**Précis:** In this prospective study, naive prostaglandin use in primary open-angle glaucoma was associated with scleral biomechanical alteration and intraocular pressure (IOP) measuring errors.

**Purpose:** The purpose of this study is to determine the effects of naive use of prostaglandin analogues (PGA) on IOP and anterior chamber volume (ACV), as well as investigate how PGAs might affect corneal and scleral stiffness and their impact on ocular rigidity.

**Materials and Methods:** This study was a prospective study of 21 recently diagnosed open-angle glaucoma patients (33 eyes) initiating medical therapy with a topical prostaglandin eye drop. Corneal morphologic and biomechanical parameters as well as IOP were measured at 3 visits over a 4-month period with the following equipment: Pentacam, Corvis ST, Ocular Response Analyzer, Goldmann applanation tonometry (GAT) and Pascal dynamic contour tonometry.

**Results:** The study demonstrated a significant decrease in mean IOP with initiation of PGA in all 4 tonometers \((P < 0.0001)\). The greatest change in IOP occurred in the first 4 weeks of treatment \((P < 0.0001)\). The mean ACV showed a significant decrease at visit 2 \((P < 0.02)\) and visit 3 \((P < 0.04)\) compared with baseline visit 1. However, there was a paradoxical increase in ACV in 37% of eyes at visit 2, despite a significant mean reduction in IOP by GAT and dynamic contour tonometry. The IOP/ACV ratio at visit 1 significantly predicted the reduction in respective measures of IOP, as well as scleral stiffness measured by stiffness parameter-highest concavity.

**Conclusion:** In clinical practice, GAT may not be the most appropriate tonometer for measuring IOP in PGA treated eyes due to the measurement errors from ocular biomechanical alteration. The IOP/ACV ratio could potentially serve as a new diagnostic parameter to determine the likelihood of PGA treatment success.

**Key Words:** prostaglandin, anterior chamber volume, biomechanics, ocular rigidity, glaucoma, intraocular pressure

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Glaucoma is the second leading cause of blindness worldwide, affecting ~67 million people. There are many factors that contribute to glaucoma progression, but intraocular pressure (IOP) remains the most important modifiable risk factor that is targeted in glaucoma therapy. IOP can be modified by 5 different mechanisms: decrease aqueous humor production, decrease outflow resistance through the trabecular meshwork, increase outflow through the uveoscleral pathway, decreasing episcleral venous pressure or a combination of each mechanism. The relationship between IOP and ocular volume was first defined by Friedenwald in 1937 who coined the term, ocular rigidity. This relationship demonstrated that a change in volume generates a change in IOP, with low ocular rigidity leading to a small change in IOP for a given change in volume, and higher ocular rigidity leading to a larger change in IOP for the given change in volume. Therefore, mechanisms to decrease IOP, would ultimately rely on a decrease in anterior chamber volume (ACV).

Traditional glaucoma therapies often suppress aqueous production or enhance outflow through the trabecular meshwork pathway. Prostaglandin analogues (PGAs) have become one of the more widely used initial therapies for the treatment of glaucoma due to its effectiveness in reducing IOP by enhanced drainage through the uveoscleral pathway. There are 4 PGAs available in the United States: bimatoprost, latanoprost, travoprost, and tafluprost. The proposed mechanism of action of PGAs is an upregulation of matrix metalloproteinases and degradation of the extracellular matrix of the ciliary muscle and sclera resulting in decreased resistance for uveoscleral outflow. Structural alteration likely causes a reduction in scleral stiffness. However, this biomechanical response has not previously been studied. In addition, although the cornea is not involved in the uveoscleral outflow pathway, the cornea is likely subject to the same structural alterations as the sclera with PGA exposure. A decrease in corneal stiffness with PGA use has been demonstrated in rabbit eyes using uniaxial strip testing. It is likely that this decrease in corneal stiffness would also lead to IOP measurement error in applanation tonometry with less force being required to appalnate and therefore producing an underestimation of IOP.

