amount (3.89%, P < 0.0001 and 0.96%, P = 0.01, respectively). Distances between retinal landmarks did not change significantly (P = 0.25). A smaller optic disc at baseline (P = 0.004) and increased central corneal thickness (CCT; P = 0.011) were associated with a greater increase in disc area relative to other fundus dimensions during IOP elevation. Disc area increased less in patients with glaucoma (P = 0.015). In a multivariate model including age, glaucoma status, CCT, and baseline disc area, there was a small but significant negative correlation between disc area enlargement and baseline optic disc diameter (P = 0.017).

CONCLUSIONS. Transient elevation of IOP in adult eyes resulted in increases in disc area and linear disc dimensions, but not in retinal dimensions. The degree of enlargement appears to be less in patients with glaucoma than without and greater with increased corneal thickness. A multivariate model showed that the amount of disc area increase was inversely proportional to baseline disc area but was not related to glaucoma status or CCT. (ClinicalTrials.gov number, NCT00328835.) (Invest Ophthalmol Vis Sci. 2010;51:2313–2316) DOI:10.1167/iovs.09-3756

S tructural changes in the optic nerve head are central to the diagnosis of glaucoma and may be involved in its pathogenesis. Biomechanical responses of the optic nerve head to elevations of intraocular pressure (IOP) have been studied in several models including monkey1,2 and human3 eyes and by computer modeling techniques4–6 There are deformations of the lamina cribrosa in human and monkey eyes in response to a transient IOP increase.2,5,6

Belcozza et al.2 examined monkey eyes, with and without induced glaucoma, and found plastic expansions of the anterior scleral canal at both Bruch’s membrane opening and anterior laminar insertions in glaucomatous eyes, but not in control eyes. Sigal et al.4 described the importance of peripapillary scleral stiffness and thickness, as well as the optic canal diameter, in determining lamina cribrosa strain.

In a study of 20 eyes (10 myopic and 10 emmetropic) without glaucoma, Azaa-Blanco et al.5 reported a significant increase in both optic cup area and optic cup volume when IOP was artificially increased. Changes in optic disc diameter were not described by those investigators, who relied on the standard practice of automated imaging of the previous contour lines in the imaging software (HRT-I; Heidelberg Engineering, Heidelberg, Germany). Finite element analysis suggests that much of this change may be in the prelaminar tissues,4 rather than in the lamina itself.

In this study, we investigated the changes in optic disc diameter in a large group of patients, with or without glaucoma, during a transient IOP increase. Although the relevance of deformations measured by confocal scanning laser tomography under conditions of acutely raised IOP to the development of glaucoma remain unknown, the deformations reflect the mechanical properties of optic nerve head (ONH) tissues. We have reported an association between corneal hysteresis and optic nerve head deformability.7 It is likely that ONH biomechanics play a significant role in the development of glaucoma.

METHODS

Patients

One hundred adult patients who had attended a specialist appointment in the preceding 12 months were recruited from general ophthalmology and glaucoma clinics in Wellington, New Zealand. All were older than 18 years with best corrected visual acuity of at least 6/12. They were assigned to either the glaucoma or the control group based on clinical findings in previous visits (Table 1). Those included in the glaucoma group had received a diagnosis of glaucoma by a glaucoma specialist (APW) and had documented glaucomatous optic disc appearance over at least two specialist visits. As a control group, patients with healthy eyes were recruited together with others who were referred to our clinic as having suspected glaucoma but who were found to have no evidence of glaucomatous optic neuropathy.

