Aqueous Humor Dynamics in Pigment Dispersion Syndrome

Carol B. Toris, PhD; Nathan R. Haecker, BS; Laura A. Teasley, MD; Guilin Zhan, MD; Vikas Gulati, MD; Carl B. Camras, MD

Objective: To assess aqueous humor dynamics in pigment dispersion syndrome (PDS).

Methods: Four groups of age-matched participants included 2 experimental groups with PDS (PDS with ocular hypertension [PDS-OHT], 17 eyes; PDS without ocular hypertension [PDS-ONT], 18 eyes) and 2 control groups without PDS (OHT, 18 eyes; ONT, 18 eyes). Assessments included intraocular pressure measured by pneumatonometry, episcleral venous pressure by venomanometry, aqueous flow and outflow facility by fluorophotometry, corneal thickness and anterior chamber depth by pachymetry, and uveoscleral outflow by mathematical calculation. Comparisons were made by analysis of variance and 2-tailed unpaired t tests.

Results: The PDS-OHT group had higher intraocular pressures than the ONT and PDS-ONT groups (P < .001) and higher episcleral venous pressure (P = .04) and lower outflow facility (P = .01) than the ONT group. Anterior chamber volume was larger in the PDS-OHT group than in the other groups (P < .05 for all). No other comparisons between the PDS-OHT group and the other groups yielded statistically significant differences at a significance level of less than .05.

Conclusions: The elevated intraocular pressure in PDS is caused by reduced outflow facility. This differs from OHT without PDS, in which reductions in uveoscleral outflow and outflow facility have been reported.

Arch Ophthalmol. 2010;128(9):1115-1118

Pigment dispersion syndrome (PDS) is a condition that occurs when the midperipheral iris contacts the lens zonules, causing pigment release from the iris pigmented neuroepithelium, which can lead to midperipheral iridial transillumination defects characteristic of the syndrome. These released pigment granules move into the anterior chamber via the convective flow of aqueous humor and eventually undergo phagocytosis and become trapped within the trabecular meshwork. Although initially thought to be uncommon, the prevalence of PDS may be higher than previously inferred. The prevalence has been reported to be as high as 2.5% in a population undergoing glaucoma screening. More important, conversion from PDS to pigmentary glaucoma occurs in as many as 10% of patients at 5 years and 15% at 15 years. Pigmentary glaucoma is found in a subset of patients who have the predisposing condition of PDS.

Based on a previous study, the elevated intraocular pressure (IOP) in patients with PDS was likely the result of outflow compromise because the aqueous flow remained normal. Uveoscleral outflow was not measured, but outflow facility was reduced in that study. Patients with ocular hypertension (OHT) and primary open-angle glaucoma also have a reduction in outflow facility. Unlike OHT and primary open-angle glaucoma, the outflow facility changes in PDS involve excessive pigment trapped in the trabecular meshwork. In early attempts to duplicate the pathophysiologic mechanisms of PDS and pigmentary glaucoma, pigment particles from the iris and ciliary body of donor monkey eyes were injected into the anterior chamber of healthy eyes of live monkeys. This produced a short-term elevation in IOP and outflow facility, but within a week, trabecular endothelial cells and macrophages cleared the debris from the trabecular meshwork, and outflow facility returned to normal. In another study, uveal pigment injected into the anterior chamber of enucleated human eyes was found trapped in the trabecular meshwork, and outflow facility was reduced after the injection. The number of melanin granules found in the anterior chamber was strongly associated with excessive IOP and visual field loss in patients with PDS. Examination of 1 pair of postmortem eyes with PDS by light and electron microscopy found pigment and cellular debris trapped in the trabecular spaces.
and the trabecular sheets collapsed. Studies by other authors also have shown that long-term pigment accumulation leads to trabecular cell damage, collapsed trabecular beams, and increased extracellular material, possibly leading to reduced outflow facility. These clinical findings and morphological changes support a transient or permanent reduction in outflow facility in PDS as being responsible for increased IOP in pigmentary glaucoma. Nothing is known about the effect of PDS on the uveoscleral outflow pathway.

Patients with OHT without PDS have a reduction in uveoscleral outflow. This question whether the uveoscleral outflow pathway in PDS and ocular hypertension is similarly compromised. To address this question, the current study investigates aqueous humor dynamics in patients with PDS with or without elevated IOP and compares them with the dynamics in ocular normotensive (ONT) volunteers and patients with OHT.

