Changes in Optic Nerve Head Circulation in Response to Vasoactive Agents: Intereye Comparison in Monkeys with Experimental Unilateral Glaucoma

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PURPOSE. To investigate circulatory changes in the optic nerve head (ONH) in response to vasoactive agents including calcium antagonists, a substrate of nitric oxide (NO), and an inhibitor of NO synthase (NOS) in monkeys with unilateral experimental glaucoma.

METHODS. Argon laser cautery to the trabecular meshwork was used to create experimental unilateral glaucoma in nine monkeys. The effects of systemic lomerizine or nilvadipine (calcium-antagonists), L-arginine (a substrate of NO), and NG-nitro-L-arginine methyl ester (L-NAME, a NOS inhibitor) on the ONH tissue blood velocity (NB ONH) was studied by the laser speckle method.

RESULTS. Lomerizine and nilvadipine significantly increased NB ONH in the untreated normal eyes (P = 0.039 and 0.008, respectively), while significant, less increases were found in the laser-treated experimental glaucomatous eyes with significant intereye differences (P = 0.036 and 0.011, respectively). Larginine significantly increased NB ONH in both eyes without intereye difference (P = 0.71). L-NAME had no significant effects on NB ONH in the experimental glaucoma eyes; however, it produced a significant decrease in the nonlaser treated eyes (P = 0.036).

CONCLUSIONS. In experimental glaucomatous eyes, the reactivity of ONH vessels to calcium antagonists was preserved, but was significantly reduced. The response to a NOS inhibitor was lost; however, reactivity to a substrate of NO was normal. These data indicate that in experimental glaucoma, vasodilator reactivity in the peripheral vasculature of the ONH is preserved, but functional alterations are likely to affect reactivity to the NO system.

Ocular circulation is impaired in patients with open-angle glaucoma (OAG) and ocular hypertension (OHT) and it has been linked to progressive visual field defects.1–11 Thus, improvement of local ocular circulation, especially in the optic nerve head (ONH), may be beneficial in the treatment of glaucomatous optic neuropathy. Calcium antagonists are vasodilators and have a long track record of being used in diseases, such as angina pectoris; therefore, they appear to be promising agents for the treatment of glaucoma.12 We have studied the ONH circulation in respect of autoregulation and effect of a calcium antagonist or nitric oxide (NO) synthetase inhibitor on it in rabbits under temporarily increased IOP.13

There are ethical difficulties in conducting pharmacological studies of ocular circulation in humans, especially in patients with OAG who already have damaged ONHs. Further, systemic factors that influence ocular circulation, such as age-related vascular changes, levels of circulating vasoactive substances (or vascular reactivity to them) differ between healthy control subjects and patients with OAG. Recruiting unilateral OAG patients for blood flow studies would also be practically and ethically difficult. Nonhuman primates have vascular structures nearly identical to those of human eyes and experiments in primate models of unilateral glaucoma avoid the above problems.

There have been numerous studies of laser-induced experimental glaucoma primate eyes where morphological changes in the ONH were evaluated by fundus photographs, confocal scanning laser tomography, optical coherence tomography, sectioned samples obtained postmortem, or analyses of 3-dimensional images reconstructed from serially sectioned thin samples.15–23 Although the ONH circulation in normal primate eyes under varying ocular perfusion pressure has been studied in vivo,24,25 few investigators have compared pharmacological reactions of the ONH circulation to systemic vasoactive drugs between experimental glaucomatous and contralateral normal eyes in primates.

In this study, we used a monkey model of unilateral experimental glaucoma to investigate the effects that system-
ically administered calcium antagonists and other agents that act via the NO system have on ONH blood flow.

