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RETINAL DISORDERS

Selective retina therapy with automatic real-time feedback-controlled dosimetry for chronic central serous chorioretinopathy in Korean patients

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Abstract
Purpose To evaluate the safety and efficacy of selective retina therapy (SRT) with real-time feedback-controlled dosimetry (RFD) in the treatment of chronic central serous chorioretinopathy (CSC).
Methods In this retrospective case series study, 50 eyes of 49 patients with chronic CSC demonstrating focal or diffuse foveal leakages on fundus fluorescein angiography (FFA) were included. Following evaluation of test spots at temporal arcades, SRT (wavelength 527 nm, pulse repetition rate 100 Hz, pulse energy ramp with maximal 15 pulses) with retinal spot diameter of 200 μm was applied to the areas of each leakage observed on fluorescein angiography. Changes in mean best corrected visual acuity (BCVA), maximum macular thickness (MMT), subretinal fluid (SRF) height, and subfoveal choroidal thickness (SCT) were evaluated at 1, 2 and 3 months after treatment. RFD was used for adjusting the pulse energy. Eyes received a mean of 21.1 ± 18.1 treatment spots with a range of energies between 50uJ and 200uJ per pulse.
Results Subretinal fluid (SRF) was completely resolved in 74% (37/50 eyes) at month 3. Mean BCVA (LogMAR) was improved from 0.44 ± 0.29 at baseline to 0.37 ± 0.32 at month 3 ($p = 0.001$). MMT was decreased from 335.0 ± 99.8 μm at baseline to 236.4 ± 66.4 μm after 3 months ($p < 0.001$). SRF height was decreased from 168.0 ± 77.3 μm at baseline to 29.0 ± 57.3 μm after 3 months ($p < 0.001$). However, the changes in SCT were not statistically significant ($p = 0.48$).
Conclusions SRT treatment with RFD showed favorable visual and anatomical outcomes in patients with chronic CSC.

Keywords Selective retina therapy · Chronic central serous chorioretinopathy · Reflectometry · Optoacoustic dosimetry · Real-time feedback-controlled dosimetry

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Introduction

Central serous chorioretinopathy (CSC) is a disease characterized by an idiopathic serous retinal detachment at the macula with or without concomitant pigment epithelial detachment (PED) [1, 2]. Diagnostic studies have shown increased choroidal thickness and extensive hyperdynamic and hyperpermeable choroidal circulation with localized areas of nonperfusion [3, 4]. Dysfunction of the RPE plays a significant role in the development of subretinal fluid (SRF) and PED [5, 6].

The incidence of CSC is the highest in young and middle-aged men, and often, acute cases are self-limiting and known to resolve with good visual recovery within 1–4 months following a period of observation in the absence of any treatment [2, 7]. Up to 50% of eyes can experience recurrence, leading to decreased visual acuity and contrast sensitivity or even permanent visual impairment in the areas of SRF [8–10]. Thus, treatment intervention was often required to promote visual recovery or

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prevent further vision loss in CSC patients who showed SRF more than 3 months [9, 10].

While there is no standard treatment for CSC, several treatment methods with variable risks and outcomes were suggested such as conventional focal laser at the site of presumed RPE decompensation, photodynamic therapy (PDT) and intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors. Each of these treatment options has the potential to cause irreversible damage to the retina, choroid or RPE, or systemic side effects [11–14]. Conventional laser treatment has been shown to promote resolution of the serous detachment, but places the patient at risk of central or paracentral scotoma and choroidal neovascularization [15, 16].