Clinical studies have shown that PGAs have been effective in reducing IOP measured by applanation tonometry by 25% to 35% with a single daily dose through the uveoscleral outflow pathway. However, a recent study looking at corneal biomechanics and viscoelastic parameters of PGA treated eyes, including corneal hysteresis (CH) and corneal resistance factor (CRF), provided evidence that this therapy may actually alter the ocular structures and influence the accuracy of IOP measurements with a
TABLE 1. Mean Values at Visit 1, 2, and 3

| Metric          | Visit 1   | Visit 2   | Visit 3 (mm Hg) | Visit 4 (mm Hg) | P (Visit 1 to 2) | P (Visit 1 to 3) |
|-----------------|-----------|-----------|-----------------|-----------------|-----------------|-----------------|
| CCT (µm)        | 561 ± 38  | 557 ± 47  | 0.144           | 0.9408          | 561 ± 47        |                 |
| ACV (µL)        | 167 ± 38  | 161 ± 39* | 0.0125          | 0.0395          | 162 ± 35*       | 0.0395          |
| GAT (mm Hg)     | 21.5 ± 5.9| 16.4 ± 4.4*| <0.0001         | 0.9995          | 16.2 ± 4.5*     | <0.0001         |
| DCT (mm Hg)     | 23.8 ± 6.2| 19.7 ± 5.6*| <0.0001         | 0.9995          | 20.1 ± 5.1*     | <0.0001         |
| OPA (mm Hg)     | 2.8 ± 1.1 | 2.3 ± 1.1* | <0.0001         | 0.0007          | 2.3 ± 0.9*      | <0.0001         |
| IOPcc (mmHg)    | 21.7 ± 6.2| 17.6 ± 5.6*| <0.0001         | 0.9995          | 17.8 ± 4.7*     | <0.0001         |
| CH (mm Hg)      | 8.9 ± 1.7 | 9.5 ± 1.6  | 0.0593          | 0.1013          | 9.3 ± 1.6       | 0.1013          |
| DA Ratio 2 mm   | 7.55 ± 1.3| 8.11 ± 1.15*| <0.0001         | 0.0018          | 7.97 ± 1.09*    | 0.0018          |
| IntInvRad 1(mm) | 4.29 ± 0.65| 4.57 ± 0.64*| <0.0001         | 0.00007         | 4.51 ± 0.56*    | 0.00007         |
| SP-A1 (mm/mm Hg)| 132 ± 26  | 123 ± 26   | 0.6244*         | 0.257†          | 126 ± 25        | 0.257†          |
| SP_HC (mm/mm Hg)| 19.9 ± 7.6| 15.8 ± 5.7 | 0.1618*         | 0.0307†         | 16.5 ± 5.6*     | 0.0307†         |

†Significant difference compared with visit 1; no significant differences in any parameter were found between visits 2 and 3.

*Significant difference compared with ANCOVA with DCT as co-variate.

ACV indicates anterior chamber volume; CCT, central corneal thickness; CH, corneal hysteresis; DA Ratio, Deformation Ratio; DCT, dynamic contour tonometry; GAT, Goldmann applanation tonometry; IntInvRad, Integrated Inverse Radius; IOPcc, corneal-compensated intraocular pressure; OPA, ocular pulse amplitude; SP-A1, stiffness parameter at first applanation; SP-HC, stiffness parameter at highest concavity.

MATERIALS AND METHODS

This study was a prospective study of recently diagnosed open-angle glaucoma patients who were initiating medical therapy with a topical prostaglandin eye drop. The study was conducted at The Ohio State University (OSU) Wexner Medical Center, Havener Eye Institute, with an institutional review board approved protocol.

