Correlations between Parameters of Aqueous Humor Dynamics and the Influence of Central Corneal Thickness

Vikas Gulati, Deepta A. Ghate, Carl B. Camras, and Carol B. Toris

PURPOSE. The individual parameters of aqueous humor dynamics may influence each other to maintain intraocular pressure (IOP) homeostasis. Central corneal thickness (CCT) is known to be associated with onset and progression of glaucoma and can potentially influence the individual parameters of aqueous humor dynamics that maintain IOP. This study investigates the correlation between parameters of aqueous humor dynamics and the influence of CCT in healthy volunteers and compares it with the correlations seen in patients with ocular hypertension.

METHODS. Aqueous humor dynamics (aqueous flow, outflow facility, and uveoscleral outflow), IOP, and pachymetry data from 94 healthy ocular normotensive (ONT) volunteers and 65 ocular hypertensive (OHT) patients was analyzed retrospectively. Linear correlations between individual aqueous humor dynamics parameters and pachymetry were evaluated using scatter plots and the Spearman correlation coefficient where appropriate.

RESULTS. In both groups, a significant \( P < 0.05 \) negative correlation was found between corneal thickness and aqueous flow (ONT, \( R^2 = 0.14; \) OHT, \( R^2 = 0.10 \)) and between corneal thickness and uveoscleral outflow (ONT and OHT, \( R^2 = 0.10 \)). A significant \( P < 0.05 \) positive correlation was found between aqueous flow and outflow facility (ONT, \( R^2 = 0.24; \) OHT, \( R^2 = 0.10 \)). In healthy controls, but not OHT patients, a significant \( P < 0.001 \) positive correlation was found between aqueous flow and uveoscleral outflow (\( R^2 = 0.15 \)).

CONCLUSIONS. Thicker corneas may be associated with lower aqueous production and lower uveoscleral outflow. The interplay between parameters of aqueous humor dynamics suggests possible autoregulatory mechanisms in the eye. OHT may differ from ONT subjects in their inability to increase the uveoscleral outflow with increases in aqueous inflow. (Invest Ophthalmol Vis Sci. 2011;52:920 –926) DOI:10.1167/iovs.10-5494

Central corneal thickness (CCT) is an important clinical parameter in the management of glaucoma. A thinner CCT has been found to be associated with advanced glaucoma damage and glaucoma progression. Several hypotheses have been proposed to explain these associations. Some evidence suggests that the thickness of the cornea may cause errors in measurement of intraocular pressure (IOP) with currently available methods of tonometry, leading to misdiagnosis or missed diagnosis. Other evidence supports an association between a thinner cornea and a weaker lamina cribrosa, suggesting abnormal structural changes throughout the outer tunic of the eye. Similarly, cornea thickness could be a marker of abnormal changes in aqueous humor dynamics. Given the similar embryological origin and anatomic proximity of the cornea and aqueous humor pathways, such an association is plausible.

The parameters of aqueous humor dynamics may influence each other to maintain the IOP within a small range of normal. A breakdown of the homeostatic mechanisms may play a role in the pathogenesis of glaucoma. Previous studies have identified mechanical and neurohumoral pathways that could possibly mediate such an interaction between the parameters of aqueous humor dynamics. To the best of our knowledge the interplay of parameters of aqueous humor dynamics has not been reported previously. This study evaluates the effects of parameters of aqueous humor dynamics on each other and compares such interactions between ocular normotensive volunteers (ONT) and ocular hypertensive patients (OHT). We also offer a possible hypothesis whereby a breakdown or inadequacy of such autoregulatory mechanisms could lead to development of elevated IOP.

METHODS

This study is a retrospective analysis of OHT and ONT participants that enrolled in fluorophotometry studies at the University of Nebraska Medical Center between 1993 and 2007. All studies were approved by the university’s Internal Review Board, and informed consent was obtained from each participant before enrollment. The research adhered to the tenets of the Declaration of Helsinki. Participants with ocular hypertension were defined as individuals with two or more documented measurements of IOP of \( >21 \) mm Hg separated in time by more than 1 month without any evidence of optic nerve or visual field damage. ONT volunteers were defined as individuals with no known history of ocular hypertension or glaucoma and IOPs of less than or equal to \( 21 \) mm Hg at the screening visit. They also were required to have normal-appearing optic nerves and anterior chamber angles. All patients underwent a screening visit comprising a detailed clinical history and slit lamp examination including tonometry, pachymetry, and gonioscopy. A dilated fundus examination was obtained within 6 months of the start of the study. OHT volunteers currently on medications underwent a washout period of 6 weeks before the screening visit. Enrolled study participants self-instilled six drops of 2% fluorescein solution (Alcon Laboratories, Ft. Worth, TX), into both eyes at 5-minute intervals starting at 6 to 10 hours before the scheduled fluorophotometric scans. Between 8:30 and 9:30 AM the following day, IOPs were measured by pneumotonometry (Classic 30; Reichert Ophthalmic Instruments, Depew, NY). Anterior chamber (AC) depth was mea-