**Materials and Methods**

**Induction of Experimental Glaucoma**

Experimental procedures were conducted in accordance with the guidelines of the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. The left eyes of nine female cynomolgus monkeys (body weights 2.6–4.8 kg) were treated with argon laser cautery to the trabecular meshwork under systemic anesthesia, as previously described.22

Prior to and after laser treatment, IOP was measured with a pneumotonometer (Alcon, Fort Worth, TX) and anterior segments were examined with a slit lamp (SL-15; Kowa Company, Ltd., Nagoya, Japan) every week under topical anesthesia. A drop of 2% pilocarpine (Santen Pharmaceutical Co., Ltd., Osaka, Japan) was applied twice a day for several weeks to avoid peripheral anterior synechiae, and topical 0.5% timolol (Santen Pharmaceutical) was applied twice daily when IOP exceeded 50 mm Hg.22 The nonlaser-treated right eyes served as controls.

Morphology of the ONH was evaluated by fundus photography (TRC-W; Topcon Corporation, Tokyo, Japan) and confocal scanning laser tomography (Heidelberg Retina Tomograph (HRT), version 2.01; Heidelberg Engineering, Heidelberg, Germany), according to methods we previously reported.22 These assessments were done prior to the laser treatment and after each of the following experiments.

**Measurement of ONH Circulation**

The effects of the test drugs on the ONH circulation were studied using the normalized blur (NB) value, a quantitative index of tissue blood velocity obtained by the laser speckle method.20–28 The apparatus uses a fundus camera (TRC-W; Topcon Corporation) and a diode laser (model 06DL105A; CVI Melles Griot, Albuquerque, NM) to allow noncontact and noninvasive measurement of blood velocity in ocular tissue. The laser beam (wavelength: 808 nm, power: 2 mW) was focused on the surface of the temporal area of the ONH, the scattered light imaged on an image sensor (BASIS; Canon, Tokyo, Japan), where the speckle pattern appeared. NB values were calculated from the ratio of the average speckle intensity to the difference between the average speckle intensity and the speckle intensity successive scanning. The penetration depth of the infrared laser (wavelength 811 nm) focused on the surface of the temporal area of the ONH was calculated as NBav. The successive values were obtained from the ratio of light imaged on an image sensor (BASIS; Canon, Tokyo, Japan), where the speckle pattern appeared. NB values were calculated from the ratio of the average speckle intensity to the difference between the average speckle intensity and the speckle intensity successive scanning. The average NB level in the largest rectangular area free of visible vessels in the temporal rim of ONH was calculated as NBp. The successive averages of NBp for three to four heartbeats were calculated as NBONH.

Previous studies have shown when rabbit ocular blood flow rate is artificially changed by increasing IOP15–27 inhalation of 10% CO₂,27 intravenous calcium antagonists,30,31 or endothelin-1,29 NBONH shows a good correlation with the blood flow rate, as determined by the hydrogen gas clearance method where a hydrogen electrode was inserted into the ONH tissue to a depth of approximately 0.7 mm.25 The penetration depth of the infrared laser (wavelength 811 nm) exceeded 1 mm in a cat optic nerve.25 Although the hydrogen gas clearance method only indirectly estimates ONH blood flow, NBONH primarily represents blood flow between prelaminar and laminar parts of the ONH.

All data obtained with the laser speckle method for each of the experiments were stored in magneto-optical disks and analyzed by an investigator who was masked to the drug treatment.28

**Effects of a Calcium Antagonist**

Circulatory reactions to calcium antagonists, lomerizine and nilvadipine, were compared between the experimental glaucomatous eyes with elevated IOP and the normotensive nonlaser-treated eyes. Experiments were performed 18 to 26 weeks after laser when the IOP of the treated eyes was greater than or equal to 3 mm Hg, consistently higher than that of the control eyes in each animal. There were greater than or equal to 4 weeks intervals between each drug administration. All procedures were performed under systemic anesthesia with a combination of 5 to 10 mg/kg ketamine and 0.5 mg/kg xylazine given intramuscularly.