Patients with known or suspected ocular perfusion abnormalities were not invited to participate in the study, because of the potential effects of the high induced IOP on retinal circulation. Patients were also excluded if changes had been made to the treatment regimen, or if they had undergone either intraocular surgery or laser trabeculectomy within the preceding 3 months. Glaucoma patients with ad-
TABLE 1. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Glaucoma</th>
<th>Control</th>
<th>2-sample t-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>38</td>
<td>62</td>
<td></td>
<td>0.014</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>29/9</td>
<td>32/30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>62 ± 13</td>
<td>60 ± 10</td>
<td></td>
<td>0.579</td>
</tr>
<tr>
<td>Diagnosis (n)</td>
<td>POAG/NTG (29)</td>
<td>Glaucoma suspect (37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PXF/PDS Glaucoma (6)</td>
<td>Narrow angle ± PI ± OHTN (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NAG (3)</td>
<td>OHTN (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cataract/other (6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment (n)</td>
<td>Medication (28)</td>
<td>Cataract extraction (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cataract Extraction (6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SLT (9)</td>
<td>Medication (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OD IOP, mm Hg</td>
<td>17.08 ± 4.5</td>
<td>17.36 ± 4.3</td>
<td></td>
<td>0.753</td>
</tr>
<tr>
<td>OS IOP, mm Hg</td>
<td>18.24 ± 4.8</td>
<td>17.60 ± 3.8</td>
<td></td>
<td>0.461</td>
</tr>
<tr>
<td>OD IOP elevation, mm Hg</td>
<td>66.59 ± 11.8</td>
<td>63.18 ± 14.1</td>
<td></td>
<td>0.594</td>
</tr>
</tbody>
</table>

POAG, primary open angle glaucoma; PXF, pseudoexfoliation; NTG, normal tension glaucoma; NAG, narrow angle glaucoma; PDS, pigment dispersion syndrome; SLT, selective laser trabeculoplasty; YAG PI, YAG peripheral iridotomy; OHTN, ocular hypertension; Other; eyelid abnormalities (n = 2), trocheal nerve palsy (n = 1), vitreous detachment (n = 1).

IOP Elevation

Acute IOP elevation was induced in the right eye of all subjects by the application under local anesthetic of a modified automated corneal shaper (Chiron; Hansa Research and Development, Miami, FL) to the cornea. Since LASIK suction rings can produce IOPs in excess of 100 mm Hg, the rigid plastic tubing connecting the suction ring to the main pump had been punctured by two 18-gauge needles which were left in situ to reduce the potential of producing intraluminal negative pressure, and therefore limiting the peak IOP elevation that could be generated. Elevation of IOP lasted 10 to 30 seconds for each patient. IOP measurement during the procedure was obtained with a rebound tonometer (iCare; Tiolat, Helsinki, Finland). IOP measurements were available for 51 patients, since technical difficulties made measurement with other available devices (including Goldmann, Tonopen [Reichert], and Pascal dynamic contour tonometers [Zeimer Ophthalmic Systems, AG, Port Switzerland] and pneumotonometers) impossible.

Optic Nerve Imaging and Data Collection

The right eye of all patients was imaged before and during IOP elevation (HRT-II; Heidelberg Engineering), with the scan focus setting adjusted in each setting to optimize image quality. The usual procedure of averaging three scans was used, combined into a mean topographic image. Both before and during IOP elevation, scans were performed with an eyelid speculum in place to control for refractive or ocular distortion effects from the speculum. Artificial tears (Bion Tears; Alcon, Fort Worth, TX) were used to lubricate the cornea and maximize image quality.

Reproducibility of contour line and disc assessment was measured by having the same operator draw contour lines for 20 scans, delete them, and then, on a different day, redraw the contour lines. The differences in area for each contour line were recorded for each eye.

Analysis

The data were collated (Excel ver. 11.1, Microsoft, Redmond, WA) and analyzed (Excel and SPSS 11.04; SPSS, Chicago, IL). Patient characteristics were analyzed with χ² tests and two-tailed Student’s t-tests. Parametric data obtained before and after the procedure within each
group were tested for relationships by using Pearson’s correlation coefficient, and nonparametric data were examined by using Spearman’s rank correlation coefficient. Multivariate analysis was performed with the general linear model (SPSS).

RESULTS

There was no significant difference in the age of subjects in the glaucoma and control groups. There were significantly more male subjects recruited in the glaucoma group, whereas the balance between the sexes was almost even in the control group ($P = 0.014$, Table 1). There was also no statistically significant difference in preprocedure IOP in either eye between the two groups, although the glaucoma group did have thinner corneas ($P < 0.001$).

