Contrast-to-noise ratio is a useful predictor of early displacement of large submacular hemorrhage by intravitreal SF_6 gas injection

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age-related macular degeneration; gas intravitreal injection; image analysis; optical coherence tomography; retinal macroaneurysm; submacular hemorrhage

Summary Statement:

We demonstrated that the contrast-to-noise ratio of submacular hemorrhage on optical coherence tomography images is a useful predictor for early displacement of large submacular hemorrhage after simple intravitreal SF_6 gas injection.

ABSTRACT

Purpose: To investigate predictors of early displacement of submacular hemorrhage (SMH) by simple intravitreal SF_6 gas injection.

Methods: This retrospective study included 16 eyes of 16 consecutive patients (age: 74.5 ± 7.7 years; 15 men) with large SMH treated with simple intravitreal SF_6 gas before inception of subretinal tissue plasminogen activator (tPA) injection at our institution. We graded SMH displacement at 1-week posttreatment as 0, 1, or 2. Central retinal thickness, central choroidal thickness, SMH height, SMH area, disease duration, use of anticoagulant or antiplatelet drugs, and contrast-to-noise ratio (CNR) of SMH on optical coherence tomography (OCT) images were recorded. Correlations between displacement grading and baseline parameter were analyzed.

Results: Univariable correlation analysis revealed association of the 1-week displacement grading with the CNR ($P = 0.004$, $r = -0.68$) and SMH height ($P = 0.03$, $r = -0.55$). The CNR was most strongly associated with 1-week displacement on multivariable correlation analysis ($P = 0.01$, $\beta = -0.60$).

Conclusions: Our findings showed that the CNR of SMH was a useful predictor of early displacement of large SMH after simple intravitreal SF_6 gas injection. When vitrectomy with subretinal injection of tPA is difficult in patients with large SMH, with low CNR on OCT, simple intravitreal SF_6 gas injection may be a treatment option.

INTRODUCTION

Large submacular hemorrhage (SMH) sometimes occurs in eyes with neovascular age-related macular degeneration (nAMD) and retinal macroaneurysm (RMA).[1] The visual prognosis in cases with large SMH is markedly poor in the absence of treatment.[2, 3] Thick SMH is one of the risk factors for visual loss.[4] Recently, intravitreal anti-vascular endothelial growth factor (VEGF) injection was shown to improve the visual prognosis of eyes with SMH with nAMD; however, the efficacy is limited, particularly in eyes with large SMH.[5] Experimental subretinal hemorrhage in rabbits resulted in irreversible retinal damage within 24 hours and almost complete absence of photoreceptor cells within 7 days.[6] However, another animal study showed the potential for improved retinal survival if the organized subretinal clot can be eliminated soon after its formation.[7]

Several treatments and treatment combinations for early displacement of SMH, including intravitreal gas injection, vitrectomy, and use of tissue plasminogen activator (tPA), have been reported.[8] Recent studies have shown that vitrectomy with subretinal tPA and air injection was effective for displacing SMHs.[9, 10] However, vitrectomy with subretinal tPA injection sometimes induces complications, including macular hole, vitreous hemorrhage, SMH recurrence, retinal pigment epithelium (RPE) tear, epiretinal membrane, and retinal detachment.[10-15] Additional treatments are necessary in these cases. On the other hand, a classic treatment of simple intravitreal gas injection without tPA is relatively safe and minimally invasive. However, it has been reported that SF_6 gas injection with tPA for SMH due to RMA results in a higher incidence of vitreous hemorrhage than that without tPA.[16] Another previous report showed that simple intravitreal gas injection without tPA could displace SMH in some cases.[17] Therefore, this treatment remains as an option if it were possible to predict good SMH displacement. Nevertheless, no such predictors have been identified to date.