**STUDY METHODS**

Enrolled in this study were patients with PDS who had IOPs of greater than 20 mm Hg at screening (PDS-OHT group, 17 eyes), PDS and no previous record of IOPs greater than 20 mm Hg (PDS-ONT group, 18 eyes), age-matched healthy volunteers with no ocular abnormalities and no record of IOP of greater than 20 mm Hg (ONT group, 18 eyes), and age-matched healthy volunteers with no ocular abnormalities and with at least 2 previous records of IOP of greater than 20 mm Hg on 2 separate visits (OHT group, 18 eyes). On the screening day, participants underwent an eye examination by an experienced glaucoma specialist (C.B.C.). Visual acuity was measured in both eyes. Intraocular pressures were measured with the use of a pneumotonometer (Model 30 Classic; Reichert Ophthalmic Instruments, Depew, New York). A slitlamp examination of the anterior segment was performed, and the presence or absence of PDS was determined. Gonioscopy was performed, and the average of the superior, inferior, nasal, and temporal chamber angles was determined, with 0 being closed and 4 being wide open. Finally, the eyes were dilated and a fundus examination was performed. Excluded from all groups were patients with visual field defects, glaucoma, ocular infection, and a history of inflammation, previous intraocular surgery, cataract, ocular trauma, ocular abnormality precluding fluorophotometric measurements, or unstable cardiovascular or pulmonary disease. Study participants in the PDS-OHT and OHT groups who had been taking medication to treat the elevated IOP discontinuumed treatment for 3 to 6 weeks before the study. The washout period depended on the prescribed ocular medication. The washout was necessary to eliminate any confounding effect of the ocular medication on IOP and aqueous humor dynamics. All participants provided informed consent following federal guidelines, and the study was approved by the University of Nebraska Medical Center institutional review board.

**MEASUREMENTS**

From 4 to 12 hours before the study visit, participants self-instilled 6 to 8 drops of fluorescein into each eye before going to sleep. The number of drops applied and the time dosing began depended on the participant’s age. Measurements commenced in the clinic the following morning. With the use of a slitlamp biomicroscope equipped with an optical pachymeter (Haag-Streit USA, Mason, Ohio), anterior chamber depth was measured using attachment II, and central corneal thickness (CCT) was measured using attachment I. Anterior chamber volume was calculated for each eye according to steps from an earlier publication. Aqueous flow (F_a) was determined between 8:30 and 10:30 AM by a fluorophotometric technique using a scanning ocular fluorophotometer (Fluorotron Master; OcuMetrics, Mountain View, California). The slopes of the disappearance rates of fluorescein from the cornea and anterior chamber and the anterior chamber volume were used in the calculation of aqueous flow.

Episcleral venous pressures (P_ev) were measured at approximately 10 AM with a commercially available episcleral venometer (Eyetech Ltd, Morton Grove, Illinois) that has been tested and validated previously. Two or 3 readings were taken in each eye and averaged. Episcleral venous pressure was assumed to remain constant throughout the study day.

Intraocular pressure was measured with the pneumotonometer at approximately 8 AM and 10:30 AM. Subsequently, 1 drop of timolol maleate, 0.5%, was instilled into each eye in participants without contraindications. If timolol treatment was contraindicated, 250 mg of acetazolamide sodium was given orally instead. Patients with contraindications to both timolol and acetazolamide were not enrolled in the study. These 2 drugs reduce IOP by suppressing the rate of aqueous humor flow. Aqueous flow and IOP measurements continued after timolol or acetazolamide administration, and the postdosing IOP and aqueous flow changes were determined. Outflow facility (C_fl) was calculated as the ratio of the change in aqueous flow to the change in IOP. Details of this method are provided elsewhere. The average of 3 outflow facility values for each eye was used to calculate the pressure-independent uveoscleral outflow (F_u), according to the modified Goldmann equation:

\[ F_u = F_a - C_fl \times (IOP - P_ev) \]

When both eyes of each participant met enrollment criteria, data from the eye with the higher pressure were used in the analysis.

The Kruskal-Wallis test, Mann-Whitney tests adjusted for multiple comparisons with the Bonferroni method, and 2-tailed unpaired t tests were used to compare the groups. Values are reported as mean (SD). P ≤ .05 was considered statistically significant.