Unlike conventional laser, treatment spots of SRT are not visible as gray or white lesions during irradiation because only RPE cells are selectively damaged by SRT without damage to the neural retina, adjacent photoreceptors or the choroid [17]. Moreover, different from a subthreshold micropulse laser (SMPL) which does not generate RPE damage, SRT spots can be detected as a hyperfluorescence on fundus fluorescein angiography (FFA) because of RPE damage. SRT induces RPE rejuvenation by stimulating RPE cell migration and proliferation into irradiated areas to improve metabolism at the SRT-treated region [17]. The delivered microsecond pulses (1.7 μs) are primarily absorbed by intracellular melanosomes of RPE cells and can selectively damage the cells by microvaporization. As the temperature increases, the formation of short-living microbubbles at the melanosomes results in significant and momentary increase in the cell volume which selectively disrupts the RPE cells [17]. As the microbubbles are indicative of the RPE damage, two methods to detect the bubbles in real time have been developed: the optoacoustics approach makes use of the ultrasonic pressure waves generated by bubble formation, which can be detected with a transducer embedded in the contact lens, and are evaluated with a so-called optoacoustic feedback value (OAV) [18]. The reflectometric dosimetry system detects modulations in the laser light backscattered from the retina/RPE during bubble lifetime, which is detected within the laser slit lamp and evaluated as optical feedback value (RV) [19, 20]. The detection rates of RPE damage by the two dosimetry systems were clinically validated in previous studies [21–23]. In addition, an SRT laser system equipped with the algorithm for real-time feedback-controlled dosimetry (RFD) using both detection system was optimized by analyzing the feedback signals from previous studies [22, 23]. Our purpose is to investigate the safety and efficacy of SRT with RFD for the treatment of chronic CSC.

Methods

We retrospectively analyzed and reviewed the medical records of 67 patients who had undergone SRT with RFD for the treatment of chronic CSC during the period from January 2015 to July 2016. This study adhered to the principles of the Declaration of Helsinki and data collection was compliant with and approved by the Institutional Review Board of Yeouido St. Mary's Hospital of the Catholic University of Korea. Written informed consent was obtained from all patients in this study after having been told about possible risks and benefits of SRT treatment.

Our inclusion criteria were as follows: (1) presence of an SRF involving the fovea in the optical coherence tomography (OCT) images for a period of 3 months or longer; (2) presence of focal or diffuse leakages on FFA caused by CSC but not by a choroidal neovascularization or other diseases; (3) availability of 3 months of medical records after SRT treatment. Eyes with other retinal diseases, including age-related macular degeneration, polypoidal choroidal vasculopathy (PCV), pathologic myopia and tilted disc syndrome were excluded. Eyes that received previous conventional laser photocoagulation or PDT were also excluded. However, eyes that had received prior treatment with intravitreal bevacizumab injection for CSC were included, if the previous treatment was performed twelve or more weeks prior to SRT. Fifty eyes of 49 patients were finally included according to the inclusion and exclusion criteria.

For the evaluation of SRT treatment with RFD, all patients received a complete ophthalmologic examination including slit-lamp evaluation and best-corrected visual acuity (BCVA) at baseline, 1, 2 and 3 months after SRT treatment. Visual acuity was estimated with a standard Snellen chart and converted to the logarithm of the minimum angle of resolution (logMAR). Imaging studies were conducted in all patients after appropriate dilatation and included color fundus photographs using a Canon fundus camera (CF-60UVi, Canon Inc., Japan), FFA, indocyanine green angiography (ICG), and fundus autofluorescence (FAF; HRA2, Heidelberg Engineering, Dosenheim, Germany). Fundus photos and FAF were taken at each monthly visit. FFA was performed at baseline and repeated for retreatment if SRF sustained or increased during follow-up. Spectral domain OCT (Cirrus, Carl Zeiss Meditec, Dublin, CA, USA) was used to measure maximum macular thickness (MMT) and detect the presence of SRF by macular scan in a 6×6 mm^2 area, using the macular cube 512×128 scan protocol at each monthly visit. Subfoveal choroidal thickness (SCT) was measured by enhanced depth imaging (EDI) mode as previously described [22].

SRT procedure

A single surgeon (YJ Roh) performed all SRT using the SRT laser system with RFD (R:GEN, Lutronic, Goyang-si, South Korea), Nd:YLF-laser at a wavelength of 527 nm, 15 micropulses per spot and single micropulse duration of 1.7 μs with a pulse repetition rate of 100 Hz. R:GEN, which

is devised with RFD, received CE marking from the EU Notified Body, approved by the Ministry of Food and Drug Safety in South Korea (MFDS) for CSC and diabetic macular edema. The device is commercially available in South Korea. A laser slit lamp and a specifically designed contact lens with an inserted ultrasonic transducer (Lutronic, Goyang-si, South Korea) was used to apply a retinal spot diameter of 200 μm. SRT spots were applied to the sites of foveal leakages or circumferentially around areas of PED, rather than confluent treatment over the area of PED as previously described [22]. Given that the SRT spots are invisible during irradiation, an effort in maintaining a one-spot space between the SRT spots was made. If SRF was observed by OCT at month 2, retreatment was performed with the same density of treatment spots. However, if SRF height at month 2 was decreased over 90% compared to that of baseline, retreatment was not performed.