The contrast-to-noise ratio (CNR) on clinical images is used to determine image quality not only in the field of radiology, but also in the field of ophthalmology.[18-20] CNR was applied as detectability indexes for objective evaluation of myopic choroidal neovascularization using optical coherence tomography (OCT) angiography images.[21] CNR is useful for objective evaluation of signal intensity in regions of interest. Since solid materials have high reflectivity in OCT images, CNR in OCT images should allow evaluation of qualitative SMH status, including its rigidity.

This study aimed to investigate predictors of the potential for early displacement of SMH by simple intravitreal SF_6 gas injection without the use of tPA, in order to identify cases in whom simple intravitreal gas injection may be considered, before resorting to vitrectomy with subretinal tPA injection.

METHODS

This retrospective study was approved by the ethics committee of Kyoto University Graduate School of Medicine (Kyoto, Japan). All study protocols adhered to the tenets of the Declaration of Helsinki. All study candidates provided written informed consent to participate in the study.

Participants

This study included the eyes of consecutive patients with large SMH who subsequently received simple SF_6 gas intravitreal injection at Kyoto University Hospital between April 2009 and May 2018. The period was after the timepoint when intravitreal ranibizumab injection became available at our institution and before the inception of vitrectomy with subretinal tPA injection at our institution. Therefore, we could select patients who received only simple intravitreal SF_6 gas injection for early displacement of large SMH during this period. The inclusion criteria for this study were the presence of SMH and subsequent treatment with simple intravitreal SF_6 gas injection. The exclusion criteria were the absence of analyzable OCT images and color fundus photographs at baseline and 1 week (within 2 weeks) after the therapy, as well as non-cooperation with data acquisition for various reasons, including dementia.

Before the gas injection, all eyes underwent a comprehensive ophthalmological examination, including autorefractometry, best-corrected visual acuity (BCVA) measurement using a Landolt chart, intraocular pressure measurement, axial length measurement by using partial coherence interferometry, indirect ophthalmoscopy, slit-lamp biomicroscopy, color fundus photography, spectral-domain OCT with enhanced-depth imaging and/or swept-source OCT, fundus fluorescein angiography, and fundus indocyanine green angiography. We obtained the patients' medical history, including the current use of anticoagulant or antiplatelet drugs and the onset of sudden central scotoma. We calculated duration from symptom onset to treatment.

We measured central retinal thickness (CRT), central choroidal thickness (CCT), and SMH height at the fovea on a horizontal B-scan OCT image (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany; or RS-3000 Advance, Nidek Corp., Gamagori, Japan) taken through the fovea, using the built-in OCT software. CRT was defined as the distance between the vitreoretinal surface and the outer border of the sensory retina. CCT was defined as the distance between the outer surface of Bruch's membrane and the chorioscleral interface. The SMH height at the fovea was defined as the distance between the outer border of the sensory retina and the inner border of the RPE. In cases where the CCT or SMH height was unmeasurable due to the SMH density, we measured them near the fovea. We also measured the SMH area on an infrared image obtained with the OCT device (Spectralis HRA+OCT, Heidelberg Engineering) within a 9 × 9-mm square, by referring to multiple OCT images. Furthermore, complications were investigated within 1 week after the injection.

Gas injection

Retinal specialists judged the necessity of intravitreal SF_6 gas injection for large SMH based on the findings from slit-lamp biomicroscopy, OCT, and color photography. First, we made a side-port at the limbus through which we drained the aqueous humor after povidone iodine sterilization. Then, intravitreal 100% SF_6 gas injection (0.3–0.6 mL) was performed at 3.5–4.0-mm posterior to the limbus. Additional aqueous humor drainage was performed as needed to adjust the intraocular pressure after gas injection. We instructed patients to remain in a prone position for at least 2–3 days after the injection.

Displacement grading

Two trained ophthalmologists (S.U. and S.Y.) independently performed grading of SMH displacement at 1 week after gas injection. The displacement grading was determined using color photographs and OCT images as follows: 0, almost no displacement; 1, mild displacement beyond the arcade; 2, good displacement outside of the fovea), referring to a previous study (Figure 1).[10] In cases with grading discrepancies, a third retinal specialist (M. Miyata) made the final judgement.