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sured using an A-scan (PacScan 300AP Digital Biometric Ruler; SonoMed, Lake Success, NY) or a slit lamp–mounted pachymeter (Haag Streit, Mason, OH). The anterior chamber volume was calculated from the AC depth measurement.\textsuperscript{18} CWT was measured using ultrasonic pachymetry (PacScan 300AP Digital Biometric Ruler). Episcleral venous pressure was measured by venomanometry (Eyetech Ltd, Morton Grove, IL), and the reported value was the mean of two to three consecutive, consistent measurements.

Fluorophotometry was performed using a scanning ocular fluorophotometer (FM-2 Fluorotron Master Ocular Fluorophotometer; OcuMetrics, Mountain View, CA) as described previously.\textsuperscript{19,20} In summary, fluorophotometry measures the rate of disappearance of fluorescein from the AC to calculate the rate of aqueous production. The protocol assumes negligible loss of fluorescein to other pathways such as diffusion through the iris and vitreous. Aqueous suppressants (topical beta blockers, carbonic anhydrase inhibitors, or both) are administered to lower the IOP, and the new lower IOP and aqueous flow are measured. These measurements are used to calculate outflow facility as the ratio of change in aqueous flow to change in IOP. Uveoscleral outflow is mathematically calculated as the difference between aqueous flow and trabecular outflow.\textsuperscript{21,22} At the end of the fluorophotometric measurements some patients also underwent tonography using the tonography module of the pneumotonometer. These data were not available for all participants.

Statistical Analyses
Normality of the distribution of data was tested by examining the histograms and performing a Shapiro-Wilk test. A Shapiro-Wilk W of $>0.05$ was evidence of a normal distribution. Pearson’s linear correlation coefficient was calculated for normally distributed data in which the study population was 55.3 ± 16.1 years.

The baseline characteristics of the two study groups are summarized in Table 1. By design, the mean IOP in the OHT group was significantly higher than that in the ONT group (22.5 ± 4.8 mm Hg vs. 15.0 ± 2.4 mm Hg). There was no significant difference in the aqueous flow between the two groups (2.63 ± 0.83 μL/min in ONT vs. 2.46 ± 0.64 μL/min in OHT). Compared to the ONT group, the OHT group had significantly lower values of fluorophotometric outflow facility (0.18 ± 0.11 μL/min/mm Hg vs. 0.28 ± 0.16 μL/min/mm Hg) and uveoscleral outflow (0.31 ± 1.17 μL/min vs. 1.07 ± 0.86 μL/min).

Correlations between individual baseline characteristics and parameters of aqueous humor dynamics were studied using a nonparametric Spearman correlation coefficient ($r_s$) because the data were not distributed normally (Shapiro-Wilk W $<0.05$) for most study parameters, with the exception of patient age and AC volume (Shapiro-Wilk W $>0.05$). A correlation matrix listing the Spearman correlation coefficient and the respective P value of the correlation studied is tabulated in Table 2. A significant negative correlation was found between age and AC volume, aqueous flow, uveoscleral outflow, and tonographic outflow facility, but not between age and fluorophotometric outflow facility. The correlation between CCT and IOP was not statistically significant.

A statistically significant negative linear correlation was found between CCT and aqueous flow in the study population as a whole ($r_s = -0.30, R^2 = 0.09, P < 0.001$), in the ONT group ($r_s = -0.38, R^2 = 0.14, P < 0.001$), and in the OHT group after the exclusion of four outliers ($r_s = -0.32, R^2 = 0.10, P = 0.014$; Fig. 1).

There was no linear correlation between CCT and outflow facility in either study group (Fig. 2). There was a statistically significant negative correlation between CCT and uveoscleral outflow in the study population as a whole ($r_s = -0.30, R^2 = 0.09, P < 0.001$) and in the OHT group ($r_s = -0.31, R^2 = 0.10, P = 0.012$) and ONT ($r_s = -0.31, R^2 = 0.10, P = 0.003$) groups (Fig. 3).

