Relationship Between Central Corneal Thickness and Changes of Optic Nerve Head Topography and Blood Flow After Intraocular Pressure Reduction in Open-angle Glaucoma and Ocular Hypertension

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Objectives: To investigate changes in optic nerve head topography and blood flow after therapeutic intraocular pressure reduction and to correlate them with central corneal thickness.

Methods: Sixteen patients with open-angle glaucoma and 16 patients with ocular hypertension underwent Heidelberg retina tomography and scanning laser Doppler flowmetry in 1 eye before and at least 2 months after a mean 35% sustained therapeutic reduction in intraocular pressure. Patients were assigned to a thin or thick group based on their median central corneal thickness.

Results: Compared with 16 patients with thick corneas (mean±SD central corneal thickness, 587±31 µm), the 16 patients with thin corneas (518±32 µm) had greater reductions in mean (36±32 vs 4±36 µm, \( P = .003 \)) and maximum cup depth (73±107 vs 4±89 µm, \( P = .02 \)). These changes were not statistically significantly different between the patients with open-angle glaucoma and those with ocular hypertension. Smaller mean±SD improvements in neuroretinal rim blood flow were seen in patients with thinner corneas compared with those with thicker corneas (35±80 vs 110±111 arbitrary units, \( P = .04 \)).

Conclusion: Patients with open-angle glaucoma and ocular hypertension with thinner corneas show significantly greater shallowing of the cup, a surrogate marker for lamina cribrosa displacement (compliance), and smaller improvements of neuroretinal rim blood flow after intraocular pressure reduction.

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ALTERED LAMINA CRIBROSA compliance has long been postulated to have a role in the development of open-angle glaucoma (OAG). Lamina cribrosa mobility has been studied in ex vivo human\(^1\)\(^-\)\(^6\) and monkey\(^7\)\(^-\)\(^8\) eyes, in living human\(^9\)\(^-\)\(^13\) and monkey\(^14\)\(^-\)\(^15\) eyes, and in histological studies.\(^8\)\(^,\)\(^15\)\(^-\)\(^18\) Findings from some studies\(^8\)\(^,\)\(^15\)\(^-\)\(^18\) suggest that there may be an initial hypercompliance in early glaucoma followed by reduced compliance (ie, increased rigidity) later in the course of the disease. In most patients with glaucoma, the central lamina cribrosa is covered by little or no neural or glial tissue. Therefore, lamina cribrosa compliance can be readily estimated using scanning confocal laser tomography by examining the position of the base of the cup relative to the retinal surface after intraocular pressure (IOP) changes.\(^9\)\(^-\)\(^12\)

Considerable evidence suggests that abnormal optic nerve blood flow has a role in the development of glaucomatous optic neuropathy.\(^20\) Recent data indicate that optic nerve head neuroretinal rim blood flow improves significantly in patients with OAG after sustained therapeutic IOP reduction.\(^21\) Among patients with ocular hypertension (OHT), such improvements were limited to vasospastic subjects.\(^22\) The prognostic significance of these blood flow changes remains to be determined.

Findings suggest that the presence of a thin cornea is linked to the development of glaucoma among patients with OHT,\(^23\) as well as to the severity of OHT\(^24\)\(^,\)\(^25\) and OAG.\(^26\)\(^,\)\(^27\) In OHT and OAG, a thin cornea is more strongly associated with disease severity than IOP.\(^23\)\(^,\)\(^27\) Underestimated Goldmann tonometric pressures seem to only partly explain the relationship between thin corneas and increased glaucoma risk. The other mechanisms underlying this relationship are unknown. Corneal thickness has been linked to scleral thickness.\(^26\)\(^-\)\(^30\) In this study, we examined the relationship between central corneal thickness and lamina cribrosa compliance. Because the blood vessels that feed the optic nerve head run through the lamina cribrosa, we also examined changes...
in neuroretinal rim blood flow that occur with IOP-dependent lamina changes.

**METHODS**

The study protocol was approved by the Ethics Committee of Maisonneuve-Rosemont Hospital, Montreal, Quebec, and all patients signed an informed consent form. Patients with OAG had gonioscopically confirmed open angles and manifested at least 2 of the following 3 criteria: characteristic nerve fiber bundle visual field defects, glaucomatous optic neuropathy, and a history of IOP greater than 21 mm Hg. Patients with OHT had a history of IOP greater than 24 mm Hg on at least 2 occasions, normal visual fields, and normal or suspect optic nerve head appearance based on slitlamp microscopy. Subjects were excluded if any abnormal ocular findings were present other than pseudophakia, if significant media opacities precluded scanning laser Doppler flowmetry (SLDF) imaging, and if they were unable to comply with the study protocol.

