Changes in the Blood Flow of the Optic Nerve Head Induced by Different Concentrations of Epinephrine in Intravitreal Infusion During Vitreous Surgery

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PURPOSE. We investigated whether intravitreal infusion solution containing epinephrine affects optic nerve head (ONH) blood flow during vitreous surgeries.

METHODS. The subjects were 22 patients with epimacular membrane or idiopathic macular hole. During vitreous surgery, ONH blood flow was examined before and 10 minutes after intravitreal infusion of solution containing epinephrine, via a laser speckle flowgraphy (LSFG) technique modified for acquiring measurements in a supine position. Epinephrine concentration was set at 1.0 mg/500 mL (1:500,000) or 0.5 mg/500 mL (1:1,000,000), with each concentration assigned to 11 consecutive patients. Relative pupil diameter, IOP, blood pressure, and pulse rate also were measured.

RESULTS. A significant reduction in blood flow throughout the ONH was induced by intravitreal infusion of epinephrine at 1:500,000, but not at 1:1,000,000. Blood flow in ONH tissue was diminished at both concentrations, while that in vessels of the ONH was not altered significantly by either concentration. Both epinephrine concentrations induced significant pupillary dilatation, but no significant changes in IOP, blood pressure, or pulse rate.

CONCLUSIONS. This study suggests that epinephrine, used in combination with intravitreal infusion solution, affects ONH blood flow during vitreous surgeries, as indicated by measurements obtained via a modified LSFG technique. Attention must be paid to the effects of intravitreal infusion of epinephrine on ocular circulation, particularly ONH blood flow.

Keywords: epinephrine, optic nerve head, blood flow, laser speckle flowgraphy, vitreous surgery, supine position

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Intraocular irrigating solution containing epinephrine usually is used to maintain mydriasis of the eye being operated on during vitreous surgery.1 There have been several reports2–8 regarding the effect of epinephrine or its prodrug, dipivefrine, on ocular blood flow. Some have reported that no effect on retinal, choroidal, or optic nerve head (ONH) blood flow was observed after a single application of epinephrine (1%–4%) eye drops in phakic eyes of monkeys or rabbits,2,4,5 while significant alterations in blood flow at those locations reportedly were induced in aphakic eyes.3,5 Others have reported that neither a single retrobulbar epinephrine (0.2%) injection nor multiple applications of epinephrine (2%) over 5 to 6 weeks altered posterior ocular blood flow in rabbits.6,7 In addition, a single administration of dipivefrine, a prodrug of epinephrine, reportedly yielded no significant change in tissue circulation in human ONH.9 It also has been reported that supplemental epinephrine (1,200,000) to retrobulbar anesthesia reduced blood velocities in the ophthalmic, central retinal, and posterior ciliary arteries of the eyes of primates and humans during cataract surgeries.9,10 To the best of our knowledge, however, to date there have been no reports on the effects of epinephrine added to intravitreal infusion solution on human ONH blood flow during surgery.

Laser speckle flowgraphy (LSFG) is an imaging technique that can analyze the blood flow of the retina, choroid, and ONH quantitatively and noninvasively.11,12 With regard to the medical equipment used to perform it, LSFG-NAVI (Softcare Ltd., Iizuka, Japan)13–17 is used currently in Japan and is commercially available. The LSFG equipment was improved to measure the ocular blood flow of patients in a supine position during surgery, although there is a report on the measurement of the ONH blood flow of subjects in a supine position that is unrelated to surgery.17

In the current study, we investigated whether epinephrine, used in combination with intravitreal infusion solution, affects ONH blood flow during vitreous surgery, via measurements obtained by LSFG.

METHODS

Subjects

We included in the study 22 eyes of 22 patients (15 with epimacular membrane and 7 with idiopathic macular hole; mean age, 70.5 ± 7.2 years; 6 males, 16 females) who underwent vitreous surgery in Toho University Sakura Medical
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Center. All procedures were in full compliance with the guidelines of the Declaration of Helsinki, and were approved by the Institutional Review Board/Ethics Committee of Toho University. All participants provided informed consent to participate, and the nature and possible consequences of the study were explained to them before the provision of this consent. Patients with glaucoma, atrial fibrillation, or uncontrolled hypertension were excluded from the study, as were patients on hemodialysis.