CNR calculation

To evaluate qualitative SMH status, we assessed the CNR using OCT horizontal B-scan images taken through the fovea. We set the small area of hemorrhage beneath the fovea as the foreground and the whole area of the vitreous cavity as the background (Figure 2). We calculated the CNR using open-source software (ImageJ, National Institutes of Health, Bethesda, MD) as follows in accordance with a previous report:[21]

$$\mathrm{CNR} = (f - b)/\sqrt{{\delta_f}^2 + {\delta_b}^2}$$

where f and b are the mean grey values of the foreground and background, respectively, and δf and δb are their standard deviations, respectively. A high CNR would indicate a solid SMH.

Statistical analysis

All data are presented as means ± standard deviations. For statistical analyses, all BCVA values were converted to logMAR units. In accordance with a previous report,[22] eyes with a BCVA of counting fingers, hand motion, and light perception, were arbitrarily assigned logMAR values of 2.6, 2.7, and 2.8, respectively. Univariable correlation analyses of the displacement grading at 1 week after treatment with the 1-week logMAR BCVA and other baseline parameters were assessed using Spearman's rank correlation coefficient. Multivariable correlation analyses were performed using displacement grading or 1-week logMAR BCVA as the dependent variable and baseline or treatment-associated parameters with *P*-values < 0.10 on Spearman's correlation test as independent variables. LogMAR BCVA was compared between baseline and 1 week after the gas injection by using the paired *t*-test. *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 27 software (IBM Corp., Armonk, NY, USA).

RESULTS

Twenty eyes of 20 patients met the inclusion criteria; however, 3 eyes were excluded because of missing 1-week OCT images, and 1 eye was excluded because the 1-week OCT image and color photograph could not be analyzed due to vitreous hemorrhage. Therefore, 16 eyes of 16 patients (age, 74.5 ± 7.7 years; 15 men, Table 1) were analyzed in this study. The cause of SMH was nAMD in all but 1 case, with RMA being the cause in the remaining case. The duration from onset to the gas injection was 20.6 ± 44.2 days. Only about one-third of patients used anticoagulant or antiplatelet drugs. Baseline CRT, CCT, and SMH height at the fovea were 186.3 ± 100.3 μm, 182.1 ± 95.7 μm, and 643.7 ± 363.5 μm, respectively. The SMH area within the 9 × 9-mm square was 33.10 ± 13.98 mm^2. The CNR of the SMH at baseline was 8.2 ± 3.8. The SMH displacement grading at 1 week after the gas injection was grade 0 in 2, grade 1 in 8, and grade 2 in 6 eyes. LogMAR BCVA had increased by 1 week after the gas injection (baseline, 0.66 [Snellen visual acuity ratio; 20/91] ± 0.61; 1 week, 1.09 [20/246] ± 0.90); however, the change was not significant ($P = 0.08$). No complications had occurred within 1 week after the injection except for 1 eye, which was excluded for analysis due to vitreous hemorrhage. There was no high myopia with AL > 26.50 mm or spherical equivalent refractive error < −6.00 D in cases without AL measurement.

Univariable correlation analysis revealed that the 1-week SMH displacement grading was significantly associated with CNR (*P* = 0.004, r = −0.68) and SMH height (*P* = 0.03, r = −0.55, Table 2). In multivariable correlation analysis, CNR was most strongly associated with the 1-week displacement grading (*P* = 0.01, β = −0.60). LogMAR BCVA at 1 week after the gas injection was significantly associated with lens status (*P* = 0.04, r = 0.46), SMH height (*P* = 0.007, r = 0.58), and the area of the SMH (*P* = 0.03, r = 0.68), and was marginally associated with the SMH displacement grading (*P* = 0.054, r = −0.49) on univariable analysis. However, on multivariable analysis, logMAR BCVA at 1 week after the injection showed no statistically significant association with any of the measured parameters.

