

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

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4 Makoto Ubuka¹, Tetsuya Sugiyama², Yasutaka Onoda¹, Tomoaki Shiba¹, Yuichi Hori¹,
5 Takatoshi Maeno¹

6
7 ¹Department of Ophthalmology, Toho University Sakura Medical Center, 564-1,
8 Shimoshizu, Sakura, Chiba 285-8741, Japan

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

11
12 **Corresponding Author:** Tetsuya Sugiyama, M.D., Ph.D., Nakano Eye Clinic of Kyoto
13 Medical Co-operative, 2, Jurakukaitou-cho, Nakagyo-ku, Kyoto 604-8404, Japan
14 Telephone: +81-75-801-4151; Fax: +81-75-822-7423
15 E-mail: tsugiyama@poh.osaka-med.ac.jp

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25 **ABSTRACT**

26 **Purpose:** To investigate whether intravitreal infusion solution containing epinephrine
27 affects optic nerve head (ONH) blood flow during vitreous surgeries.

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

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

42 **Conclusions:** This study suggests that epinephrine, used in combination with
43 intravitreal infusion solution, may decrease ONH blood flow during vitreous surgeries,
44 as indicated by measurements obtained via a modified LSF technique. Attention must
45 be paid to the effects of intravitreal infusion of epinephrine on ocular circulation,
46 particularly ONH blood flow.

47

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

50 **INTRODUCTION**

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

67 Laser speckle flowgraphy (LSFG) is an imaging technique that can analyze the blood

68 flow of the retina, choroid, and ONH quantitatively and non-invasively.^{11,12} With regard
69 to the medical equipment used to perform it, LSF_G-NAVI™ (Softcare Ltd., Iizuka,
70 Japan)¹³⁻¹⁷ is currently used in Japan, and is commercially available. The LSF_G
71 equipment was improved in order to measure the ocular blood flow of patients in a
72 supine position during surgery, although there is a report on the measurement of the
73 ONH blood flow of subjects in a supine position which is unrelated to surgery.¹⁷

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

77

78 **METHODS**

79 *Subjects*

80 Twenty-two eyes of 22 patients (15 with epimacular membrane and 7 with idiopathic
81 macular hole; mean age 70.3 ± 7.2 years; 6 males, 16 females) who underwent vitreous
82 surgery in Sakura Medical Center of Toho University were included in the study. All
83 procedures were in full compliance with the guidelines of the Declaration of Helsinki,
84 and were approved by the Institutional Review Board/Ethics Committee of Toho
85 University. All participants provided informed consent to participate, and the nature and

86 possible consequences of the study were explained to them prior to the provision of this
87 consent. Patients with glaucoma, atrial fibrillation, or uncontrolled hypertension were
88 excluded from the study, as were patients on hemodialysis.

89 ***Experimental Protocol***

90 All patients underwent micro-incision vitreous surgery with a 23-gauge instrument
91 using the Accurus[®] (Alcon, Fort Worth, TX) vented gas forced infusion (VGFI) system,
92 under topical anesthesia with retrobulbar injection of 2% lidocaine hydrochloride
93 (Xylocaine, AstraZeneca, Osaka, 2.5 ml) and 0.75% ropivacaine hydrochloride
94 (Anapaine, AstraZeneca, 2.5 ml). Patients were instructed to refrain from eating,
95 smoking, and drinking coffee or alcohol for a minimum of 3 hours prior to the surgery.
96 Mydriasis was induced by the administration of eye drops containing 0.5% tropicamide
97 and 0.5% phenylephrine hydrochloride (Mydrin[®]-P ophthalmic solution, Santen
98 Pharmaceutical Co. Ltd., Osaka, Japan), 7 times at 30 min intervals prior to the surgery.
99 After performing core vitrectomy and posterior vitreous detachment under infusion of
100 an epinephrine-free BSS PLUS[®] 500 intraocular irrigating solution (Santen
101 Pharmaceutical Co. Ltd.), the ONH blood flow of patients in a supine position was
102 measured 3 times by LSFG under a stabilized infusion pressure of 10 mmHg using the
103 VGFI system; the IOP was kept almost constant by ensuring that the distance between

104 the bottle containing the irrigating solution and the patient's eye remained constant. Ten
105 minutes after 50 ml of epinephrine (1 mg or 0.5 mg)-containing BSS PLUS[®]500
106 intraocular irrigating solution (500 ml) was infused at 10 mmHg, ONH blood flow was
107 measured again using the same method. One milligram and 0.5 mg of epinephrine were
108 each assigned to 11 consecutive patients. The characteristics of each group are shown in
109 Table 1. As shown in this table, some of the patients also underwent
110 phacoemulsification cataract surgery before vitreous surgery. Cataract surgery was
111 performed under infusion of an epinephrine-free BSS PLUS[®]500 intraocular irrigating
112 solution. None of the parameters in Table 1 differed significantly between the groups.