Lomerizine is a calcium antagonist that acts both on L- and T-type calcium channels35 and is relatively central nervous system specific34 (Nippon Organon, Osaka, Japan). Nilvadipine is another calcium antagonist with high lipid solubility35,36 (Astellas Pharma Inc., Tokyo, Japan). Lomerizine (0.01 mg/kg in saline) and nilvadipine (0.001 mg/kg in a solvent containing 20% ethanol and 10% polyethylene glycol in volume; or the same volume [0.2 mL/kg] of the nilvadipine vehicle) were given intravenously approximately 20 minutes after sufficient sedation. IOP was measured with a calibrated pneumotonometer before and 60 minutes after the drug injection. Brachial arterial blood pressure (BP) and heart rate (HR) were continuously measured with an automated infant BP meter (BP-8800; Colin Medical Technology Corporation, Komaki City, Japan) before injection of systemic anesthesia until all experimental procedures were completed. The dosages of calcium antagonists were determined by a preliminary experiment on another group of normal monkeys, those showing little effects on the BP, but evident increase in ONH blood flow. Measurements of NBONH were first performed in the untreated normal eyes and then in the glaucomatous eyes before and 5, 10, 20, 30, 40, and 60 minutes after the injection.

**Effects of a Substrate of NO and an Inhibitor of NOS**

The experiments with L-arginine or L-NAME (NG-nitro-L-arginine methyl ester) were performed 26 to 42 weeks after the laser treatment elevation in IOP. Intervals between each drug administration in each monkey were the same as above.

30 mg/kg L-arginine (Sigma Chemical, St. Louis, MO) (50 mg/mL in saline) or 30 mg/kg L-NAME (Sigma Chemical) (50 mg/mL in saline) were administrated intravenously approximately 20 minutes after the introduction of general anesthesia. The dose of L-arginine and L-NAME were determined in both unpublished pilot studies and our previously experiment.13 Brachial BP and HR were measured as described earlier and IOP was measured before and 30 minutes after the drug administration. In this series of experiments, NBONH measurements were taken at 30 minutes, instead of 60 minutes, post drug injection because the increased BP after administration of L-NAME might possibly be harmful to the monkeys.

**Statistical Analysis**

NBONH was normalized to the baseline (first measurement before drug administration at each experiment), and, thus, normalized values were compared between the glaucomatous and control eyes using the paired t-test.28 Intereye differences in the overall effects of drugs administrated on the NBONH were tested using the paired t-test based on the area under curve (AUC) of NBONH-time relationship and that of each time point using the paired t-test. A P value of less than 0.05 was considered significant. Bonferroni’s correction was applied to avoid increasing alpha errors in multiple comparisons.

**Results**

**Monkey Experimental Glaucoma**

In all nine monkeys, IOP did not increase after the initial laser treatment, but then became rapidly elevated after the second treatment and remained higher than in untreated eyes. Treatment corneal edema/slight hyphema was seen after the second treatment in three eyes, but this disappeared within a few weeks. Figures 1A and 1B show time courses of mean IOP.
of the laser-treated glaucomatous eyes and the contralateral untreated eyes. IOP values were measured under topical anesthesia alone to avoid the side effects of having repeated systemic anesthesia over 14 weeks. The IOP in the laser treated eyes showed a decreasing trend after the first 10 weeks, which became less evident after 18 weeks. However, it was significantly higher than that in the contralateral normal eye at all time points except at 42 and 43 weeks (P < 0.05, paired t-test). The HRT data obtained before and after IOP elevation is shown in Figure 1C.

**Effects of Calcium Antagonists**

As a preliminary experiment, only nilvadipine solvent (0.2 mL/kg) was administrated and its influence was studied (n = 8). BP gradually decreased after induction of general anesthesia in one monkey, possibly caused by systemic factors. Data for that particular monkey were then excluded from subsequent analysis. BP showed little change during the experiment (P > 0.50) in the remaining seven monkeys. NBONH showed little change in both eyes during the experiment (P = 0.24), while the pulse rate gradually decreased (between 30 and 60 minutes after the injection, P = 0.007–0.031), and the IOP at 60 minutes was approximately 4 to 6 mm Hg lower than before injection in both laser-treated (P = 0.012) and control (P = 0.024) eyes.