Experimental Protocol

All patients underwent microincision vitreous surgery with a 23-gauge instrument using the Accurus (Alcon, Fort Worth, TX) vented gas forced infusion (VGFI) system, under topical anesthesia with retrobulbar injection of 2% lidocaine hydrochloride (Xylocaine, 2.5 mL; AstraZeneca, Osaka, Japan) and 0.75% ropivacaine hydrochloride (Anapeine, 2.5 mL; AstraZeneca). Patients were instructed to refrain from eating, smoking, and drinking coffee or alcohol for a minimum of 3 hours before the surgery. Mydriasis was induced by the administration of eye drops containing 0.5% tropicamide and 0.5% phenylephrine hydrochloride (Mydrin-P ophthalmic solution; Santen Pharmaceutical Co., Ltd., Osaka, Japan), 7 times at 30-minute intervals before the surgery. After performing core vitrectomy and posterior vitreous detachment under infusion of an epinephrine-free BSS PLUS500 intraocular irrigating solution (Santen Pharmaceutical Co., Ltd., Osaka, Japan), 7 times at 30-minute intervals after the surgery. As an index of reproducibility, a coefficient of variance defined as 100 × (SD/mean) (%) was calculated from values derived from three continuous measurements of MBR for each case, then the mean ± SD at each time-point (pretreatment and posttreatment) was calculated for each group.

Measurement of ONH Blood Flow

The principle and method of ONH blood flow determination using LSFG were described previously. In the current study, the mean blur rate (MBR), an indicator of blood flow, was obtained by LSFG-NAV1-OPE (Softcare Ltd.), a modified type of LSFG-NAV1. The LSFG-NAV1-OPE was developed recently for ocular blood flow measurement in subjects in a supine position. Schemata and photos of this device are shown in Supplementary Figure S1. The camera equipped in LSFG-NAV1-OPE is set on tilting stages with two axes (φ and θ), and X-Y stages to adjust the field of view and to ensure the required alignment of the camera with the subject’s eye. These stages are held by a long adjustable mechanical arm, facilitating their placement above the subject’s face.

Three parameters of the MBR in the ONH were calculated using LSFG Analyzer software (v.3.0.47; Softcare Ltd.). After we had identified the margin of the ONH by hand using a round band, the software separated out the vessels using the automated definitive threshold, and analyzed the mean of the MBRs throughout the ONH (MBR-A), in vessels of the ONH (MBR-V), and in the ONH tissue (MBR-T). As an index of reproducibility, a coefficient of variance defined as 100 × (SD/mean) (%) was calculated from values derived from three continuous measurements of MBR for each case, then the mean ± SD at each time-point (pretreatment and posttreatment) was calculated for each group.

Measurement of Pupil Diameter (PD), IOP, Blood Pressure, and Pulse Rate

Relative PD (PD/corneal diameter), IOP, blood pressure, and pulse rate also were measured at the same time that ONH blood flow was measured. Pupil and corneal diameters were obtained from images recorded by a digital video recorder (D-VDR9K; Toshiba, Tokyo, Japan) during the surgery. Changes in relative PD were calculated by the following equation: 100 × (posttreatment relative PD − pretreatment relative PD)/pretreatment relative PD (%). Tonopen-AVIA (Reichert, Inc., Buffalo, NY) was used to measure IOP. Blood pressure and pulse rate were measured with a bedside monitor (BSM-5132; March 2014

Table 1. Characteristics of Each Group

<table>
<thead>
<tr>
<th></th>
<th>0.5 mg/500 mL</th>
<th>1.0 mg/500 mL</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.0 ± 9.3</td>
<td>72.6 ± 3.4</td>
<td>0.14*</td>
</tr>
<tr>
<td>Male:female</td>
<td>3:8</td>
<td>4:7</td>
<td>1.00†</td>
</tr>
<tr>
<td>ERM:MH</td>
<td>8:5</td>
<td>7:4</td>
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<tr>
<td>PVD+/−PVD−</td>
<td>9:2</td>
<td>8:3</td>
<td>1.00†</td>
</tr>
<tr>
<td>Combination of phacoemulsification +/−</td>
<td>9:2</td>
<td>7:4</td>
<td>0.64†</td>
</tr>
</tbody>
</table>

