タイトル	Changes in the blood flow of the optic nerve head induced by different concentrations of epinephrine in intravitreal infusion during vitreous surgery
別タイトル	硝子体手術中のエピネフリン眼内灌流によって惹起される視神経乳頭血流の変化
作成者（著者）	産賀, 真
公開者	東邦大学
発行日	2015.02
掲載情報	東邦大学大学院医学研究科 博士論文. 4.
資料種別	学位論文
内容記述	主査 : 富田剛司 / タイトル : Changes in the blood flow of the optic nerve head induced by different concentrations of epinephrine in intravitreal infusion during vitreous surgery /著者 : Makoto Ubuka, Tetsuya Sugiyama, Yasutaka Onoda, Tomoaki Shiba, Yuichi Hori, Takatoshi Maeno /掲載誌 : Investigative Ophthalmology & Visual Science /巻号・発行年等 : 55(3):1625-1629, 2014 /本文ファイル : 査読後原稿 /
著者版フラグ	ETD
報告番号	32661乙第2827号
学位授与年月日	2015.02.24
学位授与機関	東邦大学
DOI	info:doi/10.1167/iovs.13-13801
その他資源識別子	http://iovs.arvojournals.org/article.aspx?articleid=2190166
メタデータのＵＲＬ	https://mylibrary.toho-u.ac.jp/webopac/TD52811910

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

Makoto Ubuka[1], Tetsuya Sugiyama[2], Yasutaka Onoda[1], Tomoaki Shiba[1], Yuichi Hori[1], Takatoshi Maeno[1]

[1]Department of Ophthalmology, Toho University Sakura Medical Center, 564-1, Shimoshizu, Sakura, Chiba 285-8741, Japan

[2]Nakano Eye Clinic of Kyoto Medical Co-operative, 2, Jurakukaitou-cho, Nakagyo-ku, Kyoto 604-8404, Japan

Corresponding Author: Tetsuya Sugiyama, M.D., Ph.D., Nakano Eye Clinic of Kyoto Medical Co-operative, 2, Jurakukaitou-cho, Nakagyo-ku, Kyoto 604-8404, Japan

Telephone: +81-75-801-4151; Fax: +81-75-822-7423

E-mail: tsugiyama@poh.osaka-med.ac.jp

Word Count: Abstract: 217; main text (excluding the title page, legends, and references, but including the abstract): 2,512

Financial Disclosure: None

Funding/Support: None

ABSTRACT

Purpose: To investigate 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 min 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, intraocular pressure (IOP), blood pressure, and pulse rate were also 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, may decrease 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.

Key words: Epinephrine, optic nerve head, blood flow, laser speckle flowgraphy, vitreous surgery, supine position

INTRODUCTION

Intraocular irrigating solution containing epinephrine is usually used to maintain mydriasis of the eye being operated on during vitreous surgery.[1] There have been several reports[2-8] 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 were reportedly induced in aphakic eyes.[3,4,5] Others have reported that neither a single retrobulbar epinephrine (0.2%) injection nor multiple applications of epinephrine (2%) over 5–6 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.[8] It has also been reported that supplementing 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 non-invasively.[11,12] With regard to the medical equipment used to perform it, LSFG-NAVI™ (Softcare Ltd., Iizuka, Japan)[13-17] is currently used in Japan, and is commercially available. The LSFG equipment was improved in order 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 which 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

Twenty-two eyes of 22 patients (15 with epimacular membrane and 7 with idiopathic macular hole; mean age 70.3 ± 7.2 years; 6 males, 16 females) who underwent vitreous surgery in Sakura Medical Center of Toho University were included in the study. 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 prior to 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 micro-incision 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, AstraZeneca, Osaka, 2.5 ml) and 0.75% ropivacaine hydrochloride (Anapeine, AstraZeneca, 2.5 ml). Patients were instructed to refrain from eating, smoking, and drinking coffee or alcohol for a minimum of 3 hours prior to 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 min intervals prior to the surgery. After performing core vitrectomy and posterior vitreous detachment under infusion of an epinephrine-free BSS PLUS®500 intraocular irrigating solution (Santen Pharmaceutical Co. Ltd.), the ONH blood flow of patients in a supine position was measured 3 times by LSFG under a stabilized infusion pressure of 10 mmHg using the VGFI system; the IOP was kept almost constant by ensuring that the distance between the bottle containing the irrigating solution and the patient's eye remained constant. Ten minutes after 50 ml of epinephrine (1 mg or 0.5 mg)-containing BSS PLUS®500 intraocular irrigating solution (500 ml) was infused at 10 mmHg, ONH blood flow was measured again using the same method. One milligram and 0.5 mg of epinephrine were each assigned to 11 consecutive patients. The characteristics of each group are shown in Table 1. As shown in this table, some of the patients also underwent phacoemulsification cataract surgery before vitreous surgery. Cataract surgery was performed under infusion of an epinephrine-free BSS PLUS®500 intraocular irrigating solution. None of the parameters in Table 1 differed significantly between the groups.