DISCUSSION

As it would be useful to be able to predict whether SMH could be displaced by simple intravitreal gas injection, and as no quantitative evaluation of the qualitative SMH status has been established to date, we sought to identify parameters that may be able to predict early displacement of SMH by simple intravitreal SF_6 gas injection. Our findings suggested that the CNR of SMH on OCT images could be used to evaluate the qualitative SMH status quantitatively. The CNR was most strongly associated with displacement of SMH at 1 week after simple intravitreal SF_6 gas injection, without the use of tPA. Our findings also suggested that it is difficult to displace solid SMHs, but it is easy to displace soft SMH by simple gas injection, which is a plausible finding. The present study indicated that simple intravitreal SF_6 gas injection was a useful treatment option for early displacement of SMH in eyes with SMH with low CNR on OCT images.

Subretinal injection of tPA and/or air enables good early displacement of large SMH, even in cases with long disease duration.[9, 10, 13] However, there are some patients who are not willing to undergo surgery. Moreover, the surgery poses the risk of severe complications. It was previously reported that RPE tear occurred when tPA was injected into the sub-RPE, which implied that the procedure requires good technical skills and experience.[11] The conventional intravitreal gas injection does not require a special technique or experience, and it is minimally invasive. Since an animal study demonstrated that intravitreal tPA did not reach the subretinal clot,[23] and a comparison study showed similar displacement of the SMH after gas injections with and without intravitreal tPA,[24] we consider that intravitreal gas injection does not always need to be combined with intravitreal tPA. In the present study, a simple SF_6 gas injection without tPA was shown to be effective for early displacement of SMHs in cases with low CNR on OCT. This indicates that it is worth first attempting to use a simple SF_6 gas injection for such cases. If the SMH is not displaced sufficiently after a simple gas injection, vitrectomy with subretinal tPA injection can be performed, without increased difficulty, as an additional treatment because of the small amount of residual gas.

There were no significant correlations between the SMH displacement grading and baseline parameters, such as the duration from onset to treatment, use of anticoagulant or antiplatelet drugs, or the SMH area. The duration was not accurate because it was calculated based on patients' report. This is not a reliable parameter for predicting early displacement of the SMH. Furthermore, the effect of anticoagulant or antiplatelet drugs on SMH displacement was unclear and has not been reported previously to the best of our knowledge. The CNR can more directly reflect the SMH qualitative status than medication use. Interestingly, the CNR was not associated with duration from onset ($P = 0.65$, $r = -0.11$). Furthermore, SMH height was more strongly associated with SMH displacement than the SMH area. These OCT findings are important to predict the ease of SMH displacement by gas injection.

A previous report showed that the duration of SMH ≤ 14 days was associated with a better BCVA increase several months after treatment.[25] Another previous report showed that SMH height and diameter of SMH was associated with 3 months after treatment.[26] In the present study, the duration of the SMH was not associated with the 1-week logMAR BCVA, whereas SMH height and SMH area were significantly associated with this BCVA, and displacement grading was marginally significantly associated with logMAR BCVA at 1 week. Thus, BCVA immediately after treatment would be associated with these quantitative SMH parameters on OCT images.

We used SF_6 gas for intravitreal gas injection in the present study. C_3F_8 gas is another gas used for tamponade, which lasts approximately twice as long as SF_6 gas in the vitreous cavity; however, it may delay or compromise a patient's return to daily activities.[27] A comparison study of eyes with the macular hole showed that use of SF_6 gas resulted in a decreased incidence of cataract and ocular hypertension, with shorter tamponade duration, but with a similar macular hole closure rate.[28] To the best of our knowledge, there has been no previous report comparing effects of the two types of gas tamponade in eyes with SMH. However, it should be determined as soon as possible whether the effect of a simple gas injection on SMH displacement is sufficient, and whether an additional treatment of vitrectomy with subretinal tPA is necessary. Therefore, the use of longer-lasting gas would not be necessary in cases with SMH.