SRT with real-time feedback-controlled dosimetry

Prior to SRT treatment, an exposure evaluation test was performed in the arcades in order to estimate the individually optimal single micropulse energy and obtain a margin of safety. The desired adequate SRT was obtained when hyperfluorescence on the test spot (angiographic threshold) was observed in the absence of ophthalmoscopic visibility (ophthalmoscopic threshold) as previously described [12, 13]. Although all patients received FFA exam for test spot evaluation before SRT treatment spots irradiation, FFA was not used for treatment spot evaluation because angiographic findings of treatment spots was usually obscured by SRF and diffuse leakages from RPE lesions in CSC patients. Five to 18 preliminary test spots were applied at the superior or inferior temporal arcade vessels by using RFD (from 50 to 240 μJ). The pulse energy of the test spots was set to low pulse energy initially and was increased with each test spot. (Supplementary S1) FFA was performed 1 h after test spot irradiation to determine the adequate range of SRT spots by evaluating the visibility of the laser spot, deciding the required pulse energy for treatment. The minimum pulse energy, resulting in visible leakage at the test spot, which was observed as hyperfluorescence on FFA, was chosen for the treatment value for the 15th micropulse energy for the specific eye.

For SRT treatment, a burst of maximum of 15 micropulses of laser with linearly increasing energy (increment of 3.57% for the following micropulse) was emitted in a stepwise fashion for every individual spot. The first of the 15 micropulses was programmed to be 50% of the energy of the 15th (the last) micropulse, which may or may not be reached depending on the feedback signal from RFD. The pulse energy was escalated in equal steps with every micropulse. During irradiation, when SRT irradiation reached the therapeutic threshold at which microbubbles occur in the RPE, the laser irradiation was terminated automatically by RFD and no further micropulses were applied. Therefore, the applied pulse energy varies at each spot because the ramping micropulse stops at different place automatically by RFD (Fig. 1).

The dosimetry algorithms version 1.0 (v1.0) were optimized based on the previous studies [19, 23]. The therapeutic thresholds of optoacoustic and reflectometry dosimetry were set to 2.0 and 6.0 arbitrary units (A.U.), respectively. The algorithm v1.0-based RFD (RFD-v1.0) control system automatically ceased irradiation immediately for each individual spot when either an OAV > 2.0 or a RV > 6.0 was obtained. The algorithm for RFD was designed to cause an automatic stop in between the 1st and 15th micropulse; then, the software program was refined to avoid under- or overtreatment. Based on this algorithm of RFD-v1.0, if the automatic stop occurred between the 4th and 12th micropulses due to detecting microbubbles from RPE, it was defined as an adequate SRT spot (sideways arrow). If the automatic stop did not occur or occurred after the 12th micropulse, dosimetry showed a signal demonstrating an alarm for undertreatment (upward arrow). Moreover, the upward arrow may indicate either no RPE damage due to no automatic stop or RPE damage due to automatic stop after the 12th micropulse. Therefore, in case of an upward arrow, RPE damage may or may not be visible on FFA upon the placement of the automatic stop. As safety measures, if an automatic stop occurred before the 4th micropulse, dosimetry showed a signal representing an alarm for overtreatment (downward arrow; Fig. 1). According to