Measurement of ONH Blood Flow

The principle and method of ONH blood flow determination using LSFG were described previously.[11,12] In the current study, the mean blur rate (MBR), an indicator of blood flow,[13] was obtained by LSFG-NAVI-OPE™ (Softcare Ltd.), a modified type of LSFG-NAVI™. LSFG-NAVI-OPE™ was recently developed 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-NAVI-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).[13]

Analysis of the Reproducibility of ONH Blood Flow Measurements

As an index of reproducibility, a coefficient of variance defined as 100 x (SD/mean) (%) was calculated from values derived from three continuous measurements of MBR for each case, then the mean ± SD at each time-point (pre-treatment and post-treatment) was calculated for each group.

Measurement of Pupil Diameter, Intraocular Pressure, Blood Pressure, and Pulse Rate

Relative pupil diameter (pupil diameter/corneal diameter, relative PD), intraocular pressure (IOP), blood pressure, and pulse rate were also 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·(post-treatment relative PD – pre-treatment relative PD)/ pre-treatment 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, Nihon-Kohden, Tokyo, Japan). Ocular perfusion pressure (OPP) was then calculated as two-thirds of mean blood pressure minus IOP.

Statistical Analyses

Data are expressed as mean ± standard deviation (SD) or mean ± standard error of the 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 3.1–5.8, 5.7–6.9, and 3.8–6.5 respectively, as shown in Table 2. Their averages were (%) 4.1, 6.2, and 5.6 respectively.

Figure 1 shows representative MBR measurements before and after treatment with epinephrine in two patients; each patient received both concentrations of epinephrine. 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 mg/500 ml and 0.5 mg/500 ml concentrations were 9.75 and 4.28 respectively. 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 mg/500 ml and 0.5 mg/500 ml were 12.2 and 11.8 respectively.

Relative PD was significantly increased, 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 mg/500 ml of epinephrine 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 suggest that infusion of epinephrine at 0.5 mg/500 ml is evidently 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.[18] 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 previously been reported 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] The effects of epinephrine on the ocular vessels might therefore 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 specifically changed with regard to parts of the mechanical arm of the device, as described above in the Methods section. Since 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) were comparable with that obtained by LSFG-NAVI in the previous study[13] (3.4). Our results suggest that the reproducibility of this device is sufficient for measuring ONH blood flow in a supine position during surgery. Therefore, this device could also 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.[19,20] It has been reported that topically applied epinephrine induced a significant reduction in IOP in some patients, but not in the others,[21] and rather that it had a biphasic effect on IOP.[19,22,23] 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.[24] In the current study, IOP was kept almost constant at approximately 13 to 14 mmHg, which was within the regulatory range of pressure-flow autoregulation.[25,26] 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 min). 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 reports.

A power analysis (Means: difference between two dependent means) by G* Power software (v.3.1.3) 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 suggests 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.

REFERENCES

1. Gimbel HV. The effect of treatment with topical nonsteroidal anti-inflammatory drugs with and without intraoperative epinephrine on the maintenance of mydriasis during cataract surgery. *Ophthalmology* 1989;96:585–588.

2. Alm A. The effect of topical l-epinephrine on regional ocular blood flow in monkeys. *Invest Ophthalmol Vis Sci.* 1980;19:487–491.

3. Morgan TR, Mirate DJ, Bowman K, Green K. Topical epinephrine and regional ocular blood flow in aphakic eyes of rabbits. *Arch Ophthalmol.* 1983;101:112–116.