Analysis of correlations between indices of aqueous humor dynamics showed a statistically significant positive correlation between aqueous flow and outflow facility in the study population as a whole ($r_s = 0.49, R^2 = 0.24, P < 0.001$) and in the OHT group ($r_s = 0.32, R^2 = 0.10, P = 0.012$) groups (Fig. 4).

There was a significant positive correlation between aqueous flow and uveoscleral outflow in the study population as a whole ($r_s = 0.23, R^2 = 0.05, P = 0.005$) and in the ONT group ($r_s = 0.39, R^2 = 0.15, P < 0.001$) but not in the OHT group ($r_s = -0.03, R^2 = 0.00, P = 0.804$; Fig. 5). Because these two parameters were correlated with CCT, it was possible that the correlation between the aqueous flow and uveoscleral outflow may have been a consequence of their individual correlation with CCT. Hence the independent correlation between the two parameters was analyzed using partial correlations. After controlling for CCT, the aqueous flow-uveoscleral outflow correlation remained significant in the ONT group ($r_s = 0.29, R^2 = 0.08, P = 0.005$) and

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All ($n = 157$)</th>
<th>ONT ($n = 94$)</th>
<th>OHT ($n = 63$)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.3 ± 16.1</td>
<td>52.8 ± 17.0</td>
<td>58.1 ± 14.4</td>
<td>0.10</td>
</tr>
<tr>
<td>CCT, μm</td>
<td>542 ± 41</td>
<td>540 ± 45</td>
<td>545 ± 37</td>
<td>0.39</td>
</tr>
<tr>
<td>AC volume, μL</td>
<td>198 ± 53</td>
<td>202 ± 54</td>
<td>194 ± 52</td>
<td>0.60</td>
</tr>
<tr>
<td>$P_{cv}$, mm Hg</td>
<td>9.4 ± 1.6</td>
<td>9.2 ± 1.6</td>
<td>9.8 ± 1.7</td>
<td>0.08</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>180 ± 5.1</td>
<td>150 ± 2.4</td>
<td>225 ± 4.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aqueous flow, μL/min</td>
<td>2.51 ± 0.76</td>
<td>2.63 ± 0.83</td>
<td>2.46 ± 0.64</td>
<td>0.55</td>
</tr>
<tr>
<td>Outflow facility, μL/min/mm Hg</td>
<td>0.28 ± 0.15</td>
<td>0.28 ± 0.16</td>
<td>0.18 ± 0.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Uveoscleral outflow, μL/min</td>
<td>0.81 ± 1.08</td>
<td>1.07 ± 0.86</td>
<td>0.31 ± 1.17</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data in columns 2–4 are mean ± SD. Significant correlations ($P < 0.01$) are in boldface. AC, anterior chamber; CCT, central corneal thickness; $P_{cv}$, episcleral venous pressure.

* Calculated using the Mann-Whitney U test.
DISCUSSION

Even though CCT has been found to be associated with development and progression of glaucoma, a physiological basis of such an association is currently unknown. Several hypotheses have been proposed to explain the association, including errors in the IOP measurement due to normal variations in CCT or abnormal changes in the lamina cribrosa associated with similar changes in CCT. The present study examines an alternate hypothesis involving correlations between CCT and aqueous humor dynamics. This study was conducted to evaluate the