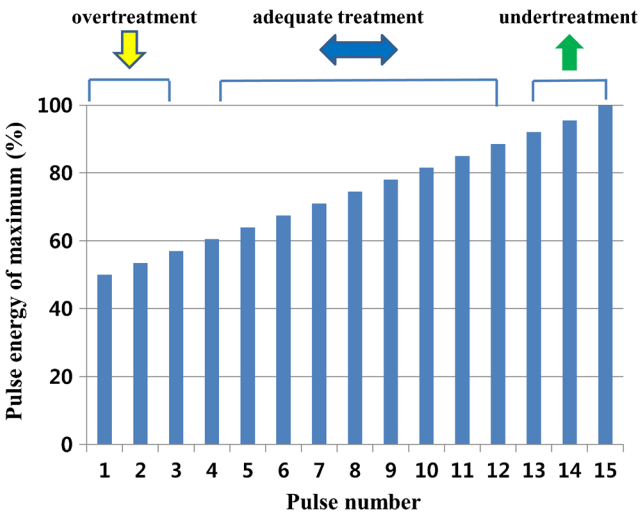

Fig. 1 The laser pulse energy was emitted in a stepwise fashion (increment of 3.57% for the following micropulse) for every individual spot. Based on the placement of the automatic stop by the algorithm of real-time feedback dosimetry (RFD-v1.0), adequate pulse energy (sideways arrow) was defined when the automatic stop occurs between 4th and 12th micropulse. The upward arrow indicates alarm for undertreatment if the automatic stop occurs after the 12th micropulse. The downward arrow indicates alarm for overtreatment if the automatic stop occurs before 4th micropulse

these signals from dosimetry, each pulse energy of the 15th micropulse, the maximal possible micropulse of each SRT spots, was adjusted by the surgeon based on the response from the previous irradiation. For instance, every time a downward arrow appeared as a response, the amount of the 15th micropulse was decreased by 10 μJ, and for an upward arrow, the amount of energy was increased by 10 μJ.

While laser energy was automatically adjusted according to the signal from dosimetry, the margin of safety was maintained regardless of the occurrence of an automatic stop because the therapeutic range of treatment spots was always within the adequate range of laser energies referenced from the test spots.

The correlation between real-time feedback signal value from the test spots and FFA visibility was analyzed for measuring the accuracy of RFD-v1.0. We defined adequate SRT spots as invisible on ophthalmoscopy but visible on FFA. They are related to the number of spots above the therapeutic threshold (OAV: 2.0 A.U. or RV 6.0A.U.), and, thus, the detection rate of RPE damage by RFD-v1.0 would be the ratio of the number of adequate SRT spots above the therapeutic threshold over the number of all FFA-visible spots.

Snellen visual acuity was converted to logMAR (the logarithm of the minimum angle of resolution) for statistical analysis. Statistical analyses were calculated using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). To analyze the change in BCVA, MMT, SRF height and SCT at baseline and at each month up to 3-month follow-up, the paired *t* test was used. A P value <0.05 was considered statistically significant.

Results

Overall, 50 eyes of 49 consecutive patients (39 men and 10 women) who had undergone SRT for the treatment of chronic CSC were included in this study. Patients were between 39 and 67 years of age (mean: 51.4 ± 8.7 years). All patients were followed for a period of at least 3 months. Mean duration of SRF was 9.6 ± 5.8 months (range 4 to 22 months). All patients showed focal or diffuse foveal leakages by FFA. Preoperative clinical characteristics of 49 patients are shown in Table 1. Nineteen eyes (38%) had received prior intravitreal injection of anti-VEGF agents (Table 1).

SRT treatment was performed in a ramp mode with automatic and immediate laser pulse cessation in case of microbubble formation indicating RPE damage was detected by optoacoustic or reflectometric feedback (Fig. 2). The mean pretreatment BCVA was improved from 0.44 ± 0.29 logMAR to 0.37 ± 0.32 logMAR at month 3 after SRT ($P = 0.001$). The mean MMT was decreased from 335.0 ± 99.8 μm at baseline to 236.4 ± 66.4 μm at month 3 ($P < 0.001$). The mean SRF height was decreased from 168.0 ± 77.3 μm at baseline to 29.0 ± 57.3 μm at month 3 ($P < 0.001$). SRF was completely resolved in 74.0% (37/50 eyes) after 3 months, as detected by OCT (Table 2).

After 3 months, 13 eyes showed remaining SRF on OCT. Six of 13 eyes showed a complete resolution of SRT at month 2; recurrence was observed at month 3. The other six eyes showed a decrease of SRF at month 3 compared to SRF at baseline. Only one eye showed no response with SRT.