4. Caprioli J, Sears M, Mead A. Ocular blood flow in phakic and aphakic monkey eyes. *Exp Eye Res.* 1984;39:1–7.

5. Jay WM, Aziz MZ, Green K. Effect of topical epinephrine and timolol on ocular and optic nerve blood flow in phakic and aphakic rabbit eyes. *Curr Eye Res.* 1984;3:1199–1202.

6. Jay WM, Aziz MZ, Green K. The effect of retrobulbar epinephrine injection on ocular and optic nerve blood flow. *Curr Eye Res.*1985;4:55–58.

7. Green K, Hatchett TL. Regional ocular blood flow after chronic topical glaucoma drug treatment. *Acta Ophthalmol (Copenh).* 1987;65:503–506.

8. Tamaki Y, Tomita K, Araie M, Tomidokoro A, Nagahara M. Effect of topical adrenergic agents on tissue circulation in human optic nerve head evaluated with a laser speckle microcirculation analyser. *Nihon Ganka Gakkai Zasshi.* 1996;100:55–62. [Japanese]

9. Netland PA, Siegner SW, Harris A. Color Doppler ultrasound measurements after topical and retrobulbar epinephrine in primate eyes. *Invest Ophthalmol Vis Sci.* 1997;38:2655–2661.

10. Huber KK, Remky A. Colour Doppler imaging before and after retrobulbar anaesthesia in patients undergoing cataract surgery. *Graefes Arch Clin Exp Ophthalmol.* 2005;243:1141–1146.

11. Tamaki Y, Araie M, Kawamoto E, Eguchi S, Fujii H. Non-contact, two-dimensional measurement of tissue circulation in choroid and optic nerve head using laser speckle phenomenon. *Exp Eye Res.* 1995;60:373–383.

12. Sugiyama T, Araie M, Rive CE, Schmetterer L, Orgul S. Use of laser speckle flowgraphy in ocular blood flow research. *Acta Ophthalmol.* 2010;88:723–729.

13. Aizawa N, Yokoyama Y, Chiba N, et al. Reproducibility of retinal circulation measurements obtained using laser speckle flowgraphy-NAVI in patients with glaucoma. *Clin Ophthalmol.* 2011;5:1171–1176.

14. Shiba T, Takahashi M, Hori Y, Maeno T, Shirai K. Optic nerve head circulation determined by pulse wave analysis is significantly correlated with cardio ankle vascular index, left ventricular diastolic function, and age. *J Atheroscler Thromb.* 2012;19:999–1005.

15. Takahashi H, Sugiyama T, Tokushige H, et al. Comparison of CCD-equipped laser speckle flowgraphy with hydrogen gas clearance method in the measurement of optic nerve head microcirculation in rabbits. *Exp Eye Res.* 2013;108:10–15.

16. Shiga Y, Omodaka K, Kunikata H, et al. Waveform analysis of ocular blood flow and the early detection of normal tension glaucoma. *Invest Ophthalmol Vis Sci.*

2013;54(12):7699–7706.

17. Shiga Y, Shimura M, Asano T, et al. The influence of posture change on ocular blood flow in normal subjects, measured by laser speckle flowgraphy. *Curr Eye Res.* 2013;38:691–698.

18. Yu DY, Alder VA, Cringle SJ, Su EN, Yu PK. Vasoactivity of intraluminal and extraluminal agonists in perfused retinal arteries. *Invest Ophthalmol Vis Sci.* 1994;35:4087–4099.

19. Langham ME, Krieglstein GK. The biphasic intraocular pressure response of rabbits to epinephrine. *Invest Ophthalmol.* 1976;15:119–127.

20. Camras CB, Podos SM, Rosenthal JS, Lee PY, Severin CH. Multiple dosing of prostaglandin F2 alpha or epinephrine on cynomolgus monkey eyes. I. Aqueous humor dynamics. *Invest Ophthalmol Vis Sci.* 1987;28:463–469.

21. Becker B, Shin DH. Response to topical epinephrine. A practical prognostic test in patients with ocular hypertension. *Arch Ophthalmol.* 1976;94:2057–2058.

22. Funk RH, Wagner W, Rohen JW. The effect of epinephrine on ciliary process vasculature and IOP studied by intraocular microendoscopy in the albino rabbit. *Curr Eye Res.* 1992;11:161–173.