Systemic medications

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<tr>
<th></th>
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<th>0.39†</th>
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</thead>
<tbody>
<tr>
<td>Ca antagonist</td>
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<td>3</td>
<td>1.00†</td>
</tr>
<tr>
<td>ARB</td>
<td>2</td>
<td>5</td>
<td>1.00†</td>
</tr>
<tr>
<td>Statin</td>
<td>2</td>
<td>5</td>
<td>1.00†</td>
</tr>
<tr>
<td>Anti-platelet</td>
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<td>5</td>
<td>0.59†</td>
</tr>
<tr>
<td>Others</td>
<td>ACEI 1</td>
<td>ACEI 1</td>
<td>1.00†</td>
</tr>
<tr>
<td>β-blocker</td>
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<td>1</td>
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</tr>
</tbody>
</table>

ERM, epiretinal membrane; MH, macular hole; PVD, posterior vitreous detachment; ARB, angiotensin receptor blocker; ACEI, angiotensin converting enzyme inhibitor.

* Unpaired t-test.
† Fisher’s exact test.
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<table>
<thead>
<tr>
<th>TABLE 2. Coefficients of Variance (%) of MBR Measurements (Mean ± SD)</th>
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<tbody>
<tr>
<td>Pretreatment Posttreatment Pretreatment Posttreatment</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>MBR-A 3.3 ± 1.7</td>
</tr>
<tr>
<td>MBR-V 6.2 ± 4.3</td>
</tr>
<tr>
<td>MBR-T 6.5 ± 4.4</td>
</tr>
</tbody>
</table>

MBR-A, mean of MBRs throughout the ONH; MBR-V, mean of MBRs of vessels of the ONH; MBR-T, mean of MBRs of the ONH tissue.

Nihon-Kohden, Tokyo, Japan). Ocular perfusion pressure (OPP) then was calculated as two-thirds of mean blood pressure minus IOP.

**Statistical Analyses**

Data are expressed as mean ± SD or mean ± SEM. Statistical analyses were performed using paired and unpaired t-tests, or Fisher’s exact test. Differences were deemed to be statistically significant if \( P < 0.05 \).

**RESULTS**

With regard to reproducibility, the coefficients of variance (%) of MBR-A, MBR-V, and MBR-T ranged from 3.1 to 5.8, 5.7 to 6.9, and 3.8 to 6.5, respectively, as shown in Table 2. Their averages were (%) 4.1, 6.2, and 5.6, respectively.

The Figure shows representative MBR measurements before and after treatment with epinephrine in two patients; each patient received both concentrations of epinephrine. The MBR-A decreased significantly after infusion with solution containing 1.0 mg/500 mL of epinephrine, but not after infusion with solution containing 0.5 mg/500 mL of epinephrine (Table 3). The mean reduction rates (%) for the 1.0 and 0.5 mg/500 mL concentrations were 9.75 and 4.28, respectively. The MBR-T was diminished at both concentrations, while MBR-V was not altered significantly at either concentration (Table 3). The mean reductions (%) in MBR-T for 1.0 and 0.5 mg/500 mL were 12.2 and 11.8, respectively.

Relative PD was increased significantly, whereas IOP, blood pressure, OPP, and pulse rate did not change significantly after the infusion of epinephrine at either concentration (Table 4). There was no significant difference between the infusion of 0.5 and 1.0 mg/500 mL of epinephrine, with regard to the changes (%) in relative PD (mean ± SD, 9.0 ± 7.6 and 9.5 ± 10.6, respectively).

**DISCUSSION**

The present study indicated that a significant reduction in overall ONH blood flow (MBR-A) was induced by intravitreal infusion of epinephrine at a concentration of 1.0 mg/500 mL, but not at 0.5 mg/500 mL. However, no statistically significant differences were apparent between these concentrations with regard to relative PD, IOP, blood pressure, or pulse rate. Taken together, these results suggested that infusion of epinephrine at 0.5 mg/500 mL evidently is sufficient for maintaining mydriasis during vitreous surgery.

Notably, MBR-T was diminished statistically significantly at both concentrations tested, but MBR-V was not. It has been reported that in a previous study, retinal arteries contracted to a significantly greater extent when adrenergic agonists including epinephrine were applied to the intraluminal surface, rather than to the extraluminal surface.\(^9\)\(^10\) This suggests that retinal vessels may be resistant to the effects of epinephrine, to some degree. On the other hand, tissue blood flow in the ONH may respond differently to blood flow in the ONH vessels, because the ONH tissue blood supply is derived from capillaries. This may explain the different results for MBR-V and MBR-T observed in our study.