Patients were recruited from optometry and ophthalmology clinics at OSU and in the greater Columbus area. The inclusion criteria for the study included prostaglandin naïve adults with a new diagnosis of open-angle glaucoma patients who were initiating medical therapy with a topical prostaglandin eye drop. The study comprised 3 visits over 12 weeks, with visit 1 as baseline before initiation of PGA therapy, visit 2 at 1 month and visit 3 at 4 months after initiation of PGA therapy. Subjects were excluded from final analysis unless they had all of the following measurements at all 3 visits. The Pentacam (Oculus GmbH, Wetzlar, Germany) was used to measure corneal shape and ACV. Corneal and scleral stiffness parameters and central corneal thickness (CCT) were measured with the Corvis ST (Oculus GmbH). Corneal stiffness metrics included Integrated Inverse Radius and Deformation Ratio 2 mm, which have been shown to be relatively independent of IOP and as well as stiffness parameter at first applanation (SP-A1). Stiffness parameter at highest concavity (SP-HC) was used to indicate scleral stiffness.16,17 The viscoelastic parameter, CH was measured with the ocular response analyzer (ORA) (Reichert Inc., Buffalo, NY). The IOP was estimated with GAT (Haag-Streit, Koeniz, Switzerland), corneal-compensated IOP (IOPcc) from the ORA, and Pascal dynamic contour tonometry (DCT) (Zeimer Ophthalmic Systems AG, Port, Switzerland), reported to be less sensitive to CCT and corneal biomechanics.18,19 In addition, ocular pulse amplitude (OPA) was measured with DCT. Measurements were acquired in triplicate and averaged for analysis. Blood pressure at the time of the appointment was recorded due to its effect on OPA. Three static pressure/volume ratios were calculated at visit 1 for each of the IOP technologies, divided by the ACV (IOP/ACV), as a surrogate for ocular rigidity before initiation of PGA therapy.

TABLE 2. Mean Change From Baseline Visit 1 to Visit 2

| N    | ΔACV         | P       | ΔGAT         | P       | ΔDCT         | P       | ΔIOPcc       | P       |
|------|--------------|---------|--------------|---------|--------------|---------|--------------|---------|
| All eyes | -5.7 ± 12.4*| 0.0130  | -5.4 ± 4.0*  | <0.0001 | -4.11 ± 4.0* | <0.0001 | -4.19 ± 4.7* | <0.0001 |
| Group A | -12.4 + 10.4*| <0.0001 | -6.1 ± 4.3*  | <0.0001 | -4.9 ± 3.9*  | <0.0001 | -5.4 ± 4.4*  | <0.0001 |
| Group B | +6.04 ± 3.8* | <0.0002 | -4.3 ± 3.1*  | 0.0005  | -2.7 ± 3.9*  | 0.0358  | -2.1 ± 4.6   | 0.1734  |

*Significant difference between visit 1 and visit 2.

Group A represents all the eyes that had a mean decrease in ACV.

Group B represents all the eyes that had a mean increase in ACV.

ACV indicates anterior chamber volume; DCT, dynamic contour tonometry; GAT, Goldmann applanation tonometry; IOPcc, corneal-compensated intraocular pressure.

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FIGURE 1. Regression plot illustrating that the IOP/ACV ratio at visit 1 predicts the change in intraocular pressure between visit 1 and visit 2. A, GAT (P = 0.0007, R² = 0.31). B, IOPcc (P = 0.0023, R² = 0.28). ACV indicates anterior chamber volume; GAT, Goldmann applanation tonometry; IOPcc, corneal-compensated intraocular pressure.

TABLE 3. Characteristics Comparing Group A and Group B

| Age (y) | Males | Females | ACV (µL) | CCT (µm) | CH (mm Hg) | GAT (mm Hg) | DCT (mm Hg) | IOPcc (mm Hg) | GAT/ACV (mm Hg/µL) | IOPcc/ACV (mm Hg/µL) | DCT/ACV (mm Hg/µL) |
|---------|-------|---------|----------|----------|------------|-------------|-------------|---------------|---------------------|---------------------|---------------------|
| Group A | 61 ± 9 | 7       | 14       | 167 ± 40 | 572 ± 42   | 9.4 ± 1.7   | 21.5 ± 5.2  | 24.0 ± 5.8    | 21.6 ± 5.3          | 0.139 ± 0.54        | 0.138 ± 0.54          |
| Group B | 59 ± 13| 5       | 7        | 167 ± 35 | 541 ± 21   | 8.1 ± 1.2   | 21.6 ± 7.3  | 23.5 ± 7.2    | 22.0 ± 7.8          | 0.127 ± 0.25        | 0.130 ± 0.027         |
| P       | 0.5853 | —       | —        | 0.9672    | 0.0217*    | 0.0211*    | 0.9753      | 0.8113         | 0.835               | 0.4024              | 0.5851              |

*Statistically significant values, P < 0.05.