### Table 2. Matrix of Correlations between Baseline Demographic and Aqueous Humor Dynamics Parameters in the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Age (y)</th>
<th>CCT (µm)</th>
<th>AC Volume (µL)</th>
<th>P&lt;sub&gt;ev&lt;/sub&gt; (mm Hg)</th>
<th>IOP (mm Hg)</th>
<th>C&lt;sub&gt;ton&lt;/sub&gt; (µL/min/mm Hg)</th>
<th>Fa (µL/min)</th>
<th>C&lt;sub&gt;f&lt;/sub&gt; (µL/min/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCT, µm</td>
<td>r&lt;sub&gt;S&lt;/sub&gt; = 0.00</td>
<td>P = 0.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>AC volume, µL</td>
<td>r&lt;sub&gt;S&lt;/sub&gt; = -0.540</td>
<td>P = 0.039</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>P&lt;sub&gt;ev&lt;/sub&gt;, mm Hg</td>
<td>r&lt;sub&gt;S&lt;/sub&gt; = -0.159</td>
<td>P = 0.054</td>
<td>0.146</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>r&lt;sub&gt;S&lt;/sub&gt; = 0.028</td>
<td>P = 0.737</td>
<td>0.942</td>
<td>0.060</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;ton&lt;/sub&gt;, µL/min/mm Hg</td>
<td>r&lt;sub&gt;S&lt;/sub&gt; = -0.260</td>
<td>P = 0.031</td>
<td>0.212</td>
<td>0.142</td>
<td>-0.205</td>
<td>-0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fa, µL/min</td>
<td>r&lt;sub&gt;S&lt;/sub&gt; = -0.235</td>
<td>P = 0.004</td>
<td>0.218</td>
<td>0.080</td>
<td>0.082</td>
<td>-0.023</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;f&lt;/sub&gt;, µL/min/mm Hg</td>
<td>r&lt;sub&gt;S&lt;/sub&gt; = 0.016</td>
<td>P = 0.853</td>
<td>0.113</td>
<td>-0.091</td>
<td>-0.392</td>
<td>0.128</td>
<td>0.457</td>
<td></td>
</tr>
<tr>
<td>Fu, µL/min</td>
<td>r&lt;sub&gt;S&lt;/sub&gt; = -0.195</td>
<td>P = 0.019</td>
<td>0.125</td>
<td>0.317</td>
<td>-0.336</td>
<td>-0.101</td>
<td>0.228</td>
<td>-0.242</td>
</tr>
</tbody>
</table>

Significant correlations (P < 0.01) are in boldface. AC, anterior chamber; CCT, central corneal thickness; C<sub>ton</sub>, fluorophotometric outflow facility; C<sub>f</sub>, tonographic outflow facility; Fa, aqueous flow; Fu, uveoscleral outflow; P<sub>ev</sub>, episcleral venous pressure; P, P value; r<sub>S</sub>, Spearman correlation coefficient.

nonsignificant in the OHT group (r<sub>S</sub> = -0.12, R<sup>2</sup> = 0.01, P = 0.351).

### Figure 1. Scatter plot of CCT and aqueous flow in ONT and OHT participants. The linear correlation was statistically significant in both the ONT (r<sub>S</sub> = -0.38, R<sup>2</sup> = 0.14, P < 0.001) and OHT groups (r<sub>S</sub> = -0.32, R<sup>2</sup> = 0.10, P = 0.014). The regression equation for the ONT group was y = -0.0098x + 7.3195 and for the OHT group was y = -0.0065x + 5.9601. Values in the OHT group were obtained after the exclusion of four outliers.
possibility of thinner corneas being associated with compromised aqueous humor outflow pathways in the eye.

The negative correlation between age and anterior chamber volume in our study is to be expected because of an increasing lens size with increasing age.23 An additional explanation is that the negative correlation may be a manifestation of the decrease in aqueous production with increasing age. The positive correlation between aqueous flow and AC volume21,24,25 and the negative correlation between age and aqueous flow have been reported previously.21,24–27 The age-related decrease in uveoscleral outflow seen in our study agrees with previous studies in monkeys28 and humans.27

An interesting finding in our study is the significant negative correlation between CCT and aqueous flow. A lower baseline rate of aqueous production, as seen in patients with thicker
corneas, could potentially offer protection against sustained elevation of IOP and increased risk of glaucoma. Even though most studies point toward outflow rather than inflow changes as the primary cause of the IOP elevation, some consideration should be made of potential inflow changes, because a lower baseline rate of aqueous production could at least partially offset the effects of compromised outflow on IOP. An individual with lower baseline aqueous inflow will require greater compromise of outflow to manifest elevated IOP. Taking the possible diurnal fluctuations into consideration (e.g., morning surge after overnight suppression or effect of fluid overload), a lower baseline aqueous production will allow for greater “physiological” changes in aqueous flow without significant elevations of IOP. This offers a possible hypothesis to explain the findings of the Ocular Hypertension Treatment Study (OHTS),1 where a thinner central cornea was found to be...
associated with the development of POAG in both univariate and multivariate models. In the OHTS study, compared with the participants with the thickest corneas (>588 μm), participants with the thinnest central corneal measurements (≤555 μm) were 3.4 times more likely to progress to glaucoma.

Our study also found a negative correlation between CCT and uveoscleral outflow. The clinical significance of this association is not known. It can be speculated that reduced uveoscleral outflow could potentially affect the CCT through elevated IOP and its effect on corneal endothelial pump function. Alternatively eyes with thicker corneas and lower aqueous flow values simply may have a lower proportion of aqueous humor leaving the eye through the pressure-independent uveoscleral pathways. However, the correlation between CCT and uveoscleral outflow was found to be statistically significant even after controlling for aqueous flow. An alternative hypothetical explanation may be a putative common mediator, possibly involved with interstitial tissue metabolism, generating a thicker cornea and, at the same time, denser tissues in the ciliary body compromising function in the uveoscleral outflow pathways.