The mean number of treatment spots applied was 21.1 ± 18.1 after test spots. The range of maximal pulse energy used for each patient was set from 50 μJ to 200 μJ (mean maximal pulse energy: 116.3 ± 27.7 μJ). However, the algorithmically determined mean pulse energy was 89.7 ± 21.3 μJ because automatic stops lowered the amount of irradiated pulse energy.

By evaluating the signals from both dosimetries, 973 of 1053 (92.4%) SRT treatment spots showed a sideways arrow indicating adequate automatic stoppage by RFD. 73 of 1053 (7.1%) SRT spots resulted in an upward arrow by RFD. This situation commonly occurs if the treatment area is changed from the test spot area due to SRF. Although 5 of 1053 (0.4%) treatment spots showed a downward arrow (alarm for overtreatment) by RFD, no visible SRT spots were observed. This observation was found when SRT was irradiated at the margin of SRF.

Eighteen eyes (36.0%) met the retreatment criteria, and additional SRT was performed at month 2. The mean number of retreatment spots was 23.7 ± 17.8. Although the irradiation was applied on the same leakage area for the retreatment, the laser pulse energy was different from the first treatment since the placement of an automatic stop by the signals from RFD was varied at each spot. The algorithmically determined mean pulse energy for retreatment was 98.8 ± 24.2 μJ.

After analyzing 157 of 218 test spots, RFD-v1.0 demonstrated 95.7% of detection rate at the therapeutic threshold (Fig. 3). Other 61 spots were excluded for analysis because of several uninterpretable factors such as blurred images of SRT spots on FFA, defocusing error, and incomplete press on the foot pedal.

All the SRT spots applied in this study were undetectable by color fundus photos during 3 months of follow-up. A transient increase in autofluorescence was noted after SRT; however, these increased patterns had faded or disappeared over the 3 months of follow-up (Fig. 4).

No SRT treatment-related complications or adverse effects were noted in this study.

Discussion

SRT has previously been studied as a treatment for acute and chronic CSC with good visual and structural outcomes resulting in absorption of SRF [21, 24–27]. Recently, we and Yasui et al. reported two clinical studies separately which

Table 1 Baseline demographics and clinical findings of 50 eyes of 49 patients with chronic central serous chorioretinopathy (CSC)

Patients characteristics	Values
Number of patients (eyes)	49 (50)
Age in years, mean ± SD	51.4 ± 8.7
Gender, N (%)	Male 39 (79.6%) / female 10 (20.4%)
Bilaterality, N (%)	Male 1 (2%)
Mean duration of SRF in months, mean ± SD (range)	9.6 ± 5.8 (4–22)
Previous treatments	
Patients who received intravitreal bevacizumab injection, N (%)	19 (38%)
Type of leakages	
Focal, N (%)	23 (46%)
Diffuse, N (%)	27 (54%)
Baseline BCVA (logMAR), mean ± SD	0.44 ± 0.29
Baseline maximum macular thickness (μm), mean ± SD	335.0 ± 99.8
Baseline maximum SRF height (μm), mean ± SD	168.0 ± 77.3

SD, standard deviation; OCT, optical coherence tomography; BCVA, best-corrected visual acuity; logMAR, logarithm of minimal angle of resolution; SRF, subretinal fluid

showed the safety of SRT by demonstrating no scotomatous change on retinal sensitivity at SRT-treated regions [23, 28]. From our knowledge, our study includes the largest case series of CSC patients who received SRT with RFD. There was a significant improvement in BCVA 3 months after treatment ($P = 0.001$), and both SRF and MMT were markedly decreased at month 3 ($P < 0.001$) in this study. In addition, both SRF and MMT were decreased significantly and continually at each month starting from the first month after the initial SRT treatment, suggesting that the SRT treatment was effective (Table 2). Compared with the number of treatment spots (from 3 to 10) in previous study [22], more SRT spots (mean number of treatment spots: 21.1 ± 18.0) were needed to cover the whole leakage areas because 27 eyes (54%) of our patients showed diffuse leakage patterns on FFA.