Group A represents all the eyes that had a mean decrease in ACV.

Group B represents all the eyes that had a mean increase in ACV.

ACV indicates anterior chamber volume; DCT, dynamic contour tonometry; GAT, Goldmann applanation tonometry; IOPcc, corneal-compensated intraocular pressure.
Statistical analyses were performed using SAS, version 9.4. For SP-A1 and SP-HC, ANCOVA was performed with DCT as a co-variate. Paired $t$ tests were performed for all other biomechanical parameters, IOP values, and ACV between all visits. Separate linear regression analyses were performed with each of the 3 IOP/ACV values at visit 1 as independent variables and respective $\Delta$IOP value as well as changes in corneal and scleral stiffness metrics as dependent variables to investigate whether these changes can be predicted. All significance values set a priori at $P<0.05$.

RESULTS

Thirty-three eyes of 21 patients (8 men and 13 women) with POAG were ultimately analyzed. The mean age was 60 years (36 to 79 y). The topical PGAs used included bimatoprost (Lumigan RC, Allergan, Madison, NJ) (4 patients), latanoprost (Xalatan, Pfizer, New York, NY) (16 patients), and travoprost (Travatan Z, Alcon, Fort Worth, TX) (1 patient).

A significant reduction in mean IOP was found, as measured by GAT, IOPcc, and DCT at visits 2 and 3 after the initiation of PGA, both compared with baseline visit 1 (Table 1). The greatest change in IOP occurred in the first 4 weeks of treatment ($P<0.0001$). No significant change in IOP was noted between visits 2 and 3 with all the above tonometric modalities, or any of the corneal/scleral stiffness metrics. A statistically significant difference was found in $\Delta$IOP between GAT versus DCT (1.4 ± 3.5; $P=0.031$), indicating significantly greater reduction in IOP as estimated by GAT than DCT.

Overall, the mean ACV showed a significant decrease at visit 2 ($P<0.02$) and visit 3 ($P<0.04$), both compared with baseline visit 1 (Table 1). Further analysis indicated that the ACV showed a decrease at visit 2 in only 21 eyes, by a mean of $-12.4±10.4\mu\text{L}$ (Table 2). There was a paradoxical increase in ACV in 12 eyes at visit 2, by a mean of $6.04±3.8\mu\text{L}$, despite a significant mean reduction in IOP by GAT and DCT tonometric technologies. Further analysis of these 2 groups showed no significant difference at baseline Visit 1 in age, ACV, GAT, DCT, IOPcc, or any of the 3 IOP/ACV ratios. However, a significant difference was found with CCT and CH significantly lower in the eyes in group B, with a significant increase in ACV (Table 3). In addition, there were 6 subjects for the 12 eyes in group B, so 4 of the 6 demonstrated this increase in ACV bilaterally.

The IOP/ACV ratio at visit 1 significantly predicted the reduction in respective measures of IOP for GAT (P = 0.0007, $R^2=0.31$; Fig 1A) and IOPcc (P = 0.0023, $R^2=0.28$; Fig 1B), but not DCT (Table 4). In addition, the IOP/ACV ratio at baseline visit 1 predicted the reduction of scleral stiffness measured by SP-HC for DCT (P = 0.0114, $R^2=0.19$; Fig 2A) and IOPcc (P = 0.0112, $R^2=0.19$; Fig 2B), but not GAT. No change in corneal stiffness metrics was predicted by the IOP/ACV ratio at visit 1 for any of the tonometric technologies.