In the lomerizine experiment, BP showed gradual decrease in one monkey, for which data were excluded. In eight monkeys, BP showed no apparent change during the experiment, but the HR gradually decreased (at 50–60 minutes after the injection, $P = 0.056–0.039$; Fig. 2A). Before the lomerizine injection, IOP was 24.1 ± 7.1 and 14.8 ± 3.5 mm Hg (mean ± SD, n = 8) in the treated and control eyes, respectively, with significant intereye difference ($P = 0.006$), and at 60 minutes, it significantly decreased to 18.4 ± 4.2 ($P = 0.002$) and 11.2 ± 2.1 ($P = 0.002$) mm Hg with significant intereye difference ($P = 0.003$). Ocular perfusion pressure (OPP) calculated as (2/3 × (mean brachial BP) - IOP) was 6.2 ± 10.4 and 15.5 ± 6.2 mm Hg before injection, and 11.8 ± 6.5 and 19.0 ± 6.1 mm Hg at 60 minutes, respectively, with significant intereye differences ($P = 0.006$ and $P = 0.003$, respectively).

The measured NBONH values were 10.1 ± 2.2 and 9.6 ± 1.5 before injection in the experimental glaucoma and control eyes, respectively. It increased by 7% at 10 minutes ($P = 0.035$) in the experimental glaucoma eye, and by 15% at 10 minutes ($P = 0.059$) in the controls with significant intereye difference ($P = 0.006$) at 30 and 40 minutes ($P = 0.032$ and 0.080; Fig. 2B). The NBONH AUC was 221 ± 599 in arbitrary units in the experimental glaucoma and 582 ± 488 in the control eyes, respectively, with significant intereye difference ($P = 0.036$).

In the nilvadipine experiment, BP showed gradual apparent decrease in two monkeys, of which data were excluded. In seven monkeys, HR showed no apparent change during the experiment, but then gradually declined (at 10, 20, 40, and 60 minutes after the injection, $P = 0.0017–0.028$; Fig. 3A). Before nilvadipine injection, IOP was 18.9 ± 2.9 and 14.0 ± 2.5 mm Hg (mean ± SD, n = 7) in the experimental glaucoma and untreated eyes, respectively, though intereye difference was insignificant ($P = 0.072$), and at 60 minutes, it decreased to 11.3 ± 2.7 ($P = 0.008$) and 9.7 ± 2.5 ($P = 0.054$) mm Hg. OPP was 11.8 ± 2.7 and 16.7 ± 3.9 mm Hg before injection and 22.7 ± 4.5 and 24.3 ± 4.8 mm Hg at 60 minutes in the experimental glaucoma and control eyes, respectively, with no significant intereye difference at both time points.

The measured NBONH were 9.8 ± 2.6 and 9.0 ± 1.0 before the injection in the glaucomatous and untreated eyes, respectively. It slightly increased by 3% at 10 minutes ($P = 0.044$ without Bonferroni’s correction) in the experimental glaucoma eye, while it increased by 12% at 5 to 10 minutes in the controls ($P = 0.013$ and 0.008) with a significant intereye difference at 10 minutes ($P = 0.008$; Fig. 3B). NBONH AUC was 78.8 ± 72.8 in arbitrary units in the glaucoma, and 230 ± 128 in the untreated eyes, respectively, with significant intereye difference ($P = 0.011$).

The results of NBONH response were summarized in the Table.

**Effects of a Substrate of NO or an Inhibitor of NOS**

In the L-arginine experiment, BP showed an apparent gradual decrease in one monkey and these data were excluded from analysis, while in eight monkeys it was stable. HR showed a slight decrease at 30 minutes ($P = 0.031$; Fig. 4A). IOP in the experimental glaucoma and
Control eyes was 16.3 ± 3.7 and 13.8 ± 4.5 mm Hg (mean ± SD, n = 8) before L-arginine injection, with significant intereye difference (P < 0.05), and remained unchanged for 30 minutes. Mean OPP was 17.8 ± 4.6 and 20.3 ± 5.7 mm Hg at 0 minutes and 13.6 ± 4.6 and 16.5 ± 4.3 mm Hg at 30 minutes. IOP was higher and OPP was significantly lower in the laser treated eyes than controls both before and 30 minutes after injection (P < 0.01 and P < 0.002, respectively).