Medical and ocular histories were recorded, and IOP, re-fractive errors, and best-corrected visual acuity were measured before the baseline study visit. A basic ophthalmologic examination, including biomicroscopy, ophthalmoscopy, and gonioscopy, was performed, and the visual field was assessed using automated perimetry (Humphrey Field Analyzer, program 24-2; Humphrey Instruments, San Leandro, Calif).

Thirty-two patients having clinical indications for IOP reduction were recruited from the hospital glaucoma clinics and underwent confocal scanning laser tomography with the Heidelberg retina tomograph (version 2.01; Heidelberg Engineering, Heidelberg, Germany) and SLDF of the optic nerve head with the Heidelberg retina flowmeter and SLDF software version 3.3 (Heidelberg Engineering) before and at least 2 months after a minimum IOP reduction of 20%. For Heidelberg retina tomographic imaging, the mean topographies were derived from 3 high-quality images. The SLDF values for neuroretinal rim blood flow were derived from the mean of 5 high-quality images as described previously.21

As indicated clinically, IOP was reduced using topical hypotensive medications, argon laser trabeculoplasty, or filtration surgery. All patients were treated by one of us (M.R.L.). One eye was studied in each patient. If both eyes required therapy, the eye with the clearest media was chosen. We used the Heidelberg retina tomography stereometric variables of mean cup depth and maximum cup depth to estimate lamina cribrosa position in micrometers before and after IOP reduction. We used the SLDF variable of flow in all pixels overlaying the neuroretinal rim to determine neuroretinal rim blood flow in arbitrary units before and after IOP reduction. Central corneal pachymetry was determined using an ultrasound pachymeter (DGH 500 Pachette; DGH Technology, Fraser, Pa) using the mean of the 3 closest of 5 consecutive measurements. Values are given as mean±SD. Statistical evaluations were performed using Pearson product moment correlation test and t test. Statistical significance was set at P<.05. Analysis of covariance (ANCOVA) was used to control for covariables.

**RESULTS**

Patient characteristics are given in Table 1. There were 16 patients with OAG and 16 patients with OHT. Patients were assigned to the thin group or to the thick group based on their median central corneal thickness (CCT). To keep the groups balanced with respect to diagnosis, the 8 patients with OAG with the thinnest corneas were grouped with the 8 patients with OHT with the thinnest corneas to form the thin group. Clinical variables other than CCT did not differ significantly between the thin (n=16) and thick (n=16) groups.

The optic nerve head stereometric variable of mean cup depth was reduced by a mean value of 36±32 µm in the thin CCT group and by 4±36 µm in the thick CCT group, a difference that was statistically significant (P=.003, ANCOVA controlling for percentage IOP reduction) (Table 2 and Figure 1). The maximum cup depth was reduced by 73±107 µm in the thin CCT group and by 4±89 µm in the thick CCT group, a difference that was statistically significant (P=.02, ANCOVA). The relationship between corneal thickness and shallowing of the cup was present in the OAG and OHT groups and was not significantly different between the groups (P=.29 and P=.18 for mean and maximum cup depths, respectively, ANCOVA) (Table 3).

### Table 1. Characteristics of Patients With Open-angle Glaucoma and Ocular Hypertension*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Thin CCT Group (n=16)</th>
<th>Thick CCT Group (n=16)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCT, µm</td>
<td>518 ± 32</td>
<td>587 ± 31</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>64.0 ± 12.8</td>
<td>62.2 ± 12.4</td>
<td>.69</td>
</tr>
<tr>
<td>Cup-disc ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically determined</td>
<td>0.58 ± 0.24</td>
<td>0.56 ± 0.26</td>
<td>.84</td>
</tr>
<tr>
<td>Vertical (HRT)</td>
<td>0.46 ± 0.19</td>
<td>0.40 ± 0.21</td>
<td>.41</td>
</tr>
<tr>
<td>Area (HRT), mm²</td>
<td>1.94 ± 0.38</td>
<td>2.11 ± 0.34</td>
<td>.20</td>
</tr>
<tr>
<td>Disc</td>
<td>1.02 ± 0.30</td>
<td>1.25 ± 0.41</td>
<td>.09</td>
</tr>
<tr>
<td>Rim</td>
<td>1.02 ± 0.30</td>
<td>1.25 ± 0.41</td>
<td>.09</td>
</tr>
<tr>
<td>Cup depth (HRT), mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.29 ± 0.12</td>
<td>0.28 ± 0.11</td>
<td>.64</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.69 ± 0.27</td>
<td>0.64 ± 0.19</td>
<td>.53</td>
</tr>
<tr>
<td>Refractive error, diopters</td>
<td>−0.2 ± 2.1</td>
<td>0.1 ± 3.5</td>
<td>.82</td>
</tr>
<tr>
<td>Mean defect of visual field, dB†</td>
<td>−3.2 ± 4.1</td>
<td>−4.1 ± 6.9</td>
<td>.68</td>
</tr>
<tr>
<td>Maximum IOP before reduction, mm Hg‡</td>
<td>29 ± 4</td>
<td>29 ± 5</td>
<td>.82</td>
</tr>
<tr>
<td>IOP before reduction, mm Hg§</td>
<td>24.6 ± 5.6</td>
<td>24.8 ± 4.8</td>
<td>.9</td>
</tr>
<tr>
<td>% IOP reduction§</td>
<td>38 ± 13</td>
<td>30 ± 12</td>
<td>.09</td>
</tr>
</tbody>
</table>