The present study had some limitations. First, the sample size was small. A further large-sample study is needed to validate our results. CNR of only a single eye with RMA was 4.79, which was relatively lower than the mean value (8.2 ± 3.8). The difference in CNR among SMH with different causes needs to be analyzed in a large-sample study. Second, we analyzed a small superficial region of the SMH in the CNR measurement. Transmission of OCT light is decreased by hyper-reflective materials, including SMH. Thus, the deep region of the SMH cannot be analyzed, in particular by spectral domain OCT. Although we did not use swept-source OCT in these patients during this study period, swept-source OCT may be more appropriate for analysis of qualitative SMH status. Third, the observation period was short. This study aimed to investigate predictors of early SMH displacement, because the necessity of vitrectomy with subretinal tPA as a rescue treatment after simple gas injection should be judged soon after gas injection. Fourth, this study design was retrospective. Retinal specialists individually selected intravitreal SF6 gas injection as the initial treatment, rather than anti-VEGF monotherapy because of large SMH. A previous comparison study showed that all treatment modalities improved BCVA in cases with small SMH (disc diameter ≥ 1 to < 4); however, surgery and gas injection were associated with better BCVA, achieving greater displacement than anti-VEGF monotherapy, in cases with large SMH (disc diameter >4).[29] Anti-VEGF monotherapy remains a treatment option for small SMH.

In conclusion, our findings showed that the CNR of SMH on an OCT image was a useful predictor for early displacement of large SMH after simple intravitreal SF_6 gas injection. When vitrectomy with subretinal injection of tPA is difficult in a patient with large SMH with low CNR on OCT, simple intravitreal SF_6 gas injection may be a treatment option.

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FIGURE LEGENDS

Figure 1. Representative images of good and poor displacement of submacular hemorrhage.

(A–D) Images of the left eye of a man in his 80s, with good submacular hemorrhage (SMH) displacement (grading of displacement, 2). Best-corrected visual acuity (BCVA) before gas injection was 0.4 (20/50). (A) A color fundus photograph taken before gas injection shows SMH involving the fovea. (B) An optical coherence tomography (OCT) horizontal scan image through the fovea before gas injection shows SMH. The contrast-to-noise ratio (CNR) was 3.75. (C) A color fundus photograph 1 week after gas injection shows good displacement of the SMH. (D) An OCT horizontal scan image through the fovea 1 week after gas injection shows a little subretinal fluid without hemorrhage.

(E–H) Images of the right eye of a man in his 70s with poor SMH displacement (grading of displacement, 0). BCVA before gas injection was 0.15 (20/133). (E) A color fundus photograph before gas injection showed SMH with partial organization. (F) An OCT horizontal scan image through the fovea before gas injection shows hyper-reflective SMH. The CNR was 11.28. (G) A color fundus photograph taken 1 week after gas injection shows no displacement of the SMH and progression of organization. (H) An OCT horizontal scan image through the fovea 1 week after gas injection shows advanced hyper-reflective SMH.