113 *Measurement of ONH Blood Flow*

114 The principle and method of ONH blood flow determination using LSFG were
115 described previously.^{11,12} In the current study, the mean blur rate (MBR), an indicator of
116 blood flow,¹³ was obtained by LSFG-NAVI-OPE[™] (Softcare Ltd.), a modified type of
117 LSFG-NAVI[™]. LSFG-NAVI-OPE[™] was recently developed for ocular blood flow
118 measurement in subjects in a supine position. Schemata and photos of this device are
119 shown in Supplementary Figure S1. The camera equipped in LSFG-NAVI-OPE[™] is set
120 on tilting stages with two axes (φ and θ), and X-Y stages to adjust the field of view and
121 to ensure the required alignment of the camera with the subject's eye. These stages are

122 held by a long adjustable mechanical arm, facilitating their placement above the
123 subject's face.

124 Three parameters of the MBR in the ONH were calculated using LSFG Analyzer
125 software (v 3.0.47; Softcare Ltd.). After we had identified the margin of the ONH by
126 hand using a round band, the software separated out the vessels using the automated
127 definitive threshold, and analyzed the mean of the MBRs throughout the ONH
128 (MBR-A), in vessels of the ONH (MBR-V), and in the ONH tissue (MBR-T).¹³

129 *Analysis of the Reproducibility of ONH Blood Flow Measurements*

130 As an index of reproducibility, a coefficient of variance defined as $100 \times (\text{SD}/\text{mean}) (\%)$
131 was calculated from values derived from three continuous measurements of MBR for
132 each case, then the mean \pm SD at each time-point (pre-treatment and post-treatment)
133 was calculated for each group.

134 *Measurement of Pupil Diameter, Intraocular Pressure, Blood Pressure, and Pulse*

135 *Rate*

136 Relative pupil diameter (pupil diameter/corneal diameter, relative PD), intraocular
137 pressure (IOP), blood pressure, and pulse rate were also measured at the same time that
138 ONH blood flow was measured. Pupil and corneal diameters were obtained from
139 images recorded by a digital video recorder (D-VDR9K, TOSHIBA, Tokyo, Japan)

140 during the surgery. Changes in relative PD were calculated by the following equation:
141 $100 \cdot (\text{post-treatment relative PD} - \text{pre-treatment relative PD}) / \text{pre-treatment relative PD}$
142 (%). Tonopen-AVIA[®] (Reichert Inc., Buffalo, NY) was used to measure IOP. Blood
143 pressure and pulse rate were measured with a bedside monitor (BSM-5132,
144 Nihon-Kohden, Tokyo, Japan). Ocular perfusion pressure (OPP) was then calculated as
145 two-thirds of mean blood pressure minus IOP.

146 *Statistical Analyses*

147 Data are expressed as mean \pm standard deviation (SD) or mean \pm standard error of the
148 mean (SEM). Statistical analyses were performed using paired and unpaired *t*-tests, or
149 Fisher's exact test. Differences were deemed to be statistically significant if $p < 0.05$.

150

151 **RESULTS**

152 With regard to reproducibility, the coefficients of variance (%) of MBR-A, MBR-V, and
153 MBR-T ranged from 3.1–5.8, 5.7–6.9, and 3.8–6.5 respectively, as shown in Table 2.

154 Their averages were (%) 4.1, 6.2, and 5.6 respectively.

155 Figure 1 shows representative MBR measurements before and after treatment with
156 epinephrine in two patients; each patient received both concentrations of epinephrine.
157 MBR-A decreased significantly after infusion with solution containing 1.0 mg/500 ml

158 of epinephrine, but not after infusion with solution containing 0.5 mg/500 ml of
159 epinephrine (Table 3). The mean reduction rates (%) for the 1.0 mg/500 ml and 0.5
160 mg/500 ml concentrations were 9.75 and 4.28 respectively. MBR-T was diminished at
161 both concentrations, while MBR-V was not altered significantly at either concentration
162 (Table 3). The mean reductions (%) in MBR-T for 1.0 mg/500 ml and 0.5 mg/500 ml
163 were 12.2 and 11.8 respectively.

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

169

170 **DISCUSSION**

171 The present study indicated that a significant reduction in overall ONH blood flow
172 (MBR-A) was induced by intravitreal infusion of epinephrine at a concentration of 1.0
173 mg/500 ml, but not at 0.5 mg/500 ml. However, no statistically significant differences
174 were apparent between these concentrations with regard to relative PD, IOP, blood
175 pressure, or pulse rate. Taken together, these results suggest that infusion of epinephrine

176 at 0.5 mg/500 ml is evidently sufficient for maintaining mydriasis during vitreous
177 surgery.