*Abbreviations: CCT, central corneal thickness; HRT, Heidelberg retina tomography; IOP, intraocular pressure.

†Data are given as mean ± SD unless otherwise indicated.

‡Maximum recorded untreated IOP for the eye.

§At the time of the second imaging session.

### Table 2. Change in Topography After Sustained Intraocular Pressure (IOP) Reduction Among Combined Patients With Open-angle Glaucoma and Ocular Hypertension*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Thin CCT Group (n=16)</th>
<th>Thick CCT Group (n=16)</th>
<th>Unit Difference</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cup Depth, µm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>−36 ± 32</td>
<td>−4 ± 36</td>
<td>−32</td>
<td>.003</td>
</tr>
<tr>
<td>Maximum</td>
<td>−73 ± 107</td>
<td>−4 ± 89</td>
<td>−69</td>
<td>.02</td>
</tr>
</tbody>
</table>

*Abbreviation: CCT, central corneal thickness.

†Analysis of covariance controlling for percentage IOP reduction.
We also looked for significant changes of cup depth in individual eyes. The standard deviation of cup depth for the 3 images performed at each of 2 sessions (before and after IOP reduction) was calculated. Then, the number of eyes in which the cup depth changed by more than 4 SDs for that eye was calculated. One eye for which we were unable to locate the original images was excluded from this analysis. For mean cup depth, 8 of 15 eyes showed significant shallowing in the thin CCT group, while 3 of 16 eyes showed significant shallowing in the thick CCT group, a difference that was significant by χ² analysis (P = .04). The same analysis for maximum cup depth yielded 4 of 15 eyes showing at least 4-SD shallowing in the thin CCT group compared with 1 of 16 eyes in the thick CCT group, a difference that was not significant (P = .1). We further confirmed the difference in topographical changes by performing the Mann-Whitney rank order test for changes of mean and maximum cup depth. This test confirmed that, compared with the thick CCT group, the thin CCT group had significantly greater reductions in mean cup depth (P = .02), while the greater reduction in maximum cup depth in the thin CCT group did not reach statistical significance (P = .13).

Table 3. Change in Topography After Sustained Intraocular Pressure Reduction Among Patients With Open-angle Glaucoma (OAG) vs Ocular Hypertension (OHT)*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Change in Mean Cup Depth, μm</th>
<th>Change in Maximum Cup Depth, μm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thin CCT Group</td>
<td>Thick CCT Group</td>
</tr>
<tr>
<td>OAG (n = 16)</td>
<td>−43 ± 29</td>
<td>−7 ± 41</td>
</tr>
<tr>
<td>OHT (n = 16)</td>
<td>−29 ± 34</td>
<td>−1 ± 33</td>
</tr>
<tr>
<td>Combined (n = 32)</td>
<td>−36 ± 32</td>
<td>−4 ± 36</td>
</tr>
</tbody>
</table>

Abbreviation: CCT, central corneal thickness.
*Data are given as mean ± SD.

Smaller improvements in neuroretinal rim blood flow were seen in patients with OAG and OHT with thinner corneas compared with those with thicker corneas. This difference was statistically significant in the patients with OAG and OHT and remained significant after controlling for percentage IOP reduction (P = .04, ANCOVA). This difference was significant in the OAG group but not in the OHT group (Table 4 and Figure 2). We also looked for significant changes of rim flow in individual eyes. The standard deviation of rim flow for the 5 images performed at each of 2 sessions was calculated. Then, the number of eyes in which the rim flow changed by more than 4 SDs for that eye was calculated. Seven of 16 eyes showed significant increases in rim flow in the thick CCT group, while 2 of 16 eyes showed such increases in the thin CCT group, a difference that was significant by χ² analysis at P = .05. Using a cutoff of 3 SDs gave a more significant χ² result of P = .01 (9 of 16 in the thick CCT group vs 2 of 16 in the thin CCT group).