**RESULTS**

Seventeen eyes were included in the PDS-OHT group and 18 eyes in the other 3 groups. Three volunteers with PDS had one eye assigned to the PDS-ONT group and the other eye to the PDS-OHT group. The mean age in the individual groups ranged from 40.9 to 44.8 years, with no significant difference among the groups. The baseline IOPs in the PDS-OHT (23.7 [3.4] mm Hg) and OHT (22.2 [3.7] mm Hg) groups were significantly higher than in the ONT (15.4 [2.1] mm Hg) and PDS-ONT (17.1 [2.3] mm Hg) groups. The outflow facility in the ONT group (0.30 [0.20] µL/min/mm Hg) was significantly (P = 01) higher than in the OHT and PDS-OHT groups (0.15 [0.11] and 0.17 [0.11] µL/min/mm Hg, respectively). The mean outflow facility in the PDS-ONT group (0.22 [0.12] µL/min/mm Hg) fell between the corresponding values in the PDS-OHT and ONT groups but was not significantly different from either group. The PDS-OHT group had a significantly larger mean anterior chamber volume (235 [46] µL) than the OHT group (212 [48] µL). When both PDS groups were pooled and compared with the pooled non-
PDS groups, the uveoscleral outflow was significantly higher in PDS (1.42 [1.01] vs 0.90 [0.90] µL/min; P = .03). The results are summarized in the Table.

### Table. PDS and Aqueous Humor Dynamics

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>PDS-OHT (n=17)</th>
<th>PDS-ONT (n=18)</th>
<th>OHT (n=18)</th>
<th>ONT (n=18)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>40.9 (10.3)</td>
<td>44.8 (7.9)</td>
<td>42.4 (9.4)</td>
<td>41.1 (9.9)</td>
<td>.58</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>23.7 (3.4)</td>
<td>17.1 (2.3)</td>
<td>22.2 (3.7)</td>
<td>15.4 (2.1)</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Pev, mm Hg</td>
<td>10.4 (2.4)</td>
<td>9.4 (1.7)</td>
<td>10.0 (1.4)</td>
<td>8.7 (1.3)</td>
<td>.04</td>
</tr>
<tr>
<td>Fa, µL/min</td>
<td>3.16 (0.86)</td>
<td>3.29 (1.12)</td>
<td>2.55 (1.08)</td>
<td>3.02 (1.35)</td>
<td>.23</td>
</tr>
<tr>
<td>Fu, µL/min/mm²</td>
<td>0.17 (0.11)</td>
<td>0.22 (0.12)</td>
<td>0.15 (0.11)</td>
<td>0.30 (0.20)</td>
<td>.01</td>
</tr>
<tr>
<td>Pev, mm Hg</td>
<td>1.18 (1.18)</td>
<td>1.64 (0.79)</td>
<td>0.74 (0.93)</td>
<td>1.07 (0.85)</td>
<td>.05</td>
</tr>
<tr>
<td>ACvol, µL</td>
<td>257 (46)</td>
<td>220 (50)</td>
<td>212 (48)</td>
<td>217 (47)</td>
<td>.03</td>
</tr>
<tr>
<td>CCT, µm</td>
<td>550 (35)</td>
<td>530 (38)</td>
<td>540 (34)</td>
<td>543 (48)</td>
<td>.53</td>
</tr>
<tr>
<td>Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Abbreviations: ACvol, anterior chamber volume; CCT, central corneal thickness; Cfl, outflow facility; Fa, aqueous flow; Fu, uveoscleral outflow; IOP, intraocular pressure; OHT, ocular hypertension; ONT, ocular normotension; PDS, pigment dispersion syndrome; Pev, episcleral venous pressure.  
*Groups are described and measurements are calculated as described in the “Study Population” subsection of the “Methods” section. For each participant, the eye with the highest IOP that met all study criteria was included in the analysis. Unless otherwise indicated, data are expressed as mean (SD).  
* Determined by analysis of variance.  
† Indicates average of pressures measured at 8:00 and 10:30 AM.  
‡ Indicates significant difference between the PDS-OHT and OHT groups.  
§ Indicates significant difference between the PDS-OHT and PDS-ONT groups.  
‖ Indicates significant difference between the OHT and ONT groups.  
§§ Indicates significant difference between the PDS-ONT and ONT groups.  
‖‖ Indicates significant difference between the PDS-OHT and OHT groups.  
‖‖‖ Indicates significant difference between the PDS-ONT and OHT groups.  
‖‖‖‖ Indicates significant difference between the PDS-OHT and ONT groups.  
‖‖‖‖‖ Indicates significant difference between the PDS-ONT and OHT groups.