178 Notably, MBR-T was diminished statistically significantly at both concentrations
179 tested, but MBR-V was not. It has been reported that in a previous study, retinal arteries
180 contracted to a significantly greater extent when adrenergic agonists including
181 epinephrine were applied to the intraluminal surface, rather than to the extraluminal
182 surface.¹⁸ This suggests that retinal vessels may be resistant to the effects of epinephrine,
183 to some degree. On the other hand, tissue blood flow in the ONH may respond
184 differently to blood flow in the ONH vessels, because the ONH tissue blood supply is
185 derived from capillaries. This may explain the different results for MBR-V and MBR-T
186 observed in our study.

187 It has previously been reported that epinephrine at 1:200,000 significantly reduced
188 blood velocities in retrobulbar arteries, including the ophthalmic, central retinal, and
189 posterior ciliary arteries.^{9,10} In the current study, the applied concentration of
190 epinephrine was 1:1,000,000 in the case of 0.5 mg/500 ml, 5 times less than was used in
191 those studies.^{9,10} The effects of epinephrine on the ocular vessels might therefore have
192 been weaker in our study. Regardless, it is important to consider the effect of intravitreal
193 infusion of epinephrine on ocular circulation, particularly with regard to tissue

194 circulation of the ONH, during surgery.

195 In the current study, we measured ONH blood flow in a supine position during
196 surgery. For that purpose, we used the recently developed LSF_G-NAVI-OPE™,
197 modification of the LSF_G-NAVI-MRC™ that was specifically changed with regard to
198 parts of the mechanical arm of the device, as described above in the Methods section.
199 Since this is the first report on the measurement of ocular blood flow using this
200 modified device, the reproducibility of the measurement was examined. The coefficient
201 of variance (%) for the measurement of MBR-A in this study (4.1) were comparable
202 with that obtained by LSF_G-NAVI in the previous study¹³ (3.4). Our results suggest that
203 the reproducibility of this device is sufficient for measuring ONH blood flow in a supine
204 position during surgery. Therefore, this device could also be useful for obtaining
205 measurements from patients who cannot stand up, or examination of changes that occur
206 when going from a sitting position to a supine position, or the reverse.

207 In the present study, there was significant pupillary dilatation but no significant
208 changes in IOP, blood pressure, OPP, or pulse rate after intravitreal infusion of
209 epinephrine. The observation of significant pupillary dilatation caused by topical
210 epinephrine is concordant with previous reports.^{19,20} It has been reported that topically
211 applied epinephrine induced a significant reduction in IOP in some patients, but not in

212 the others,²¹ and rather that it had a biphasic effect on IOP.^{19,22,23} With regard to the
213 effects of topical epinephrine on blood pressure and pulse rate, there is a report that
214 these did not change significantly after administration of 2% epinephrine.²⁴ In the
215 current study, IOP was kept almost constant at approximately 13 to 14 mmHg, which
216 was within the regulatory range of pressure-flow autoregulation.^{25,26} In addition, OPP
217 was not altered significantly, suggesting that ocular hemodynamic conditions were
218 maintained constant during the study procedures.

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

224 The current study had several limitations. The thresholds of dose-dependency were
225 not thoroughly examined, since we only assessed two epinephrine concentrations.
226 Whether a reduction in ONH blood flow of approximately 10% has an irreversible
227 impact on the function of the eye (including the ONH) may depend on the duration of
228 that reduction. However, in the current study the duration of the reduction was not
229 known, because we only measured ONH blood flow at one time point (10 min). Taking

230 measurements at later time-points was not ethically feasible, because the data for the
231 study were acquired during surgeries. In addition, the present study was performed
232 without a placebo control group because of a similar reason (ethical issues). Instead, we
233 adopted the data under stable conditions and averaged them; we also assigned one of the
234 groups to a low concentration of epinephrine, which was 5 times less than the
235 concentration used in the previous reports.

236 A power analysis (Means: difference between two dependent means) by G* Power
237 software (v.3.1.3) showed that a total sample size of 32 is needed for an effect size of
238 0.45 (calculated from the MBR-A values), error probability (α) of 0.05 and power (1- β)
239 of 0.8. Therefore, the total sample size of 22 in the current study would be smaller than
240 the ideal sample size. However, since the practical number of patients that could be
241 enrolled from one institution over a certain period for such a study would be
242 approximately 20, the sample size of 22 might be acceptable for an exploratory study.