NBONH was 10.0 ± 2.3 and 9.7 ± 1.4 before L-arginine injection in the glaucoma and control eyes, respectively, and NBONH showed similar changes in both eyes, it increased by 7% and 5% at 5 and 10 minutes (P = 0.002 and 0.001) in the experimental glaucoma, respectively, and by 7% at 5 minutes (P = 0.004) in the contralateral untreated eye (Fig. 4B). The NBONH AUC was 90.6 ± 173 in arbitrary units in the experimental glaucoma, and 68.3 ± 57.1 in the contralateral untreated eye, respectively, without a significant intereye difference (P = 0.71).

In the L-NAME experiment, BP was not stabilized in one monkey, for which data were excluded. In eight monkeys, BP increased (P = 0.005-0.027) and HR decreased (P < 0.001) 10-30 minutes after L-NAME injections (Fig. 5A) as reported in other animal species.37-41 IOP of the experimental glaucoma and control eyes was 20.8 ± 4.6 and 17.4 ± 4.3 mm Hg (mean ± SD, n = 8) before L-NAME injection, and decreased to 16.1 ± 3.8 and 14.0 ± 3.5 mm Hg (P = 0.005 and P < 0.001) at 30 minutes with significant intereye difference, both before and 30 minutes after injection (P < 0.001 and P = 0.038). The corresponding mean OPP was 13.0 ± 8.8 and 16.4 ± 8.7 mm Hg, and 29.9 ± 6.5 and 32.0 ± 7.1 mm Hg, respectively, with significant intereye difference. (P < 0.001 and P = 0.038).

NBONH was 10.5 ± 2.1 and 9.8 ± 1.7 before L-NAME injection in the experimental glaucoma and control eyes, respectively, and decreased by 9% and 8% at 20 and 30 minutes in the control eyes (P = 0.030 and 0.040), while remaining almost unchanged in the glaucomatous eyes (Fig. 5B) Point wise, intereye difference was significant (P = 0.017). NBONH AUC was 39.6 ± 115 in arbitrary units in the experimental glaucoma, and −176 ± 151 in the contralateral untreated eye, with significant intereye difference (P = 0.036).

The results of NBONH response were summarized in the Table.

**DISCUSSION**

Experimental glaucoma models with ocular hypertension (OHT) have also been created in mice,32-45 rats,44-47 and rabbits,48,49, however, only monkeys have an ONH structure and vasculature similar to human eyes.14 Accordingly, the monkey experimental glaucoma, initially described by Gaasterland and Kupfer,50 serves as a good model for
investigations into the pathophysiology of ONH circulation in glaucoma.

OHT is the sole cause of glaucoma in the experimental glaucoma monkey model, but investigators have found similarity between the eyes of experimental monkey glaucoma and human glaucoma. Altered morphologic appearance or extracellular matrix of the ONH, ganglion cell apoptosis, nerve fiber layer defects, neuron loss in lateral geniculate nucleus, and histochemical changes in cortical neurons have been found in human glaucoma and experimental glaucoma monkey eyes.

HRT provides a highly objective analysis of ONH morphology. The reproducibility of HRT findings has been confirmed in normal monkey eyes. In this study, HRT parameters remained stable until after the 16th week, which agreed with earlier reports.

The unilateral glaucoma model enables the contralateral eye to serve as a control. The similarity between local vascular reactivity, systemic parameters, and plasma levels of vasoactive substances between the two eyes provides an ideal platform to study pharmacological agents on the ONH circulation. It also overcomes the ethical issues and impact of circulatory disorders that make studies on patients with OAG difficult to undertake.

Nilvadipine primarily acts on L-type calcium channels, while lomerizine also acts on T-type calcium channels. However, these calcium antagonists showed about the same effects on the ONH circulation in both glaucomatous and normal eyes.