IOP Elevation

IOP during suction cup application was recorded with rebound tonometry (iCare; Tiolat). Since we did not have access to the rebound tonometer at the beginning of the study, not all the subjects had IOP readings taken during IOP elevation. We measured 17 patients in the glaucoma group with an average of 66.6 mm Hg, and 34 in the control group with an average of 63.2 mm Hg ($P = 0.4$). Rebound tonometry may overestimate IOP relative to Goldmann measurements, so Goldmann IOPs during pressure elevation may have been a little lower.

Reproducibility of Contour Lines

Reproducibility of the areas enclosed by the contour lines was excellent, with an average difference between separate measures of the same eye of 0.89% (0.01 mm$^2$), with an SD of 2.26% (0.01 mm$^2$).

Change in Optic Disc Area

During IOP elevation, mean optic disc area increased by 3.9% ($P < 0.0001$, paired Student’s $t$-test) relative to baseline. Disc area increased under elevated IOP almost twice as much in patients without glaucoma (5.4%) as in patients with glaucoma (2.3%, $P = 0.015$), as seen in Figure 2. There was no difference in baseline disc area between the glaucoma and control groups ($P = 0.51$, unpaired Student’s $t$-test).

Optic Disc Linear Changes

Linear distances between disc landmarks also increased by 1.0% on average ($P = 0.01$, paired students’ $t$-test) relative to baseline. Linear disc measurement increases were 1.3% and 0.9% in the glaucoma and control groups, respectively.

Linear Retinal Change

Linear distances between retinal landmarks did not change significantly, either in the entire group ($P = 0.25$) or in the glaucoma group ($P = 0.09$), suggesting that the apparent disc enlargement was not due to optical or other generalized effects. This finding is not surprising, given that the automatic HRT alignment and scaling algorithm uses retinal feature detection to achieve superimposition of sequential images.

Other Correlations with Disc Area Change

Pearson correlation coefficients examining disc area change were significant for smaller optic discs at baseline ($P = 0.004$; Fig. 2) and increased CCT ($P = 0.011$), but not axial length ($P = 0.37$) or spherical equivalent ($P = 0.39$).

In a general linear model with disc area increase as the dependent variable and disc area at baseline, age, glaucoma status, CCT, and sex as covariates (Table 2), only disc area at baseline correlated significantly with increase in disc area ($P = 0.017$).

DISCUSSION

In this study, retinal tomography (HRT-II; Heidelberg Engineering) showed that transient elevation of IOP in adult eyes both with and without documented glaucoma resulted in enlargement of the optic nerve head. Using computer models derived from donor and monkey eye data, Sigal et al. described a potential relationship between optic disc diameter increase and cup size, which implied that an increase in optic disc diameter in raised IOP conditions ought to be proportional to baseline disc diameter. The results of this study suggest that the opposite may occur: as baseline optic disc area increased, the amount of increase in disc area during raised IOP decreased. This relationship was statistically significant, but small, with a small correlation coefficient (Fig. 2). To our knowledge such a relationship has not been previously in human studies.

Limitations of this study include the subjective task of outlining the optic nerve head in the HRT software. We attempted to address this by first using a relatively large number of subjects. Second, we supported this optic disc area data derived from manual contour line placement by making linear disc measures, to unequivocal landmarks on the disc such as vessel bifurcations or locations where vessels crossed the disc edge. The reproducibility of our manual contour line placements was excellent.

The contour line application to subsequent images in the normal tomographic progression analysis is based on the align-

**Table 2. Tests of Between-Subjects Effects**

<table>
<thead>
<tr>
<th>Source</th>
<th>F</th>
<th>P</th>
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<tbody>
<tr>
<td>Glaucoma status</td>
<td>0.735</td>
<td>0.393</td>
</tr>
<tr>
<td>Disc area at baseline</td>
<td>5.881</td>
<td>0.017</td>
</tr>
<tr>
<td>Age</td>
<td>0.020</td>
<td>0.888</td>
</tr>
<tr>
<td>CCT</td>
<td>2.446</td>
<td>0.121</td>
</tr>
<tr>
<td>Sex</td>
<td>2.099</td>
<td>0.151</td>
</tr>
</tbody>
</table>

Dependent variable, disc area increase.
ment and scaling of serial images based on retinal feature detection. The automated contour line placement for images captured under IOP elevation would be accurate if the amount of change in disc area resulting from the IOP elevation process was identical with that of the surrounding retinal image. If the change in position of the retinal features was not identical with the disc changes—other words if the disc stretched more or less than the surrounding tissues—the automated contour line placement would be inaccurate.

