Glaucoma is a pressure-sensitive, chronic progressive optic neuropathy, and a leading cause of visual loss and blindness. The only currently available treatment for glaucoma is reduction of IOP by modifying the physiologic variables that determine IOP. The contributions of these variables to steady-state IOP is best described by the modified Goldmann equation

\[
IOP = \frac{1}{c} (Q - U) + EVP,
\]

where \( Q \) is the rate of aqueous humor formation, \( IOP \) is the intraocular pressure, \( EVP \) is the episcleral venous pressure, \( c \) is the conventional outflow facility, and \( U \) is the pressure-insensitive uveoscleral outflow rate. This model distinguishes the two paths of aqueous humor loss from the eye, the trabecular route, and the uveoscleral route. Flow through the uveoscleral route is thought to be insensitive to pressure, while aqueous humor flow rate through the trabecular route depends on a hydrostatic pressure difference \( (IOP - EVP) \) and the resistance to aqueous outflow \( (1/c) \). Intraocular pressure is easily measured in the clinic, although EVP is much more difficult to measure. Nevertheless, accurate estimates of EVP are critical to understanding aqueous humor dynamics and are necessary to calculate the flow rate through the uveoscleral path.\(^1\)\(^-\)\(^4\) Episcleral venous pressure has been measured invasively by direct cannulation of episcleral veins in animals,\(^5\)\(^-\)\(^8\) but in humans it must be measured noninvasively by measuring the pressure required to collapse an episcleral vein to a predetermined endpoint.\(^2\)\(^-\)\(^6\)\(^-\)\(^9\)\(^-\)\(^11\) This measurement generally requires topical anesthesia.

The effect of topical anesthesia on EVP in humans is unknown. Zamora and Kiel reported a significant decrease in the EVP in rabbits after instilling topical proparacaine, while they measured pressure directly in a cannulated episcleral vein. A similar effect in human eyes, if it exists, could bias our measurements of IOP under topical anesthesia. It also would influence the calculation of aqueous humor dynamics parameters, such as uveoscleral outflow. In this study, we measured EVP in human volunteers before and after topical proparacaine anesthesia.

**Materials and Methods**

Healthy subjects who were habitual soft contact lens wearers with refractive errors ranging between –4.00 and +2.00 diopters, were recruited from students and employees of Mayo Clinic, Rochester, MN, USA and local area residents. All subjects underwent a complete dilated eye examination, and individuals with glaucoma, IOP of 22 mm Hg or above, history of intraocular surgery or trauma, retinal pathology, diabetes, or current use of beta blockers or corticosteroids were excluded. In addition, subjects who could not tolerate the touch of the measurement tip of the episcleral venomanometer against their conjunctiva without topical anesthesia were excluded. Habitual soft contact lens wearers were selected for this reason. Participants were asked to avoid excess caffeine intake or large deviations from their normal sleep cycle on the day of the examination. All subjects provided written consent to participate after discussion of the risks of the study. Our study followed the Declaration of Helsinki (1989) and was approved by Institutional Review Board at Mayo Clinic.

**Measurement Protocol**

The study was completed in two visits. On the first visit, baseline EVP was measured in both eyes without topical anesthesia. Subjects then were assigned to receive one drop of topical proparacaine 0.5% randomized to the right or left eye. Episcleral
Kiel8 reported a 30% decrease in EVP after application of topical anesthetic if such a difference actually existed (subjects gave a 95% chance of finding a difference of 1.4 mm Hg). Anesthetic in anesthetized rabbits. A sample size of 30 eyes of 15 volunteers in the study. Subjects included 12 females and 3 males, all regular contact lens wearers who were tolerant of eye contact by the venomometer tip without anesthesia. Mean age was 32.8 years (range, 20–53 years). All subjects were Caucasian and low myopes, with a mean spherical equivalent of 0.05 diopters (reflecting the ethnic profile of Olmsted County, MN, USA, and the surrounding area) and low myopes, with a mean refractive error of −2.7 ± 0.7 diopters (spherical equivalent).