It has been reported previously that epinephrine at 1:200,000 significantly reduced blood velocities in retrobulbar arteries, including the ophthalmic, central retinal, and posterior ciliary arteries.\(^9\)\(^10\) In the current study, the applied concentration of epinephrine was 1:1,000,000 in the case of 0.5 mg/500 mL, 5 times less than was used in those studies.\(^9\)\(^10\) Therefore, the effects of epinephrine on the ocular vessels might have been weaker in our study. Regardless, it is important to consider the effect of intravitreal infusion of epinephrine on ocular circulation, particularly with regard to tissue circulation of the ONH, during surgery.

In the current study, we measured ONH blood flow in a supine position during surgery. For that purpose, we used the recently developed LSFG-NAVI-OPE, modification of the LSFG-NAVI-MRC that was changed specifically with regard to parts of

<table>
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<tr>
<th>TABLE 3. Changes in MBR Values After Infusion of Epinephrine (Mean ± SD)</th>
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<tbody>
<tr>
<td>Pretreatment Posttreatment</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>MBR-A 17.5 ± 5.0</td>
</tr>
<tr>
<td>MBR-V 32.5 ± 6.9</td>
</tr>
<tr>
<td>MBR-T 10.2 ± 2.5</td>
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</table>
the mechanical arm of the device, as described above in the Methods section. Since to our knowledge this is the first report on the measurement of ocular blood flow using this modified device, the reproducibility of the measurement was examined. The coefficient of variance (%) for the measurement of MBR-A in this study (4.1) was comparable to that obtained by LSFG-NAV in the previous study (3.4). Our results suggested that the reproducibility of this device is sufficient for measuring ONH blood flow in a supine position during surgery. Therefore, this device also could be useful for obtaining measurements from patients who cannot stand up, or examination of changes that occur when going from a sitting position to a supine position, or the reverse.

In the present study, there was significant pupillary dilatation, but no significant changes in IOP blood pressure, OPP, or pulse rate after intravitreal infusion of epinephrine. The observation of significant pupillary dilatation caused by topical epinephrine is concordant with previous reports. It has been reported that topicaly applied epinephrine induced a significant reduction in IOP in some patients, but not in the others, and rather that it had a biphasic effect on IOP. With regard to the effects of topical epinephrine on blood pressure and pulse rate, there is a report that these did not change significantly after administration of 2% epinephrine. In the current study, IOP was kept almost constant at approximately 13 to 14 mm Hg, which was within the regulatory range of pressure-flow autoregulation. In addition, OPP was not altered significantly, suggesting that ocular hemodynamic conditions were maintained constant during the study procedures.

Regarding the pharmacokinetics of epinephrine, since some of the patients underwent cataract surgery before vitreous surgery, the presence of a lens or intraocular lens might have induced differences. However, because the percentage of cases involving combined cataract surgery was not significantly different between the two groups, the difference in pharmacokinetics should affect the results similarly in each group.

The current study had several limitations. The thresholds of dose-dependency were not thoroughly examined, since we only assessed two epinephrine concentrations. Whether a reduction in ONH blood flow of approximately 10% has an irreversible impact on the function of the eye (including the ONH) may depend on the duration of that reduction. However, in the current study, the duration of the reduction was not known, because we only measured ONH blood flow at one time point (10 minutes). Taking measurements at later time points was not ethically feasible, because the data for the study were acquired during surgeries. In addition, the present study was performed without a placebo control group because of a similar reason (ethical issues). Instead, we adopted the data under stable conditions and averaged them; we also assigned one of the groups to a low concentration of epinephrine, which was 5 times less than the concentration used in the previous report.

A power analysis (Means, difference between two dependent means) by G*Power software (v.3.1.3; developed by Franz Faul, Kiel University, Kiel, Germany) showed that a total sample size of 32 is needed for an effect size of 0.45 (calculated from the MBR-A values), error probability (α) of 0.05 and power (1-β) of 0.8. Therefore, the total sample size of 22 in the current study would be smaller than the ideal sample size. However, since the practical number of patients that could be enrolled from one institution over a certain period for such a study would be approximately 20, the sample size of 22 might be acceptable for an exploratory study.

In conclusion, the present study suggested that epinephrine decreases ONH blood flow during vitreous surgery when used in combination with intravitreal infusion solution, as indicated by measurements obtained via an LSFG technique modified for assessing subjects in a supine position.

Acknowledgments
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