Retreatment seems to be effective in consideration of the complete resolution observed by month 3 in 11 of the 18 eyes which had retreatment at month 2 (Figs. 5, 6). Including the 6

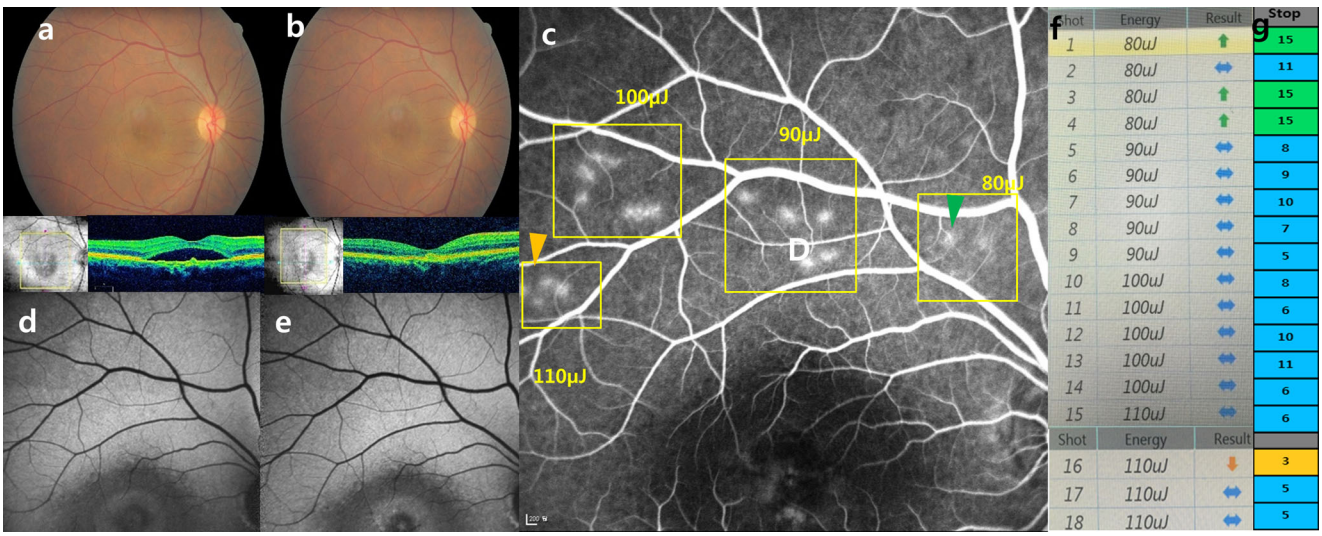

Fig. 2 Representation of real-time feedback-controlled dosimetry (RFD) during selective retina therapy (SRT) procedure. (a) Initial presentation with subretinal fluid (SRF) on OCT. (b) No visible SRT spot and SRF on fundus photography 3 months after SRT. (c) Eighteen test spots (yellow boxes) were shown on FFA 1 h after SRT irradiation. No visible test spot on fundus autofluorescence 1 month (d) and 3 months (e) after SRT treatment. (f) Screen image of signal from RFD. Three of four with 80-μJ test spots (shot No.1–4) displayed upward arrows due to an automatic stop at the 15th micropulse, indicating alarm for undertreatment. These three spots resulted in almost invisible leakage compared to the evident leakage from shot no. 2 (green arrowhead). Test shot no.16 showed a downward arrow (orange arrowhead) due to an automatic stop at the 3rd micropulse indicating alarm for overtreatment. The same amount of pulse energy, such as 80 μJ and 110 μJ, may yield different arrows due to the automatic stop occurring at different placement of the micropulse by RFD for each irradiated spot. The energy range of 25 treatment spots was between 90 μJ and 110 μJ for this patient. (g) SRT device records the placement of each automatic stop, and the column shows extracted data from the record

Table 2 Best-corrected visual acuity (BCVA), maximum macular thickness (MMT) and subretinal fluid (SRF) height of patients at pre-treatment and at 1-,2- and 3-months follow-up

	BCVA (logMAR)				Maximum macular thickness (μm)				Subretinal fluid height (μm)			
	Pre	1 month	2 months	3 months	Pre	1 month	2 months	3 months	Pre	1 month	2 months	3 months
Mean	0.44	0.42	0.39	0.37	335.0	261.2	240.6	236.4	168.0	73.4	38.9	29.0
Standard deviation	0.29	0.31	0.32	0.32	99.8	70.3	60.5	66.4	77.3	67.3	57.9	57.3
P value		0.13	0.010*	0.001*		<0.001*	<0.001*	<0.001*		<0.001*	<0.001*	<0.001*

logMAR, logarithm of minimal angle of resolution

*$P < 0.05$

eyes which recurred 3 months after SRT treatment but showed no SRF at month 2, 43 eyes (86%) of our patients experienced complete resolution of SRF at least once within 3 months of follow-up. Only one eye from retreatment did not show any decrease of SRF 3 months after SRT treatment. Similar to our former results, SRT showed no influence on the change of SCT. Therefore, we speculate that SRT treatment might be related with RPE rejuvenation rather than the choroidal hyperpermeability [22].