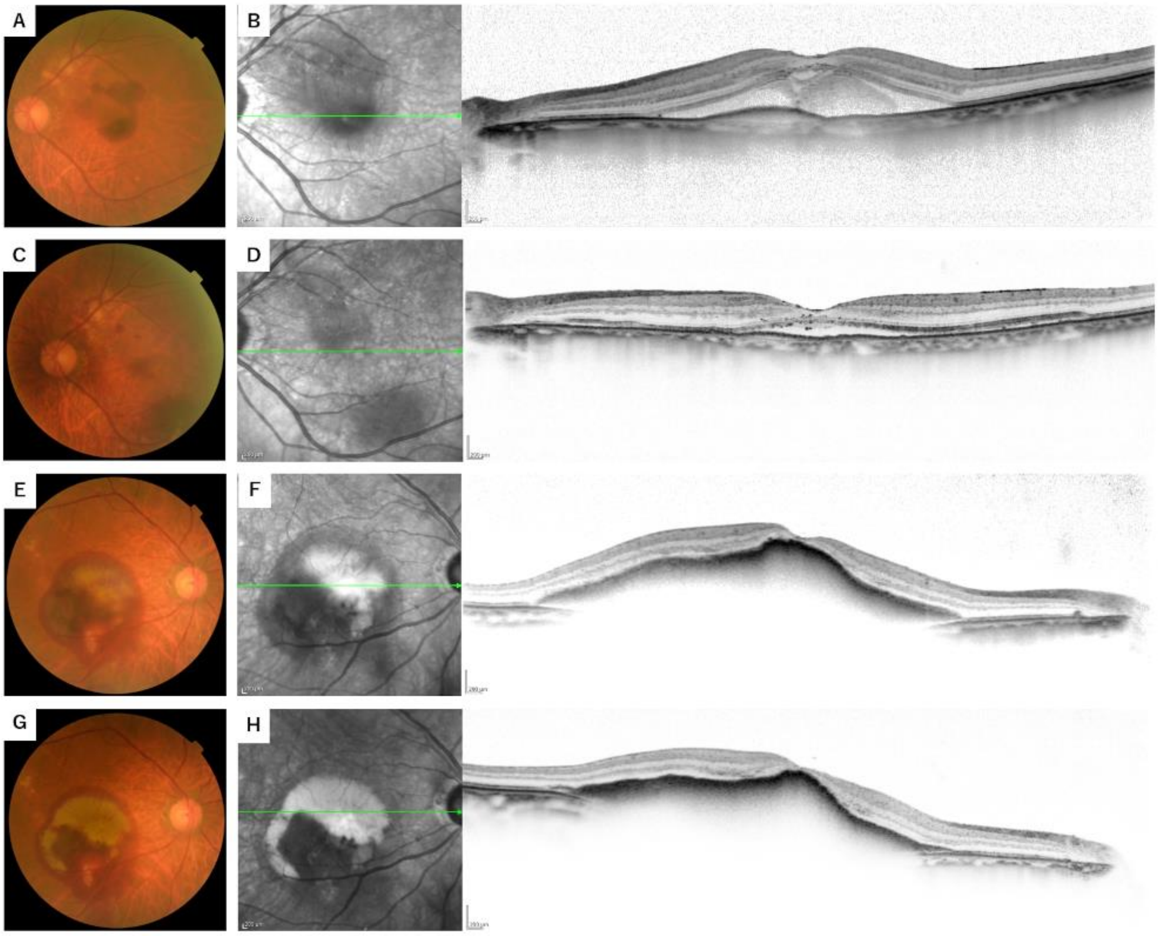

Figure 2. Measurement region of submacular hemorrhage and vitreous cavity for calculating contrast-to-noise ratio.

A representative image of an optical coherence tomography horizontal scan through the fovea. We set a small area of hemorrhage beneath the fovea (region within the red line) as the foreground and the whole area of the vitreous cavity (region within the green line) as the background.

