Effect of Moderate Intraocular Pressure Changes on Topographic Measurements With Confocal Scanning Laser Tomography in Patients With Glaucoma

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Objective: To evaluate optic disc topography changes after intraocular pressure (IOP) modulation in patients with glaucoma.

Methods: Twenty-three patients with glaucoma were studied. Three mean optic disc topography images were obtained with the Heidelberg Retina Tomograph II at baseline and weeks 1, 2, 4, and 8 (visits 1, 2, 3, 4, and 5, respectively). Topical medications were discontinued in the study eye after visit 1 and resumed after visit 4 but maintained in the contralateral control eye. Central corneal thickness was measured at the last visit. Topographic changes were determined by stereometric parameters (rim area and mean cup depth) and at discrete topographic locations using the Topographic Change Analysis program (from the Heidelberg Retina Tomograph II).

Results: In the study eyes, IOP increased significantly (5.4 mm Hg at visit 4; \( P < .001 \)) after withdrawal of topical medications but returned to baseline levels after resuming medications; no statistically significant topographic changes, however, were observed. Moreover, no relationship between change in IOP and stereometric parameters was observed. Central corneal thickness was not associated with changes in optic disc topography induced by IOP modulation.

Conclusion: In patients with glaucoma, significant but relatively moderate IOP increases and decreases on the order of 5 mm Hg did not appear to have an effect on optic disc topography.

tions within the borders of the optic disc, using the Topographic Change Analysis (TCA) program of the Heidelberg Retina Tomograph II (HRTII) (Heidelberg Engineering GmbH, Dossenheim, Germany), were used. Additionally, we wanted to evaluate if central corneal thickness (CCT) influences the IOP-induced changes on optic disc topography. Thinner CCT has been associated with glaucomatous optic disc damage (including documented progressive cupping and presence of optic disc notching) with a damaged visual field in at least one eye (defined as presence of an abnormal Glaucoma Hemifield Test result) and open angles on gonioscopy; (2) clear media; and (3) IOP controlled with at most 2 topical medications. Patients in whom visual fields in both eyes had a mean deviation worse than −12 dB and/or had involvement of 1 of the 4 paracentral points were excluded from the study. The study protocol was approved by the Queen Elizabeth II Health Sciences Centre Research Ethics Committee and was carried out in adherence with the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

PROCEDURES

The patient’s least damaged eye was chosen as the study eye in cases of disease asymmetry (defined as mean deviation difference between the 2 eyes > 2 dB); otherwise, the study eye was randomly assigned. After the baseline visit (visit 1), topical medications were discontinued in the study eye. The fellow eye was maintained on its regular therapy. Patients were then reexamined after 1, 2, and 4 weeks (visits 2, 3, and 4, respectively). After visit 4, medications were resumed in the study eye and patients attended a final study visit 4 weeks later (visit 5).

At each visit, 3 mean topography images were obtained with the HRTII, followed by IOP measurement images using Goldmann applanation tonometry to minimize the effects of corneal staining on the quality of the HRT images. Visual field tests were performed at visit 1 and visit 5 using the 24-2 SITA-Standard program of the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, Calif). If at any visit during medication washout the IOP in the study eye exceeded 30 mm Hg, the topical medication was immediately resumed and that visit was considered the last one without medication, and the patient was seen again after 1 month for visit 5. Central corneal thickness was measured using an ultrasound pachymeter (DGH-550 Pachette 2; DGH Technology Inc, Exton, Pa) at the last study visit.

ANALYSIS

Two experienced observers (M.T.N. and M.M.C.) reviewed the HRT images, drew the contour lines to outline the optic disc boundary, and checked the alignment of the image series, making manual alignment corrections where necessary.

Stereometric indexes were exported using version 1.4.1.0 of the Heidelberg Eye Explorer software. The HRT software provides many global and sectorial indexes of optic disc topography, many of which are highly related, but we decided when the study was designed to report on the global rim area and mean cup depth indexes only. These indexes were chosen because they are clinically meaningful, well understood, are thought to directly reflect lamina cribrosa shifts induced by changes in IOP, and tend to have lower variability than others. We specifically avoided analyzing all global and sectorial indexes provided by this instrument because we would end up with several comparisons and, by chance alone, we would expect to find significant differences in some of them. We used the median value of the 3 mean topography images obtained at each visit to reduce the effect of occasional outliers, therefore reducing variability between visits. Topographical changes were calculated by subtracting the baseline median value from the median value at each visit so that negative values refer to a reduction and positive values to an increase, with respect to the baseline visit. Changes were analyzed in absolute units (eg, in millimeters of mercury for IOP and millimeters squared for optic disc rim area) as well as in relative units (percentage of change from baseline).