As with a previous study, we found that the main factor accounting for the increased IOP in PDS is the increased resistance to flow through the trabecular meshwork (decreased outflow facility). Similar effects on outflow facility have been reported for other diseases associated with elevated IOP, including primary open-angle glaucoma, OHT, exfoliation syndrome without or with glaucoma. Our patients with PDS and normal IOP (≤20 mm Hg) had outflow facility values that were not significantly different from those of healthy age-matched controls, although the mean value fell between the values for the healthy control group and the PDS-OHT group. This suggests that changes in the trabecular meshwork may be occurring in PDS-ONT, accounting for the slight, although not statistically significant, increase in IOP compared with healthy controls.

In PDS and pigmentary glaucoma, it has been hypothesized that pigment is sloughed from the posterior iris surface by lens zonules that rub against the iridial tissue. Structural abnormalities of the middle third of the eye have been noted in PDS. The size of the iris appears to be overly large relative to that of the anterior segment. The iris–trabecular meshwork distance is greater in PDS, and the iris insertion is more posterior. These structural features account for the deep anterior chambers measured peripherally and centrally. The sloughed pigment is flushed from the posterior chamber through the pupil and into the anterior chamber, where it becomes trapped in the trabecular meshwork, resulting in increased outflow resistance. For the fluid to continue to drain from the eye, the IOP must increase to a new steady-state level. This hypothesis is attractive in that it takes into account the large anterior chamber depth and provides a plausible explanation for the increased IOP and reduced outflow facility in PDS.

Pigment and morphological changes to eyes with pigmentary glaucoma and PDS may not be limited to the trabecular meshwork. If pigment and debris are flushed into the chamber angle and trabecular meshwork, then they also might be distributed into the ciliary muscle interstitial spaces and may affect uveoscleral drainage of aqueous humor. In the present study, there was no significant difference in uveoscleral outflow in the PDS groups with or without elevated IOP and their respective age-matched control groups. However, when both PDS groups were combined, a significantly higher uveoscleral outflow was noted compared with the combined non-PDS groups. This is in contrast to exfoliation syndrome, in which uveoscleral outflow was significantly lower than normal.

Our data did show a higher mean uveoscleral outflow in PDS with normal IOP compared with age-matched controls and patients with PDS and elevated IOP, even though the difference did not reach statistical significance (P = .05), likely because of the small sample size of the study groups. This could indicate that the patients with PDS and higher available uveoscleral outflow rates can maintain lower IOPs compared with those with lower uveoscleral outflow rates. Also, a higher uveoscleral outflow in the PDS groups could be a consequence of a low-grade inflammatory response to the released pigment. This statement is supported by a study in monkeys with experimentally induced ocular inflammation that had higher uveoscleral outflow rates than healthy monkeys.

The average CCT was not statistically different among groups in this study, although the PDS-OHT group had slightly thicker corneas than the 2 ONT groups. Correc-
tions in CCT were considered but were not applied to the study data for several reasons. First, the CCTs were near the population means, and mean differences between groups were not statistically significant. Second, a universally acceptable and well-proved CCT correction formula is not yet available. Third, correction formulas apply to applanation tonometry and not to pneumatonometry. It is unlikely that CCT contributed to the results of this study.

In summary, the elevated IOP in patients with PDS is caused by a reduction in outflow facility. Aqueous flow remains normal. Uveoscleral outflow was unchanged in PDS and OHT compared with healthy controls but was higher than in OHT without PDS. Increased uveoscleral outflow may be a plausible explanation for the normal IOP in these cases despite the pigment dispersion process compromising the outflow facility. Outflow facility in patients with PDS and normal IOP fell between values for healthy controls and for patients with PDS and elevated IOP.

Submitted for Publication: November 5, 2009; final revision received February 3, 2010; accepted February 18, 2010.

Correspondence: Carol B. Toris, PhD, Department of Ophthalmology and Visual Sciences, Mail Code 985840, University of Nebraska Medical Center, Omaha, NE 68198-5840 (ctoris@unmc.edu).

Author Contributions: Dr Toris had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

Funding/Support: This study was supported by an unrestricted grant and by a Senior Scientific Investigator award (Dr Camras) from Research to Prevent Blindness, Inc.

Additional Contributions: Jane Meza, PhD, assisted with the statistical analyses.

REFERENCES