Table. Episcleral Venous Pressure With and Without Topical Anesthetic

<table>
<thead>
<tr>
<th>Eye</th>
<th>Time After Anesthetic, min</th>
<th>Mean ± SD, mm Hg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye treated with anesthetic</td>
<td>Baseline</td>
<td>7.3 ± 2.8</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>7.2 ± 2.2</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>7.6 ± 2.7</td>
</tr>
<tr>
<td>Contralateral eye</td>
<td>Baseline</td>
<td>7.1 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6.9 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>7.3 ± 2.6</td>
</tr>
</tbody>
</table>

Episcleral venous pressure measured at 5 or 10 minutes after topical anesthesia was not significantly different from EVP at baseline in either the treated eye or in the contralateral eye. Venous pressure was remeasured in both eyes 5 minutes after instillation of the topical anesthetic. Episcleral venous pressure was measured again in both eyes 10 minutes after instillation of the topical anesthetic. On the second study visit, all measurements were repeated with topical anesthesia applied to the contralateral eye. Contact lenses were removed before all EVP measurements.

Computerized Venomanometry

The method for measuring EVP has been described in detail elsewhere.2 In brief, through a slit-lamp biomicroscope, episcleral veins were identified as vessels that were straighter and deeper than conjunctival vessels and often were bifurcated. The transparent inflatable chamber of the venomanometer was placed against the conjunctiva over the area of the episcleral vein, and a computer-controlled motor drive pressurized the measurement tip at a constant rate. As the pressure increased, the vein collapsed, and this process was recorded by a high-definition video camera. Each video frame was synchronized with pressure inside the chamber. Image analysis software was used to determine changes in the vessel brightness and the pressure in the chamber when the vein just began to collapse was assumed to be equal to the EVP.7,12

Statistical Analysis

This study was powered to detect a 20% decrease in EVP after treatment with topical anesthetic, assuming a starting pressure of 7.6 ± 2.6 mm Hg (mean ± SD).2 In comparison, Zamora and Kiel8 reported a 30% decrease in EVP after application of topical anesthetic in anesthetized rabbits. A sample size of 30 eyes of 15 subjects gave a 95% chance of finding a difference of 1.4 mm Hg if such a difference actually existed (α = 0.05 and β = 0.2). Comparison of EVP measurements between time points and between eyes was performed by using repeated measures ANOVA. As well, comparisons of EVP measurements in eyes with and without topical anesthesia at individual time points, and comparison between right and left eyes, were performed by using paired t-tests. Statistical significance was assumed if P < 0.05.

RESULTS

We included 30 eyes of 15 volunteers in the study. Subjects included 12 females and 3 males, all regular contact lens wearers who were tolerant of eye contact by the venomanometer tip without anesthesia. Mean age was 32.8 ± 12.0 years (range, 20–53 years). All subjects were Caucasian (reflecting the ethnic profile of Olmsted County, MN, USA, and the surrounding area) and low myopes, with a mean refractive error of −2.7 ± 0.7 diopters (spherical equivalent).

The Table summarizes the EVP measurements before and after instillation of topical anesthetic eyedrops. There was no significant difference in the best estimate of EVP between eyes that received anesthetic and contralateral eyes based on repeated measures ANOVA (P = 0.53). As well, there was no significant difference in the best estimate of EVP between the right and left eyes (7.1 ± 2.6 and 7.2 ± 2.6 mm Hg, respectively, P = 0.9).

There was no overall difference between EVP in the anesthetic-treated and contralateral eyes (P = 0.53). For eyes that received topical anesthetic, the baseline estimate of EVP at 0% vessel compression was 7.5 ± 2.8 mm Hg. At 5 and 10 minutes after receiving anesthetic, there was no significant change in the EVP (7.2 ± 2.2 and 7.6 ± 2.7 mm Hg, P = 0.53 and P = 0.49, respectively). Similarly, with all other compression endpoints, mean EVP 5 or 10 minutes after topical anesthesia was not significantly different from EVP at baseline in either the eye that received anesthetic or the contralateral eye (P > 0.10; minimum detectable difference, 1.4–1.9 mm Hg, α = 0.05, β = 0.20, n = 30 eyes).

DISCUSSION

Our study did not detect any effect of topical anesthetic on EVP in humans, in contrast with the significant decrease in the EVP after instillation of proparacaine in rabbits reported by Zamora and Kiel.9 Several differences between rabbits and humans could explain this observation.