The current version of the HRTII software provides for 2 different reference planes on which some of the stereometric indexes are based. Since the reproducibility of the optic disc rim area measurements within each visit was significantly better with the 320-µm reference plane compared with the standard reference plane (mean coefficient of variation of the median value in the control eyes, 2.4% and 3.3%, respectively; P<.002, Wilcoxon), the analyses reported in this article refer to the data obtained with the 320-µm reference plane.

Optic disc changes were also evaluated using the probability maps of the TCA program, which compare the relative height of each superpixel in the follow-up images with that of the baseline image. Areas with statistically significant depression or elevation on 3 consecutive mean topographies are highlighted in red or green, respectively. Because we obtained 3 consecutive mean topographies during each visit, we were able to use the last image obtained in each visit (which would represent consecutive changes that occurred in all 3 images from that visit) and compare it with the baseline image. Custom software written in Matlab (version 6; MathWorks, Natick, Mass) was used to calculate the size of the largest cluster of red and green superpixels within the contour line. The size of the clusters was expressed as a proportion of the total number of superpixels within the disc area to account for the possible large variation in disc size between patients. As with the stereometric analysis, we related the size of the largest cluster of red and green superpixels within the optic disc area to the observed IOP changes.

Changes in the investigated variables (IOP, optic disc rim area, mean cup depth) during the 5 visits were evaluated statistically by repeated-measures analysis of variance (ANOVA) using the General Linear Model module of SPSS version 12.0 (SPSS Inc, Chicago, Ill). Differences between study and control eyes and changes of the investigated variables between 2 study visits in the same group of eyes were evaluated statistically with the Wilcoxon test. The influence of CCT on changes of stereometric parameters was evaluated by multivariate analysis, with IOP and CCT as covariates.
RESULTS

CHARACTERISTICS OF STUDY PATIENTS

The mean age of the 23 patients included in this study was 62.3 years (range, 37 to 87 years). There were 12 male and 11 female patients. The baseline characteristics of the study and control eyes are given in Table 1. The only statistically significant difference between study and control eyes was that the latter were on average 0.4 diopter more myopic (P = .04). The mean ± SD difference in mean deviation between the study and control eyes approached statistical significance (−2.1 ± 2.3 dB and −4.6 ± 0.3 dB, respectively; P = .07), largely because of the inclusion of 4 patients with asymmetric disease in whom the eye with the more damaged visual field was selected as the control eye, as per protocol. There was, however, no apparent difference in the amount of optic disc damage between study and control eyes, with similar average rim area and rim area deviation (a variable that expresses the degree, in standard deviations, that the rim area adjusted by disc size deviates from a normal population) between the 2 groups (P > .19).

CHANGE IN IOP

In the study eyes, the IOP increased significantly at visits 2, 3, and 4 (P < .001). At visit 4, for example, 4 weeks after the baseline visit (visit 1), the IOP in the study eyes had increased, on average, by 5.4 mm Hg, or 33% (Figure 1A and C). At visit 5, 4 weeks after medications had been resumed, the IOP in the study eyes decreased significantly compared with visit 4 (mean ± SD, 22.27 ± 4.12 mm Hg and 17.39 ± 2.67 mm Hg for visits 4 and 5, respectively; P < .001) but was not significantly different than visit 1 (P = .55). In the control eyes, the IOP did not vary significantly during the 5 visits (P > .22) (Figure 1B and D).

VARIATION IN STEREOMETRIC PARAMETERS DURING THE 4 FOLLOW-UP VISITS

In the study eyes, repeated-measures ANOVA did not reveal any significant changes in rim area and mean cup depth during the 5 visits (all P > .42) (Figure 2). In the control eyes, no significant changes were observed in rim area during the 5 visits (P = .39), but a borderline statistical significance (P = .04) was observed in changes of mean cup depth, most likely a false-positive finding caused by outliers. The data points in Figure 2, for example, show the individual rim area changes as compared with baseline during visits 2 to 5. In the study eyes, none of the group means (shown by horizontal lines) were statistically different from zero, irrespective of whether the changes were expressed in absolute (millimeters of mercury) (A and B) and relative (percentage) (C and D) terms. Withdrawal of topical medications increased IOP by approximately 5 mm Hg (means, solid horizontal lines [A]) or 30% (means, solid horizontal lines [C]) in visits 2 to 4. The IOP returned to baseline levels at visit 5, 4 weeks after medications were resumed. In the fellow eyes, which continued therapy throughout the study, no systematic changes of IOP were observed (B and D).