### Table. Summary of NBONH Response

<table>
<thead>
<tr>
<th>Agent</th>
<th>Lomerizine</th>
<th>Nilvadipine</th>
<th>L-arginine</th>
<th>L-NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum NBONH change after administration/ time point</td>
<td>7% increase/ 10 min</td>
<td>3% increase/ 10 min</td>
<td>7% increase/ 5 min</td>
<td>2% increase/ 20 min</td>
</tr>
<tr>
<td>Experimental glaucomatous eyes</td>
<td>15% increase/ 10 min</td>
<td>12% increase/ 5–10 min</td>
<td>7% increase/ 5 min</td>
<td>NS</td>
</tr>
<tr>
<td>Contralateral normal eyes (control)</td>
<td>0.032</td>
<td>0.008</td>
<td>NS</td>
<td>0.017</td>
</tr>
<tr>
<td>Overall NBONH change after administration (AUC of NBONH–time relationship)</td>
<td>221</td>
<td>79</td>
<td>91</td>
<td>40</td>
</tr>
<tr>
<td>Experimental glaucomatous eyes</td>
<td>582</td>
<td>230</td>
<td>68</td>
<td>176</td>
</tr>
<tr>
<td>Contralateral normal eyes (control)</td>
<td>0.046</td>
<td>0.011</td>
<td>NS</td>
<td>0.036</td>
</tr>
</tbody>
</table>

NS, no significant change was found.

* P value of paired t-test with Bonferroni’s correction at the time point.

** P value of paired t-test based on the area under curve.
normal eyes, a transient blood flow increasing action that was significantly less in experimental glaucoma than normal eyes. Significant IOP reduction was found in both sets of eyes, possibly secondary to prolonged general anesthesia (> 60 minutes) because no significant IOP-lowering effect of these calcium antagonists have been reported in rabbits or humans, and a similar finding was also observed after injection of nilvadipine solvent. An increase of NBONH occurred at 5–10 minutes, which subsequently declined and stabilized at 40–60 minutes. Significant ONH blood flow increase after lomerizine or nilvadipine administration has been reported in rabbits and normal tension glaucoma patients using the laser speckle method. However, the extent of this increase was significantly smaller in the experimental glaucoma eyes than in the control eyes. This attenuated effect on the ONH circulation in the glaucoma eye could be attributable to the lower OPP in those glaucoma eyes with higher IOP. However, it must be noted that the intereye difference obtained with the laser speckle method indicates the reaction to drugs relative to the baseline value, but not in the absolute value of blood flow, which is likely to be affected by the OPP. Significantly less peak effects relative to the baseline in the experimental glaucoma eyes would appear to suggest that ONH damage diminishes vascular smooth muscle cell reactivity to calcium antagonists. However, this must be confirmed under conditions of similar IOP between experimental glaucoma and controls.

NO is a potent vasodilator. L-NAME is a nonselective inhibitor of NOS. Decreased ocular blood flow and increased blood flow have been reported for L-NAME and L-arginine administration, respectively, in many animal species, including as rabbits, cats, pigs, and rats. It was reported in rabbits that NBONH was decreased by intravenous L-NAME, and that this could be antagonized by L-arginine administration.

L-NAME has been reported to increase systemic BP and HR in rabbits, while L-arginine did not show any significant change. In both experimental glaucoma and control eyes. The IOP reduction may be explained by decreased aherosclerotic plaque production owing to L-NAME-induced disruption of ciliary blood flow. The influence of general anesthesia on IOP appeared to be small because the interval of IOP measurements was as short as 30 minutes in these two series of experiments.

L-NAME caused a decrease in NBONH only in the control eyes. OPP which should accelerate the circulation, was found to be higher in controls. Thus, there was dissociation in circulatory reaction to L-NAME between the experimental glaucoma and control eyes. However, NBONH increased similarly in both eyes after L-arginine administration. Vasodilatory reactivity of the ONH peripheral vasculature of the experimental glaucoma eyes to L-arginine was different from that to calcium antagonists. This is partly explained by the differing mechanisms of action of NO and calcium antagonists, and suggests that NO may be more effective in improving ONH circulation than calcium antagonists in glaucomatous eyes with high IOP.