The most obvious difference between the two studies, other than the species, was the methods used to measure EVP. In the animal studies, EVP was measured directly by vessel cannulation, a method that cannot be used in humans. However, EVP measured in humans by using earlier “pressure chamber” techniques is subject to a number of limitations.2,3 This measurement is primarily limited by the variability and imprecision associated with the lack of a clear endpoint to indicate when a vessel has collapsed by a specific amount, or more critically, when the vessel has just begun to collapse, which indicates that the applied pressure is equal to the venous pressure. As well, manually-operated devices can be biased by the user because the user can feel the rotation of the pressure dial during the measurement and can inadvertently (and subconsciously) adjust the dial position by the appearance of the vein. The subjectivity of this measurement makes detection of small changes in EVP difficult. In our study, we used an objective technique for computerized venomanometry, based on the same principles as the older methods, but with the chamber pressure being increased at a constant rate by a motor drive, and the collapse of the vein being recorded in a video stream. Each video frame was synchronized with a pressure measured by a pressure transducer. Image processing techniques permitted objective identification of EVP at the very beginning of vessel collapse, which provides the best estimate of EVP based on ideal tube laws and previous studies by Gaasterland and Pederson.2,7 Although other endpoints may provide overestimates of EVP, they may still be used to assess changes, and similar analyses for the 90% and 50% patency endpoints also showed no significant difference after application of topical anesthetic drops.

Zamora and Kiel suggested that the episcleral circulation is under tonic neural control and that either an upstream resistance site is under tonic vasodilatory control or a downstream site is under vasoconstrictor control. If either of these sites were blocked by topical anesthetic, EVP would decrease. This is consistent with the effect of other vasoactive substances, such as nitroprusside, verapamil, or nitric oxide on episcleral veins.13–16 The lack of a decrease in EVP after topical application of proparacaine in human subjects in our study can...
be explained by several factors. First, the intact conjunctiva in our subjects may have reduced penetration of anesthetic to the episcleral vessels. In contrast, invasive techniques in animal studies involve cannulation of episcleral veins after removal of the overlying conjunctiva, exposing the veins to higher concentrations of anesthetic. This may have produced the transient drop in EVP reported by Zamora and Kiel, but absent in our study. Second, in animal studies, the use of general anesthesia may have altered the neurohormonal balance of the episcleral veins, rendering them more susceptible to anesthetic effects. Third, the anatomy and physiology of the episcleral veins and their role in IOP hemostasis in rabbits may be different from that in human eyes. Fourth, Zamora and Kiel only applied topical anesthetic to a small region of the eye. The episcleral vasculature forms a plexus, and localized application of topical anesthetic may have induced a local vasoconstriction or vasodilation of episcleral vessels and changes in EVP in a small region. This could potentially lead to shunting of blood to other regions, reducing local EVP. In contrast, diffuse application of topical anesthetic over the entire surface of the eye in humans may result in no generalized decrease in EVP. It also is possible that chronic contact lens use that was sufficient to desensitize the afferent nerves in the limbal region (and allow tolerance to touch without anesthetic) could potentially modify the efferent nerves and mask a neurogenic response. Finally, it is possible that our subjects experienced a small decrease in EVP that was not detected by our sample size.

Zamora and Kiel also reported a decrease in IOP after applying topical anesthetic, although the magnitude of this decrease was less than that of EVP. Similarly, Sarchahi and Bozorgi reported a significant decrease in IOP (more than 33%) in rabbits 10 minutes after use of topical anesthetics. In humans, however, instilling topical anesthetics appears to have a smaller effect on IOP. While some investigators have suggested a small decrease in IOP with topical anesthetics, others have found no change. As well, some studies have suggested that topical anesthesia may result in changes in corneal thickness, and this could artifactually change the IOP measurement. In our study, we did not measure IOP in order to avoid the risk of possible effects of ocular manipulation on EVP. However, our results suggested that if topical anesthetics reduce IOP in humans, the reduction is unlikely to be caused by a change in EVP.

Finally, there was no difference compared to baseline in EVP at 5 or 10 minutes after topical anesthesia in either the treated or untreated eyes. This suggests that topical anesthesia has no delayed effect, and that EVP estimates are not affected by repeated measurements.

In summary, measurement of EVP in humans is not affected by topical anesthesia, either directly or by systemic absorption. This provides reassurance that EVP measured noninvasively but with topical anesthetic can be used in investigations of aqueous humor dynamics, particularly for calculating uveoscleral flow, which cannot be measured directly. In studies of aqueous humor dynamics in humans, topical anesthetic will not inadvertently alter EVP or induce spurious results.

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References