VARIATION IN TCA PROBABILITY MAPS DURING THE 4 FOLLOW-UP VISITS

We also evaluated the sizes of the largest clusters of red and green superpixels within the optic disc (Figure 4).

Table 1. Baseline Characteristics of Study and Control Eyes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Eyes</th>
<th>Control Eyes</th>
<th>P Value†</th>
</tr>
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<tbody>
<tr>
<td>Baseline IOP, mm Hg</td>
<td>17.30 ± 3.27 (14 to 26)</td>
<td>17.17 ± 3.43 (10 to 24)</td>
<td>.67</td>
</tr>
<tr>
<td>CCT, µm</td>
<td>540 ± 31 (470 to 586)</td>
<td>540 ± 33 (458 to 591)</td>
<td>.73</td>
</tr>
<tr>
<td>Refractive error, D</td>
<td>−0.10 ± 2.18 (−4.00 to + 4.00)</td>
<td>−0.50 ± 2.10 (−3.50 to + 4.00)</td>
<td>.04</td>
</tr>
<tr>
<td>MD, dB</td>
<td>−2.1 ± 2.3 (−11.1 to + 1.0)</td>
<td>−4.6 ± 6.3 (−24.2 to + 0.6)</td>
<td>.07</td>
</tr>
<tr>
<td>Disc area, mm</td>
<td>2.14 ± 0.45 (1.49 to 3.10)</td>
<td>2.20 ± 0.46 (1.20 to 3.15)</td>
<td>.44</td>
</tr>
<tr>
<td>Rim area, mm</td>
<td>1.32 ± 0.46 (0.69 to 2.81)</td>
<td>1.21 ± 0.32 (0.66 to 1.77)</td>
<td>.54</td>
</tr>
<tr>
<td>RAD, SD</td>
<td>−1.38 ± 1.42 (−4.96 to 1.60)</td>
<td>−1.89 ± 1.33 (−5.07 to 0.91)</td>
<td>.19</td>
</tr>
</tbody>
</table>

Abbreviations: CCT, central corneal thickness; D, diopter; IOP, intraocular pressure; MD, mean deviation; RAD, rim area deviation; SD, standard deviation.

*Data are expressed as mean ± SD (range) unless otherwise specified.
†Wilcoxon test.
The mean total number of superpixels within the contour line in the studied eyes was 1105 (range, 655 to 1670). Several study eyes showed red cluster sizes greater than 2% of the superpixels within the contour line (corresponding to approximately 20 superpixels in an average disc) in visits 2 to 4, suggestive of significant depression compared with baseline. However, this also occurred in the control eyes and is therefore unlikely to be due to the effect of IOP increase alone. Similar to the findings with the stereometric parameters, there were no clearly apparent differences in the study eyes between visits 2 to 4 (elevated IOP) and visit 5 (when IOP decreased back to baseline levels). Although the clusters appeared slightly larger in the study eyes as compared with the control eyes (Figure 4), this was not statistically significant in a pairwise analysis ($P = .16$). There were also no statistical differences in the cluster sizes with green superpixels between study and control eyes ($P = .65$).

**Figure 5** shows an example of the images obtained through the 5 visits in the study eye of 1 patient, with the corresponding TCA obtained on the third image for each visit compared with baseline. In this particular example, we could not observe change in optic disc topography either by TCA or stereometric parameters, despite an IOP increase of 8 to 9 mm Hg after cessation of topical therapy.

**RELATIONSHIP BETWEEN TOPOGRAPHICAL CHANGES, IOP CHANGES, AND CCT**

Despite the moderate IOP modulation in the study eyes, we did not find evidence for a relationship between change in IOP and change in rim area or mean cup depth in the study eyes (Table 2) (Figure 6).

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Despite the moderate IOP modulation in the study eyes, we did not find evidence for a relationship between change in IOP and change in rim area or mean cup depth in the study eyes (Table 2) (Figure 6).
In a multivariate analysis including change in IOP (using data from the visit with the highest change in IOP as compared with baseline) and CCT as covariates, CCT did not exert a statistically significant effect \((P > .31)\) on the relationship between IOP change and change in rim area \((\text{Figure 7})\) or mean cup depth (data not shown).