**DISCUSSION**

In a majority of eyes, our hypothesis that use of PGA would decrease ACV as a mechanism to decrease IOP might be accepted. However, it was surprising to note that 37% of eyes showed an increase in ACV despite a lowering of IOP. PGA reduces IOP primarily by increasing drainage through the uveoscleral outflow pathway, but also by decreasing resistance through the trabecular meshwork to a smaller degree. Through this mechanism, the ACV should also decrease unless an alteration in the fundamental corneal and/or scleral properties occurred, generating a reduction in ocular rigidity. It is well known that the stiffness response will be reduced with a reduction in IOP due to the nonlinear properties of the cornea. Yet, this does not explain an increase in ACV accompanied by a decrease in IOP. Both Deformation Ratio and Integrated Inverse Radius showed significant increases within the first month after receiving PGA, which is consistent with a reduction in corneal stiffness. These 2 parameters have been shown to be relatively independent of IOP. In contrast, SP-A1 was not significantly affected when DCT IOP was included as a co-variate, while SP-HC was significantly lower with DCT IOP included as a co-variate. This indicates that the reduction in ocular rigidity is likely driven predominantly by the reduction of scleral stiffness, the site of action of PGAs.

PGA is effective by remodeling the extracellular matrix within the ciliary muscle and sclera. The increased metalloproteinase 1, 2, and 3 concentration found in the sclera, allows for an increase in scleral permeability, accompanied by a decrease in scleral stiffness according to the results of the current study. Figure 3 shows a schematic of 2 ocular rigidity curves, and how an increase in volume can be accompanied by a decrease in pressure if ocular rigidity is also reduced. This is a likely explanation for the 12 eyes in the current study where this phenomenon was observed. As the scleral stiffness is reduced with PGA therapy, so is the resistance to deformation, allowing greater volume to accumulate simultaneously as IOP is lowered. In addition, these eyes had a significantly thinner CCT and lower CH at baseline, perhaps allowing greater response to the reduction in ocular rigidity. A true measurement of ocular rigidity is invasive in nature, so is not appropriate for routine assessment. However, this increase in volume combined with a decrease in IOP is strong evidence that a reduction in ocular rigidity occurs with PGA therapy.

Early studies of ocular rigidity by Ridley and Clark Janet, found the pressure-volume relationship within the eye to increase in an exponential growth curve pattern. At lower pressures, volume could be increased with less impact on increasing the IOP and therefore more distensible. However, at higher pressures, a small increase in volume could greatly impact the IOP. Friedenwald converted the nonlinear pressure-volume curve representing ocular rigidity

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**TABLE 4. Regression of Baseline IOP/ACV Versus Change in IOP, Scleral, Corneal Stiffness**

| Parameter                  | Visit 1 GAT/ACV (mm Hg/μL), $P$, $R^2$ | Visit 1 DCT/ACV (mm Hg/μL), $P$, $R^2$ | Visit 1 IOPcc/ACV (mm Hg/μL), $P$, $R^2$ |
|----------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
| $\Delta$IOP                | $P=0.007$; $R^2=0.31$                  | $P=0.054$; $R^2=0.023$                | $P=0.0023$; $R^2=0.28$                |
| $\Delta$SP-HC               | $P=0.117$; $R^2=0.0114$               | $P=0.0112$; $R^2=0.19$               | $P=0.093$; $R^2=0.376$               |
| $\Delta$SP-A1              | $P=0.80$; $R^2=0.167$                | $P=0.942$; $R^2=0.517$               | $P=0.501$                            |
| $\Delta$DA Ratio           | $P=0.482$; $R^2=0.881$               | $P=0.517$                            |                                        |
| $\Delta$IntInvRad          | $P=0.054$; $R^2=0.023$                | $P=0.0023$; $R^2=0.28$               |                                        |

Values are between visit 1 and visit 2. $\Delta$ indicates anterior chamber volume; DA Ratio, Deformation Ratio; DCT, dynamic contour tonometry; GAT, Goldmann applanation tonometry; IntInvRad, Integrated Inverse Radius; IOP, intraocular pressures; IOPcc, corneal-compensated intraocular pressure; SP-A1, stiffness parameter at first applanation; SP-HC, stiffness parameter at highest concavity.

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[Notes and references are omitted for brevity.]
to a linearized constant by using a logarithmic function.\(^4\) In a normal eye, ocular rigidity would be constant. However, if the properties of the cornea or sclera are altered, this creates a new curve, as seen in Figure 3.