It has been reported that a better IOP response to medications is found in patients with thinner compared to thicker corneas. This could be due to better penetration of medications through thinner corneas and better delivery of drugs to the target tissues. The association between thinner corneas and higher aqueous flow and uveoscleral outflow seen in this study can provide a possible alternate explanation for why thinner corneas may have better IOP response to medications that affect the aqueous flow or uveoscleral outflow. Eyes with thinner corneas and associated higher aqueous flow and uveoscleral flow may be more amenable to pharmacologic manipulation than eyes with thicker corneas. The greater the aqueous flow rate, the greater the potential reduction by a drug. This rationale is similar to the higher IOP decrease seen in eyes with higher baseline IOPs.

Significant positive correlation between aqueous flow and outflow facility may suggest autoregulatory mechanisms operating in the eye. A high aqueous flow rate will need to have a high outflow facility, uveoscleral outflow, or both to maintain the IOP in the normal range. A neuroendocrine role for the ciliary body, targeting the ciliary body and conventional aqueous humor outflow pathways, and mechanical outflow effects of changes in AC volume have been previously reported. The biological basis for communication between the inflow and outflow mechanism may lie in a better elucidation of these communication channels.

The ONT volunteers showed a positive correlation between aqueous flow and uveoscleral outflow, a relationship that was not seen in the patients with ocular hypertension. This could indicate a possible pathophysiologic difference between ONT and OHT whereby an unavailability of additional pressure-independent outflow in subjects with higher aqueous flow may lead to the development of elevated IOP. This is at best a hypothesis that requires further validation by additional studies.

The present study has several limitations to consider while interpreting the results. The study has a retrospective design; however, the typical limitations of a retrospective study such as lack of control or placebo are not relevant to the design of this study. Also the division between the two study groups is more arbitrary than clinical, based on an IOP level rather than degree of glaucomatous damage. The two groups in our study consist of individuals falling into two different ranges of IOP rather than two clinical diagnoses. However, this is no different from such a distinction made in any clinical practice to diagnose ocular hypertension. The possibility of lower aqueous flow being an artifact of measurement with thicker corneas cannot be absolutely ruled out. The current methods take CCT into account in the equations used to calculate aqueous flow. Even though the correlations were statistically significant, the magnitude of correlations was small. The $R^2$ value for significant correlations in this study ranged from 0.076 to 0.240. This means that the variation in independent parameters explained only 8% to 24% of the variation in the dependent parameter. Also the correlations in the study are only a demonstration of association and by no means proof of causation.

The correlation between CCT and aqueous flow was significant only after the removal of outliers. As can be seen from the scatter plot in Figure 1, the data points from both the ONT and the OHT group were very similarly distributed. Hence the lack of statistical significance in the OHT group was likely due to the effect of the outliers. The study evaluates multiple correlations, an approach that raises the likelihood of "false positive" statistically significant correlations. Bonferroni or a similar correction was not used to adjust for the multiple comparisons because most of the correlations found in the study had a $P$ value <0.001, and these findings would remain statistically significant after a correction. The clustering of correlations in a particular analysis can be taken as proof of a real correlation rather than a false positive. For example, the correlation between CCT and uveoscleral outflow was statistically significant in the group as a whole and in the ONT subgroup. It also was significant in the OHT subgroup but would become nonsignificant after applying a correction. Given the behavior of the parent data set, the correlation is likely to be a real correlation rather than a false positive. In this case scenario the lack of correlation seen in the OHT group, after applying the Bonferroni correction, will be an artifact of correction rather than a true absence of a significant correlation.

Despite the above limitations, the study demonstrates a statistically significant association between CCT and aqueous flow and uveoscleral outflow. The clinical significance of this association remains to be determined. A summary of the significant correlations found in the study is shown as a schematic in Figure 6. The study provides support for possible autoregulatory mechanisms facilitated by the ciliary body, whereby an eye may be capable of increasing the outflow facility in response to the demands of increasing aqueous flow. The study also offers a novel pathophysiologic mechanism that may contribute to the development of ocular hypertension, which may possibly lie in a faulty autoregulation of uveoscleral outflow leading to elevated IOP.

![Figure 6](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932965/)
References