Table 2. Correlation Between Absolute Change in Stereometric Parameters and TCA and Absolute Change in IOP\(^{*}\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study Eyes</th>
<th>Control Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation</td>
<td>(P) Value</td>
</tr>
<tr>
<td>Rim area</td>
<td>0.116</td>
<td>.28</td>
</tr>
<tr>
<td>Mean cup depth</td>
<td>-0.029</td>
<td>.79</td>
</tr>
<tr>
<td>Red superpixels</td>
<td>-0.021</td>
<td>.85</td>
</tr>
<tr>
<td>Green superpixels</td>
<td>0.087</td>
<td>.42</td>
</tr>
</tbody>
</table>

Abbreviations: IOP, intraocular pressure; TCA, topographic change analysis. 
\(^{*}\)Using data from visit with highest IOP compared with baseline visit.

Figure 5. Example of data from the study eye of 1 randomly selected patient. After the baseline visit (visit 1), topical medications were discontinued and the IOP rose from 16 mm Hg to 24 mm Hg. After visit 4, the medications were resumed and the IOP returned to 18 mm Hg on visit 5. At each visit, 3 topography images were generated (first 3 rows, with the respective rim area shown in the right upper corner). The bottom row of images shows the Topographical Change Analysis depicting the third mean topography of visits 2 to 5. Superpixels found to be significantly depressed or elevated in all 3 images from visits 2 to 5 when compared with the first mean topography obtained at baseline (visit 1) are shown in red and green, respectively. The numbers in the right upper corner represent the size of the largest cluster of red superpixels inside the contour line.
Similarly, we did not find evidence for systematic changes in the TCA probability maps with IOP fluctuation (Table 2) (Figure 8). The variation in IOP explained less than 1% of the variation in the superpixel cluster size.

STATISTICAL POWER

We analyzed the statistical power of our study to detect various magnitudes of change in the stereometric parameters rim area and mean cup depth based on the variability observed in the control eyes. For simplicity, we based our power calculations on a paired t test, although our analyses using repeated-measures ANOVA would yield slightly higher power. From Figure 9 it is apparent that our study was adequately powered to detect small changes in rim area and mean cup depth (for example, the power to detect an absolute change of >0.02 mm or relative change >2.5% was >80%, with an α of .05), if such systematic changes had existed.

COMMENT

In this study, the IOP in the study eyes increased on average 5.4 mm Hg (33%) by visit 4 and decreased by the same amount on visit 5, while remaining fairly constant in the control eyes. Despite these significant IOP increases and decreases in the study eyes, no significant topographic changes were observed in the optic discs. We evaluated topographic disc changes with both a global (stereometric parameters) and a discrete (TCA) analysis. This study was well powered to detect relatively small
changes in the stereometric parameters evaluated, had they occurred (Figure 8). The changes we observed in IOP were relatively modest, albeit statistically significant, and it is possible that with more marked IOP increase and decrease we would observe corresponding changes in optic disc topography. The magnitude of the IOP changes observed in this study, however, mimics what can occur in patients being treated medically, for instance after initiating or adding therapy in patients with elevated IOP or by IOP fluctuations caused by poor compliance with medical therapy. Our results suggest that IOP increases or decreases of this magnitude, sustained for a period of a few weeks, do not affect optic disc topography measured with the HRT in a meaningful or consistent manner. We only evaluated optic disc topography after a few weeks of consistent IOP change; therefore, we cannot rule out the possibility that acute IOP changes of similar magnitude might lead to topographic optic disc changes that did not persist after few weeks.

One of the factors that can influence the ability to detect changes in stereometric parameters over time is variability of the reference plane that is used to define most of the parameters.21 The standard reference plane of the HRT II is defined as 50 µm below the height of the contour line between 35° and 356°, which is assumed to correspond to the height of the papillomacular nerve fiber bundle, supposedly only affected in very advanced stages of glaucoma.22 Another approach presently available in the HRT software is to use a fixed reference plane, at 320 µm.20 There is currently no agreement regarding the ideal reference plane for HRT analysis, and several investigators have proposed new ways of calculating reference planes, not yet fully evaluated or available in the HRT software.20,22-25 For this reason, we decided to evaluate changes in stereometric parameters using the 2 available reference planes, the standard and the fixed one at 320 µm. Since the variability we observed was smaller with the fixed reference plane, we presented our results using this reference plane, although an analysis based on the standard reference plane yielded similar results. The TCA program, which evaluated change in discrete topographic locations as opposed to stereometric parameters, is independent of any reference plane.