The results of this preliminary study suggest that patients with OHT and OAG with thin central corneas have greater forward displacement of the base of the cup, a surrogate marker for lamina cribrosa position, following IOP reduction than their cohorts with thicker central corneas. Patients with thin central corneas also seem to have smaller improvements in neuroretinal rim blood flow after IOP reduction than patients with thicker central corneas.

A thin central cornea is emerging as a major risk factor for severity of OHT and OAG.23-27 Diurnal and long-term IOP fluctuations are also a major risk factor for progression in OAG.22-24 These results suggest that a thin central cornea may be a marker for physiological differences in the biomechanical properties of the lamina cribrosa. In other words, it may be that a thin central cornea is connected to a thin sclera, which, in turn, is connected to a thin lamina. Assuming identical material properties, a thin lamina should demonstrate greater compliance (less rigidity) than a thick lamina. A thin lamina should then manifest greater displacement in response to diurnal or therapeutic IOP fluctuations. Greater laminar displacement could lead to increased damage to adjacent axons by different mechanisms.37

Larger increases in rim blood flow after IOP reduction were observed in the thick CCT group. Because patients with thick central corneas may have a reduced risk of progressing or of reaching an advanced state of glaucoma,21-27 this finding suggests that improved blood flow in response to therapy may be a good prognostic sign in glaucoma. In patients with thin central corneas, it is conceivable that the vasculature has become more damaged due to repetitive movements of the more compliant lamina. In these patients, the vasculature may be less able to respond to IOP reduction with a beneficial increase in blood flow. Smaller increases in optic nerve head blood
Our findings also suggest a potential method for determining the risk level for an individual patient with glaucoma. Patients with high lamina cribrosa mobility or poor vascular response to IOP reduction may be at greater risk of progressive disease and may be targeted for more aggressive or alternate therapies. Although the results presented herein are preliminary and the mechanistic links are speculative, they serve as a conceptual framework for more detailed future studies.

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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Thin CCT Group, AU</th>
<th>Thick CCT Group, AU</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAG (n = 16)</td>
<td>46 ± 82</td>
<td>150 ± 106</td>
<td>.048</td>
</tr>
<tr>
<td>OHT (n = 16)</td>
<td>23 ± 63</td>
<td>71 ± 110</td>
<td>.34</td>
</tr>
<tr>
<td>Combined (n = 32)</td>
<td>35 ± 60</td>
<td>110 ± 111</td>
<td>.04</td>
</tr>
</tbody>
</table>

Table 4. Change in Neuroretinal Rim Blood Flow After Sustained Intraocular Pressure Reduction*

Abbreviations: AU, arbitrary units; CCT, central corneal thickness; OAG, open-angle glaucoma; OHT, ocular hypertension.

*Data are given as mean ± SD unless otherwise indicated.

Figure 2. Change in neuroretinal rim blood flow. AU indicates arbitrary units; OAG, open-angle glaucoma; and OHT, ocular hypertension.

flow may also be present on IOP reduction because the microvasculature passing through the lamina cribrosa may become compressed by the large forward displacement of the lamina sheets. Laminar sheet compression is common in glaucoma.16 These data suggest an interrelationship between the mechanical and vascular properties of the optic nerve head.

However, our data on neuroretinal rim blood flow may, in fact, be misleading. In the eyes with more compliant laminas, it is possible that laminar (as opposed to neuroretinal rim) blood flow after IOP reduction was greatly increased. This increase in laminar blood flow (not measured by our method) may have manifested as a less impressive increase in neuroretinal rim blood flow because of shunting. Future research should examine lamina cribrosa blood flow and neuroretinal rim blood flow.

A review of the literature suggests that, after an initial hypercompliant phase, the lamina cribrosa becomes more rigid in glaucoma.1-9,14,15,35,36 One interpretation of these findings is that increased laminar rigidity contributes to axonal loss. Another interpretation is that increased laminar rigidity follows axonal loss. Findings from the present study suggest that patients with thick central corneas have a more rigid lamina cribrosa. Because other studies25-27 have demonstrated a lower risk of progression in patients with thick central corneas, increased laminar rigidity may be a biological response that is protective to axons in this disease. Although the mechanisms of this protection remain unknown, the results of our study suggest that improved blood flow to the neuroretinal rim after IOP reduction may be involved in this protective effect.

REFERENCES