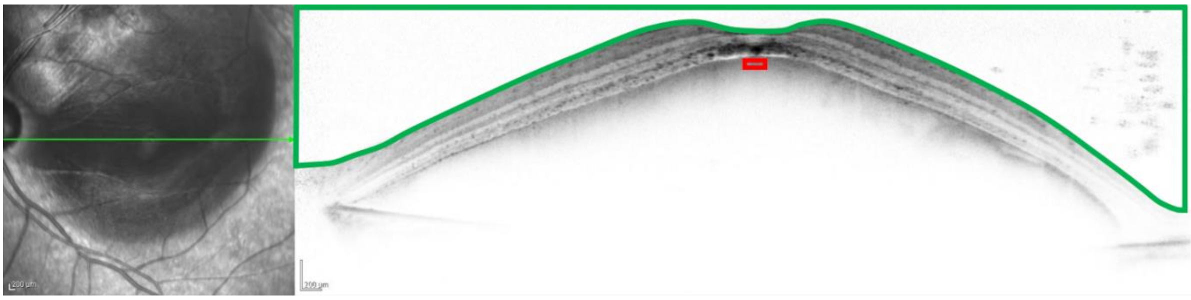

Table 1. Patients' characteristics

Eyes, n (patient, n)		16 (16)
Age at baseline, years (range)		74.5 ± 7.7 (56–83)
Male sex, n (%)		15 (94)
Disease, nAMD/RMA, n		15/1
Duration from onset to treatment, days		20.6 ± 44.2
Use of anticoagulant or antiplatelet drugs at baseline, n (%)		5 (31)
Pseudophakia at baseline, n		4 (25)
LogMAR BCVA	Baseline (Snellen)	0.66 (20/91) ± 0.61
	1 week after treatment (Snellen)	1.09 (20/246) ± 0.90
	Change	0.43 ± 0.93
Axial length [a], mm (range)		23.24 ± 0.98 (21.70–25.16)
CNR at baseline		8.2 ± 3.8
CRT (sensory retina) at baseline, μm		186.3 ± 100.3
CCT at baseline, μm		182.1 ± 95.7
SMH height at baseline, μm		643.7 ± 363.5
SMH area within a 9 mm × 9-mm square at baseline, mm^2		33.10 ± 13.98
Displacement of grading at 1 week after treatment, 0/1/2, n		2/8/6

Data are presented as means ± standard deviations where applicable.

nAMD = neovascular age-related macular degeneration; RMA = retinal macroaneurysm; logMAR BCVA = logarithm of the minimal angle of resolution best-corrected visual acuity; CNR = contrast-to-noise ratio; CRT = central retinal thickness; SMH = submacular hemorrhage; CCT = central choroidal thickness

Displacement grading at 1 week after treatment: 0, almost no displacement; 1, displacement beyond the arcade but residual at the fovea; 2, displacement outside of the fovea

[a] The data for axial length were not available for 4 eyes.

Table 2. Correlation between Baseline or Treatment-Associated Parameters and the Grading of Displacement or 1-week LogMAR BCVA

	Grading of Displacement at 1 week after Treatment				LogMAR BCVA at 1 week after Treatment			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	P	**r**	***P***	**β**	***P***	**r**	***P***	**β**
Age at baseline	0.84	0.06	–	–	0.61	−0.12	–	–
Sex (1, male; 2, female)	0.25	0.31	–	–	0.93	0.02	–	–
Duration from onset to treatment	0.31	0.27	–	–	0.46	−0.18	–	–
Use of anticoagulant or antiplatelet drugs at baseline (0, none; 1, use)	0.47	0.11	–	–	0.91	0.03	–	–
Lens status at baseline (1, phakia; 2, pseudophakia)	0.44	−0.21	–	–	0.04*	0.46	0.40	0.35
LogMAR BCVA at baseline	0.47	−0.20	–	–	0.26	0.26	–	–
Axial length [a]	0.91	0.13	–	–	0.13	0.46	–	–
CNR	0.004*	−0.68	0.01*	−0.60	0.37	0.21	–	–
CRT (sensory retina)	0.24	0.31	–	–	0.63	0.12	–	–
CCT	0.50	0.18	–	–	0.43	0.19	–	–
SMH height	0.03*	−0.55	0.17	−0.29	0.007*	0.58	0.64	0.20
SMH area within a 9 × 9-mm square	0.58	−0.15	–	–	0.001*	0.68	0.75	0.14
Grading of displacement of SMH at 1 week after treatment	–	–	–	–	0.054	−0.49	0.34	−0.33

nAMD = neovascular age-related macular degeneration; RMA = retinal macroaneurysm; logMAR BCVA = logarithm of the minimal angle of resolution best-corrected visual acuity; CNR = contrast-to-noise ratio; CRT = central retinal thickness; SMH = subretinal hemorrhage; CCT = central choroidal thickness

Grading of displacement of SRH at 1 week after treatment: 0, almost no displacement; 1, displacement beyond the arcade but residual at the fovea; 2, displacement outside of the fovea

[a] The data for axial length were not available for 4 eyes.

* Statistically significant (*P* < 0.05)