In this study, the measured disc size changes were relative to any possible absolute change in the peripapillary retina adjusted for by the HRT alignment software. The linear retinal measurements should not have, and did not, demonstrate change in this study; the automated HRT alignment and scaling software uses retinal feature recognition. It is possible that there was a larger true change in disc size than was detected in this study, if the posterior pole area that was scanned by the HRT was also stretched. If the retina was stretched, as the optic nerve head apparently was, then the HRT scaling algorithm would have reduced the measured change in disc size, which may, in part, account for the relatively small but highly significant changes observed in disc area and linear disc measurements at increased IOP.

We drew the contour lines manually, rather than using the automated contour line import function. In contrast, the manual process we used involved manual placement of contour lines around the edge of the optic disc. The disc edge landmarks and retinal landmarks were measured at separate sessions, and the results from the linear disc measurements supported those for disc area.

Although the control cohort had a similar number of male and female patients, the glaucoma cohort of the study group had a strong bias toward male patients. We did not find any correlation between increase in disc area under raised pressure and the sex of the individual. It is unlikely that sex-related bias in the glaucoma cohort had a tangible influence on the results.

Potential confounding factors in this study are the other changes that may occur in the globe during the application of the LASIK suction ring and IOP increase. These changes, such as possible changes in corneal curvature and axial length may alter the optics of the eye and magnification of fundus structures. A study assessing change in axial length during LASIK suction ring application in eight cadaveric eyes appeared to show an increase in axial length. However, axial length measurements in cadaveric eyes outside the orbital cavity may differ from those performed in vivo. A later in vivo study of 21 eyes during LASIK surgery showed no changes in axial length or anterior chamber depth.

Downs et al. have described viscoelastic properties of the peripapillary sclera in normal monkey eyes and in those with early glaucoma. We found a significant enlargement in optic disc size in glaucomatous and nonglaucomatous patients with transient IOP elevation. In the single variable analysis, enlargement was greater in patients who did not have glaucoma compared with those who did, which supports the notion described by Downs et al. that tissue properties change in the optic disc region of eyes exposed to chronic elevations in IOP. As described earlier, baseline disc area was inversely correlated with the amount of disc enlargement, but there was no difference in baseline disc area between the glaucoma and control groups; therefore, this finding is unlikely to be due to differences in baseline characteristics.

The enlargement of optic disc size under transient IOP increase was, in contrast to that predicted by theoretical models, inversely correlated with baseline optic disc area. We also found an unexpected and difficult to conceptualize relationship with CCT, where the amount of disc area increase correlated with increasing CCT. This relationship disappeared when other variables, including glaucoma status, were included in the multivariate model. Glaucoma status was not significant in the multivariate model, suggesting that factors other than glaucoma status may account for this finding in glaucomatous eyes.

IOP was transiently raised to quite high levels in this study: approximately 64 mm Hg. We might have achieved similar deformations at lower IOPs, but the design and methods of the study made investigation of a dose–response relationship impossible. If the deformations that were observed were also to occur with smaller IOP changes, there could be implications for optic disc imaging modalities with algorithms that assess structural progression. Any such effect is likely to be very small, however, and perhaps not clinically relevant. IOP increase in our study was transient (10–30 seconds), and imaging was performed during the period of high pressure. An interesting area of further research would be to assess these changes during a longer period of raised IOP to see whether they persist, increase, or even decline. Measurements could also be taken some time after the pressure increase to further assess the viscoelastic properties of the optic disc.

The results of this study complement results generated in theoretical models based on primate or cadaveric data. We have demonstrated for the first time in a human clinical study that optic disc diameter increases with raised IOP, and that the amount of increase correlates with baseline optic disc size.

Acknowledgments

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References