There was a significant decrease in the mean IOP between visits 1 and 2, and visits 1 and 3 in all tonometry modalities. There was no significant change in IOP between visits 2 and 3. Thus, this indicates that PGA greatest effects on IOP occurs in the first 4 weeks of initiating treatment. GAT, the gold standard technique for measuring IOP, demonstrated the greatest decrease in IOP from baseline at visits 2 and 3 (\(P<0.0001\)). However, the accuracy of its measurement has been shown to be influenced by corneal biomechanical properties, CCT and notably by PGA use.\(^24\) Several studies, including an ex vivo cadaver eye study, showed that DCT and ORA are less influenced by biomechanics in obtaining measurements close to intracameral IOP measurements.\(^25,26\)

DCT is a direct, nonapplanating tonometer that directly measures IOP and OPA with a pressure sensor tonometer tip at the corneal apex.\(^27\) ORA is a noncontact tonometer that uses an air puff to deform the cornea and an empirically developed corneal compensated IOP measurement.\(^28\) When comparing the mean change of IOP measurements between GAT and DCT at visit 2, there was a significantly greater reduction of IOP measured using the GAT compared with DCT. This is likely due to an overestimation of the reduction in IOP when using GAT due to a change in biomechanical properties of the cornea and sclera with PGA treatment. POAG corneas treated with PGA may

**FIGURE 2.** Regression plot illustrating that the IOP/ACV ratio at visit 1 predicts the change in scleral stiffness between visit 1 and visit 2. A, DCT (\(P=0.0114, R^2=0.19\)). B, IOPcc (\(P=0.0112, R^2=0.19\)). ACV indicates anterior chamber volume; GAT, Goldmann applanation tonometry; IOPcc, corneal-compensated intraocular pressure; SP-HC, stiffness parameter at highest concavity.
be more compliant than healthy eyes as reported by Costin et al. 29

In the current study, the ratio of IOP/ACV at visit 1 predicted the change in IOP at visit 2 in 2 tonometers, except for DCT. Consistently, a higher IOP/ACV ratio at visit 1 with GAT and IOPcc, predicted a greater reduction in the respective IOP (Fig. 1). In addition, a higher IOP/ACV ratio predicted a greater reduction in scleral stiffness at visit 2 in 2 tonometers except for GAT when using the associated IOP value for calculation of IOP/ACV (Table 4). Interestingly, the reduction in scleral stiffness is consistent with the site of action of the prostaglandins. Change in corneal stiffness metrics were not significantly related to baseline IOP/ACV ratio. The IOP/ACV ratio at baseline using IOPcc from the ORA was the only modality that showed a statistically significant prediction of the reduction in both IOPcc and scleral stiffness in subsequent visits.

In clinical practice, the results from our study suggest that GAT overestimates response, and therefore may not be the most appropriate tonometer for measuring IOP in PGA treated eyes. This is due to measurement errors produced by the alteration in scleral and corneal stiffness seen in glaucomatous eyes treated by PGA. DCT IOP or IOPcc from the ORA, may be more reliable as they are less influenced by ocular biomechanics. In addition, the pressure/volume ratio was shown to have a predictive element to determine which patients may best respond to PGA. Patients with a higher ratio have the propensity for a greater reduction in IOP. Therefore, the IOP/ACV ratio could potentially serve as a new diagnostic parameter to determine the likelihood of PGA treatment success.

The major limitation of our study was its small sample size. Future studies could repeat the current study with a larger sample size and evaluation of IOP, ACV, and scleral stiffness using a different glaucoma medication to determine if these changes are specific to PGA, as we hypothesize.

In summary, our study demonstrated a reduction in IOP between visits 1 and 2 with all tonometric modalities accompanied by a reduction in corneal and scleral stiffness. In addition, all changes to IOP occurred in the first 4 weeks of initiating PGA treatment. There were no significant changes in IOP between visits 2 and 3. We showed that the use of PGA can cause a reduction in IOP without a concurrent reduction in ACV due to structural alterations of the sclera and its effects on ocular rigidity. The baseline IOP/ACV ratio at visit 1 can also predict change in IOP and change in scleral stiffness in subsequent visits. Greater IOP/ACV ratio at visit 1, corresponding to a stiffer eye, predicts a larger reduction in IOP and scleral stiffness. The IOP/ACV ratio may present a new parameter in the diagnostic evaluation and treatment of glaucoma.

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