23. Percicot CL, Schnell CR, Debon C, Hariton C. Continuous intraocular pressure measurement by telemetry in alpha-chymotrypsin-induced glaucoma model in the rabbit: effects of timolol, dorzolamide, and epinephrine. *J Pharmacol Toxicol Methods.* 1996;36:223–228.

24. Robinson F, Chen S, Petrig BL, Grunwald JE, Riva CE. The acute effect of topical epinephrine on macular blood flow in humans. *Invest Ophthalmol Vis Sci.* 1992;33:18–22.

25. Riva CE, Hero M, Titze P, Petrig B. Autoregulation of human optic nerve head blood flow in response to acute changes in ocular perfusion pressure. *Graefes Arch Clin Exp Ophthalmol.* 1997;235:618-626.

26. Pillunat LE, Anderson DR, Knighton RW, Joos KM, Feuer WJ. Autoregulation of human optic nerve head circulation in response to increased intraocular pressure. *Exp Eye Res.* 1997;64:737-744.

Figure Legend

Figure 1. Representative changes in ONH blood flow after intravitreal infusion of epinephrine, as measured by the LSFG-NAVI-OPE™ device.

Supplementary Material

Figure S1. Schematic views (A, B) and photos (C, D) of the recently developed device of laser speckle flowgraphy, LSFG-NAVI-OPE™ which is a modification of the LSFG-NAVI™.

Table 1. Characteristics of each group.

	0.5 mg/500 ml	1.0 mg/500 ml	P value
Age (years)	68.0 ± 9.3	72.6 ± 3.4	0.14†
Male : Female	3 : 8	4 : 7	1.00††
ERM : MH	8 : 3	7 : 4	1.00††
PVD+ : PVD-	9 : 2	8 : 3	1.00††
Combination of phacoemulsification(+:-)	9:2	7:4	0.64††
Systemic medications			
Ca antagonist	6	3	0.39††
ARB	2	3	1.00††
statin	2	3	1.00††
Anti-platelet	1	3	0.59††
Others	ACEI 1 α blocker 1	ACEI 1 β blocker 1	1.00††

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

Table 2. **C**oefficients of variance (%) of MBR measurements（Mean ± SD）

	0.5 mg/500 ml		1.0 mg/500 ml	
	Pretreatment	Post- treatment	Pretreatment	Post- treatment
MBR-A	3.3 ± 1.7	3.1 ± 1.8	4.0 ± 1.6	5.8± 3.0
MBR-V	6.2 ± 4.3	6.0 ± 3.4	5.7 ± 3.1	6.9 ± 4.1
MBR-T	6.5 ± 4.4	6.5 ± 4.4	3.8 ± 2.6	5.7 ± 3.3

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.

Table 3. Changes in MBR Values after infusion of epinephrine（Mean ± SD）

	0.5 mg/500 ml			1.0 mg/500 ml		
	Pretreatment	Post-treatment	P value	Pretreatment	Post-treatment	P value
MBR-A	17.5±5.0	16.4±6.0	0.18	20.5±7.3	18.4±6.6	0.008
MBR-V	32.5 ± 6.9	32.2 ± 9.9	0.89	36.4 ± 14.3	34.7 ± 14.0	0.28
MBR-T	10.2 ± 2.5	9.0 ± 2.8	0.003	13.1 ± 4.3	11.5 ± 4.0	0.0004

Table 4. Changes in Relative PD, IOP, Blood Pressure,OPP, and Pulse Rate After Infusion of Epinephrine（Mean ± SD）

	0.5 mg/500 ml			1.0 mg/500 ml		
	Pretreatment	Post-treatment	P value	Pretreatment	Post-treatment	P value
Relative PD	0.58±0.09	0.63±0.08	0.006	0.60±0.10	0.65±0.08	0.018
IOP (mmHg)	14.1±2.3	13.1±1.9	0.14	14.6±6.9	13.9±7.8	0.34
Mean blood pressure (mmHg)	94.9±12.4	94.2±13.2	0.29	97.9±9.4	93.8±11.3	0.06
OPP(mmHg)	49.2±8.7	49.7±9.6	0.53	50.7±8.1	48.6±9.5	0.28
Pulse rate (beats/min)	67.3±11.8	65.7±7.2	0.53	67.9±13.1	66.7±13.7	0.21