The measured NB value was not significantly reduced in the experimental glaucoma eyes compared to contralateral eyes, either at the same time or in the same eyes before glaucoma was established; however, the validity of our glaucoma model was not limited by this finding. We have already reported, the NB value correlates with not only velocity and number of blood cells in the target tissue, but also with the reflectance and penetration depth of the laser. We suspect that the glaucomatous ONH tissue is likely to be altered histologically so that it causes changes in reflectance and the effective penetration depth of the laser. Laser penetration depth determines the sampling volume and the number of blood cells contained there, which strongly determines the NB value.

Thus, based solely on the NB value it is not possible to totally determine whether blood flow in the ONH tissue increased or decreased after experimental glaucoma was established, and so it is more of a speculation based on the findings and our current knowledge of the pathophysiology of reduced blood flow in patients with glaucoma. This limitation is outside the purpose of this study, and the possible influence of overestimation or underestimation in the NB value was minimized in the study design by the fact that the NB value was normalized to the baseline value and compared between glaucomatous and normal eyes on a percentage change basis.

The reason why NBONH did not decrease in the glaucomatous eyes after the L-NAME administration is unclear. Because an NBONH increase, due to the L-arginine administration, was retained in both groups of eyes, the lack in the effect of L-NAME cannot be explained by disruption or occlusion of blood vessels or down regulation of NOS in the ONH of the experimental glaucoma eyes. Similar findings were reported for an alpha-1 agonist. ONH vessels in the experimental glaucoma eye might be functionally changed. The constitutive activity of NOS might be relatively depressed, and, thus, there is room left to be further functional depression by L-NAME. This theory is consistent with the observation of Pang et al. who found glaucomatous optic neuropathy was not associated with up regulated expression of NOS-2 in the retina, ONH, or optic nerve. Suppression of NOS activity fits with findings of another recent study of isolated vessels from human normal tension glaucoma patients: showing that endothelium derived hyperpolarizing factor activity might be enhanced to compensate for reduced NO activity. However, NO production/enhanced NOS expression in the retina in rat experimental glaucoma and the ONH of human glaucoma patients is reported. Elucidation of the NO-associated functional status of ONH vasculature in experimental glaucoma monkey waits for future studies.

A possible limitation of this study is that relatively deeper sedation was needed to avoid small saccadic eye movement that interferes with the accurate ONH circulation measurements. Thus, cardiovascular conditions during the experiment represented by lower BP and HR might be somewhat different from those under conscious condition, and might modify the action of drugs currently used. The lower BP in this study than that reported in previous reports could be attributed to deep sedation or from measurement error. Unfortunately, the BP meter was not calibrated by cannulated BP monitoring; however, as far as the drug effects were measured, a lower BP and HR is not thought to affect the conclusions of this current study.

In summary, we created laser-induced unilateral experimental glaucoma in monkey eyes and, in comparison to control eyes, assessed reactivity of the ONH peripheral vasculature to calcium antagonists, L-arginine, an NO-substrate, and L-NAME, an NOS inhibitor. The results suggest that calcium antagonists and L-arginine significantly increased the ONH circulation in both experimental glaucoma and untreated eyes, but decreased reactivity of the ONH peripheral vasculature to calcium antagonists in experimental glaucoma eyes. L-NAME decreased the ONH circulation only in the contralateral untreated eyes, which suggests that in eyes with experimental glaucoma there are NO-associated functional alterations in the ONH vasculature.
The finding that reactivity to vasodilatory agents such as calcium antagonists, Larginine or a prostaglandin receptor-agonist58 was maintained but reactivity to vasoconstricting agents such as L-NAME and alpha-1 agonist58 was diminished, may have clinical implications in the management of OAG/OHT.

References