Other investigators have evaluated topographic changes following IOP reduction, with variable results. Irak et al26 reported a significant decrease in cup area and cup volume following trabeculectomy with a follow-up of 4 months (average IOP reduction of 11 mm Hg or approximately 45%). In contrast, Topouzis et al20 reported no significant topographic changes 4 and 8 months after trabeculectomy, despite IOP reduction of approximately 49%. Lesk et al,27 in a similar study, observed a significant correlation between topographic changes and percentage of IOP reduction following trabeculectomy, with a mean follow-up of 26 weeks. Bowd et al28 failed to show a significant change in topographic parameters after reducing IOP with topical latanoprost (mean reduction of 25%, for an average of 2.7 weeks). However, when analyzing the subset of subjects with the highest IOP reduction (average of 36%), significant topographic changes were observed. It is apparent from the previous reports that topographic optic disc changes occurred more often in eyes with the greatest IOP reduction (normally ≥40%), although not consistently in every study. In our study, the observed IOP reduction between visits 4 and 5 (induced by resumption of medication) was lower, on the order 22% (average, 4.9 mm Hg), which can help explain why we did not observe any systematic change in optic disc topography induced by reduced IOP. Another possible difference between our study and those that observed topographic changes following trabeculectomy is that factors other than IOP reduction, such as subclinical optic disc edema after surgery, might influence optic disc topography and could take several months to subside.26

Few studies have evaluated the effects of IOP elevation on optic disc topography and those that have been published looked only at the effects of acute IOP elevation. Azaurre-Blanco et al27 and Piette et al28 observed significant optic disc cup enlargement and decrease of rim parameters in normal and myopic eyes following a marked and acute IOP elevation induced by ophthalmodynamometry. These changes were reversible, returning to baseline levels within 2 minutes of normalization of IOP. To the best of our knowledge, our study is the first to evaluate topographic changes following sustained, moderate elevation of IOP during a few weeks in a group of patients with glaucoma. We failed to observe any systematic change in optic disc topography in these eyes, both in terms of stereometric parameters or discrete topographic locations. In some eyes, however, we observed topographic changes on the order of 5% to 10% compared with baseline, but these changes are likely within the expected measurement variability, since they also occurred in several of the control eyes with stable IOP. Moreover, we did not observe any relationship between changes in rim area and mean cup depth and the amount of IOP elevation.

Changes in optic disc surface and position of lamina cribrosa have also been observed following acute IOP manipulation in experimental animal studies in dogs29 and monkeys.30 Morgan et al29 showed optic disc surface and lamina cribrosa movement shortly following IOP elevation and/or with cerebrospinal fluid pressure elevation in dogs, demonstrating that the transliminal pressure gradient is important in determining the position of the structures of the optic nerve head. Bellezza et al30 have demonstrated both plastic (permanent) and transient (hypercompliant) posterior displacement of the lamina cribrosa in the monkey glaucoma model. Other studies from the same laboratory have elucidated the stress and strain induced by elevated IOP in different areas of the optic nerve head and peripapillary retina.31,32

It is evident from our results, as well as from previous publications, that factors besides the magnitude of the IOP change might be important in determining topographic optic disc changes after IOP modulation in glaucomatous eyes. We could speculate that optic disc compliance, stage of optic disc damage, type of optic disc cupping, and age, among other factors, could be relevant. One of the factors that might be important to optic disc compliance is scleral or lamina cribrosa thickness.33 Unfortunately, there is currently no clinical method to measure posterior scleral thickness or lamina cribrosa thickness or compliance. Since the cornea and sclera form a continuous collagenous structure, it is logical to assume that the thickness of these 2 structures would be correlated, even though this correlation has not yet been demonstrated in human eyes. In this study, we decided to evaluate if CCT, as a possible surrogate in-
dex of scleral thickness and maybe lamina cribrosa compliance, was correlated with topographic optic disc changes induced by IOP modulation. Our results showed, however, that CCT was not associated with the response of the optic discs to IOP modulation, at least with the magnitude of IOP changes induced with our experiment.

In conclusion, despite adequate power, we did not observe significant and systematic changes in optic disc topography with sustained IOP changes (caused by cessation and reintroduction of topical ocular hypotensive medication) on the order of 20% to 30%. It is possible, however, that some individuals with a more compliant optic nerve head might experience marked changes in optic disc topography induced by IOP changes of this magnitude, which may have to be evaluated on an individual basis. In fact, in our study population, we did have some examples where this appeared to be the case, but overall, the fluctuations observed in the study eyes were no different from what occurred in the control eyes, in which the IOPs were stable. The clinical implications of our findings are that HRT images obtained at different levels of IOP within the 20% to 30% range during follow-up can be used to assess progressive glaucomatous damage in most patients. Our results do not apply, however, to IOP changes of greater magnitude. They do not apply either, to IOP reduction induced by glaucoma surgery, when probably factors other than just the IOP reduction might be relevant. In these circumstances it might be advisable to establish a new HRT baseline to evaluate optic disc progression with this technique.

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