Figure 1

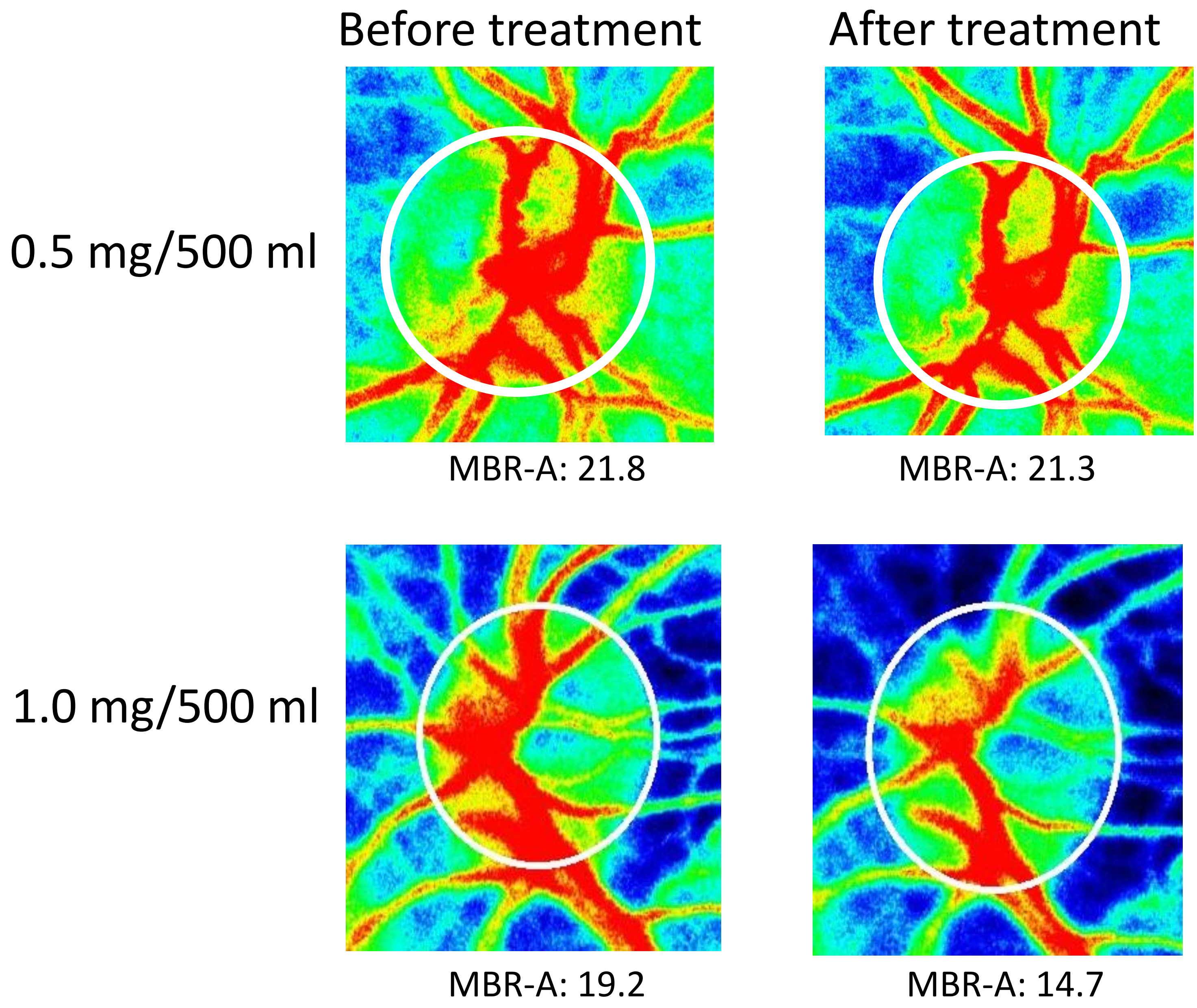
Before treatment
After treatment
0.5 mg/500 ml
MBR-A: 21.8
MBR-A: 21.3
1.0 mg/500 ml
MBR-A: 19.2
MBR-A: 14.7

Figure S1