Prior SRT studies used a range of treatment of pulse energies between 100 and 350 μJ for Caucasians compared to 65–90 μJ for Asian patients [25–27]. Although the racial variances of melanin pigment density in RPE are not well known, we suspect that large amounts of melanin pigment in the RPE in Asian eyes is responsible for a lower microbubble formation threshold. Highly pigmented eyes may need careful consideration for the susceptibility to retinal damage. Therefore, FFA for test spots is mandatory before SRT to identify the therapeutic range of an adequate SRT spot. RFD techniques may assist the ophthalmologists to apply the appropriate energy level and maintain safety regardless of intra- and interpersonal melanin differences without performing the FFA procedure.

Recently, we reported that SRT showed a safe and effective modality for treating CSC patients by adjusting the laser pulse energy strictly based on the fluorescein angiographic finding of test spots [22].

In the previous study, when we chose the minimum pulse energy among FFA-visible spots after evaluating SRT test spots, undertreatment occurred occasionally because of SRF. Therefore, RFD which provides signals for an instant adjustment in the pulse energy seems beneficial for avoiding undertreatment.

The current study is the first to analyze RFD in patients with CSC as the primary method of dosimetry. As soon as undertreatment is indicated, the maximum pulse energy is increased instantly until the signal reached an adequate therapeutic threshold by the surgeon. RFD supports the clinician with real-time feedback of treatment by reacting to the development of transient microbubbles, which are produced by the application of SRT when the desired mechanical disruption of RPE cells occurs. Because SRT with RFD did not induce visible changes of SRT spots ophthalmoscopically, we speculate that the automatic stop provided enough of a safety margin by lowering the irradiated pulse energy. Therefore, the automatic stop by RFD was useful to not only prevent

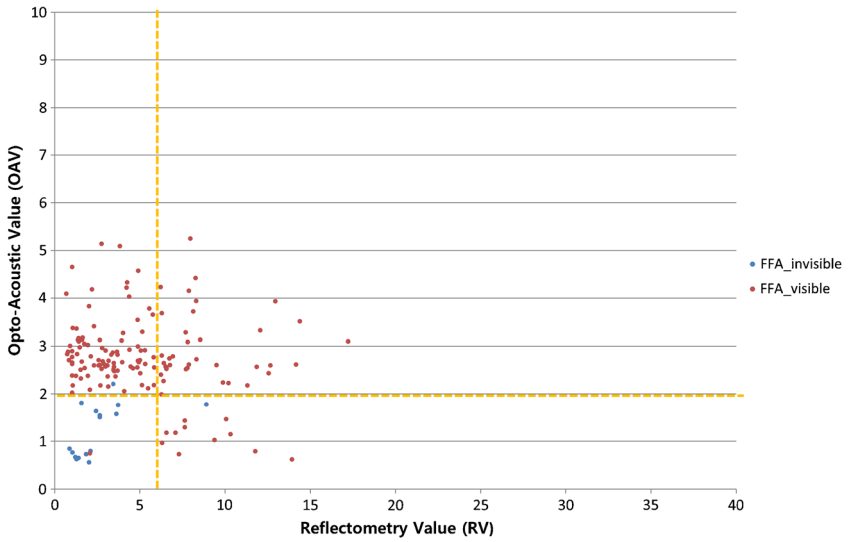

Fig. 3 Scatter plot of optoacoustic value (OAV) and reflectometry value (RV) in selective retina therapy (SRT) test spots according to the visibility of SRT spots on fundus fluorescein angiography(FFA). The ratio of the number of adequate SRT spots above the therapeutic threshold (OAV:2.0 A.U. or RV:6.0 A.U.) and the number of all FFA-visible spots (red circles) indicates the detection rate of RPE damage by real-time feedback-controlled dosimetry (RFD-v1.0). The detection rate of RFD-v1.0 was 95.7%