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

247

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- 324

325 **Figure Legend**

326

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

329

330 Supplementary Material

331

332 Figure S1. Schematic views (A, B) and photos (C, D) of the recently developed device

333 of laser speckle flowgraphy, LSF_G-NAVI-OPE™ which is a modification of the

334 LSF_G-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. Coefficients of variance (%) of MBR measurements (Mean \pm SD)

	0.5 mg/500 ml		1.0 mg/500 ml	
	Pretreatment	Post- treatment	Pretreatment	Post- treatment
MBR-A	3.3 \pm 1.7	3.1 \pm 1.8	4.0 \pm 1.6	5.8 \pm 3.0
MBR-V	6.2 \pm 4.3	6.0 \pm 3.4	5.7 \pm 3.1	6.9 \pm 4.1
MBR-T	6.5 \pm 4.4	6.5 \pm 4.4	3.8 \pm 2.6	5.7 \pm 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 \pm 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 \pm 5.0	16.4 \pm 6.0	0.18	20.5 \pm 7.3	18.4 \pm 6.6	0.008
MBR-V	32.5 \pm 6.9	32.2 \pm 9.9	0.89	36.4 \pm 14.3	34.7 \pm 14.0	0.28
MBR-T	10.2 \pm 2.5	9.0 \pm 2.8	0.003	13.1 \pm 4.3	11.5 \pm 4.0	0.0004

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

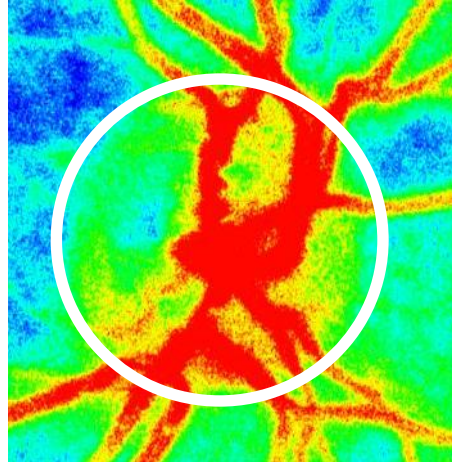
	0.5 mg/500 ml			1.0 mg/500 ml		
	Pretreatment	Post-treatment	P value	Pretreatment	Post-treatment	P value
Relative PD	0.58 \pm 0.09	0.63 \pm 0.08	0.006	0.60 \pm 0.10	0.65 \pm 0.08	0.018
IOP (mmHg)	14.1 \pm 2.3	13.1 \pm 1.9	0.14	14.6 \pm 6.9	13.9 \pm 7.8	0.34
Mean blood pressure (mmHg)	94.9 \pm 12.4	94.2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

Figure 1

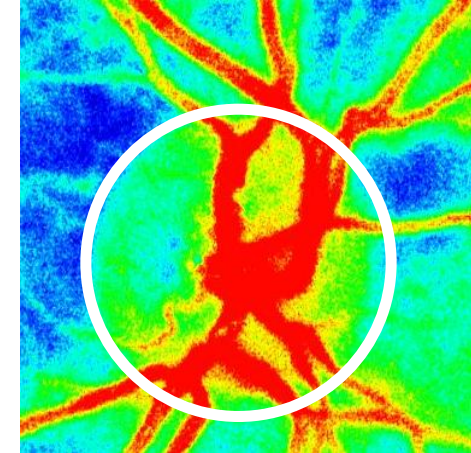
Before treatment

After treatment

0.5 mg/500 ml

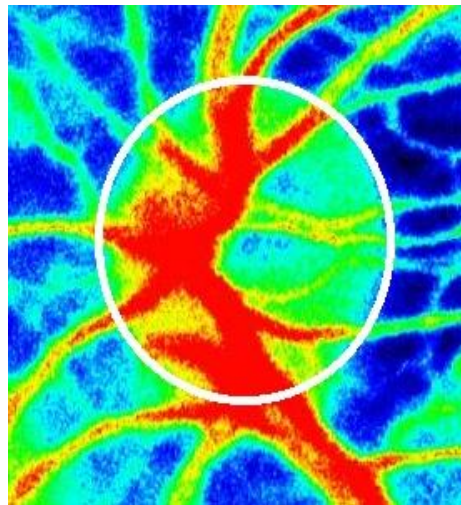


MBR-A: 21.8

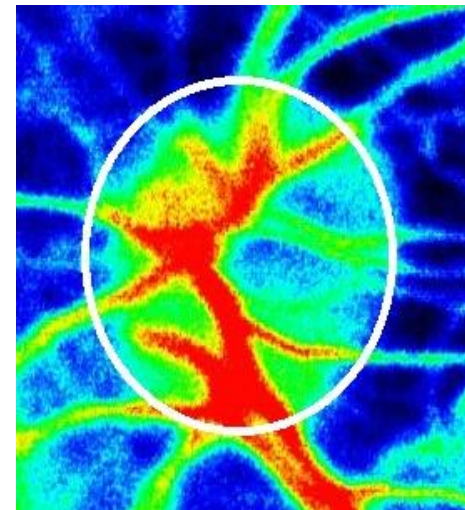


MBR-A: 21.3

1.0 mg/500 ml



MBR-A: 19.2



MBR-A: 14.7

Figure S1