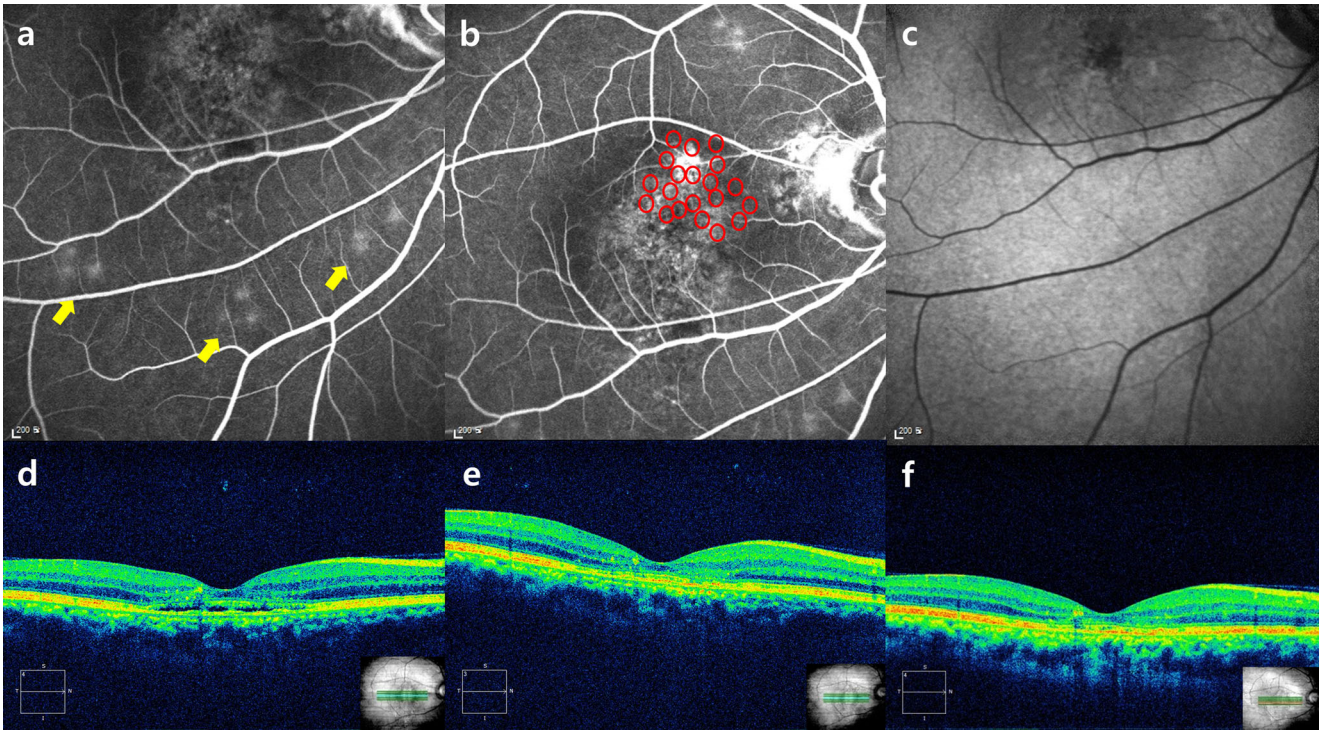

Fig. 4 Case 5. A 55-year-old man presented with a 1-year history of blurred vision in the right eye. (a) Multiple diffuse leaking points at the macula and hyperfluorescence at nine test spots (yellow arrow) on fundus fluorecein angiography (FFA) were observed after irradiating test spots. (b) Selective retina therapy (SRT) treatment (26 spots) was applied with a grid pattern at the diffuse leaking area on FFA. (c) Hyperautofluorescence at test spots on fundus autofluorescence disappeared after 3 months. (d) Subretinal fluid (SRF) was observed on optical coherence tomography (OCT) at initial presentation. (e) SRF was completely resolved 1 month after SRT. (f) Complete resolution of SRF was shown on OCT 3 months after treatment

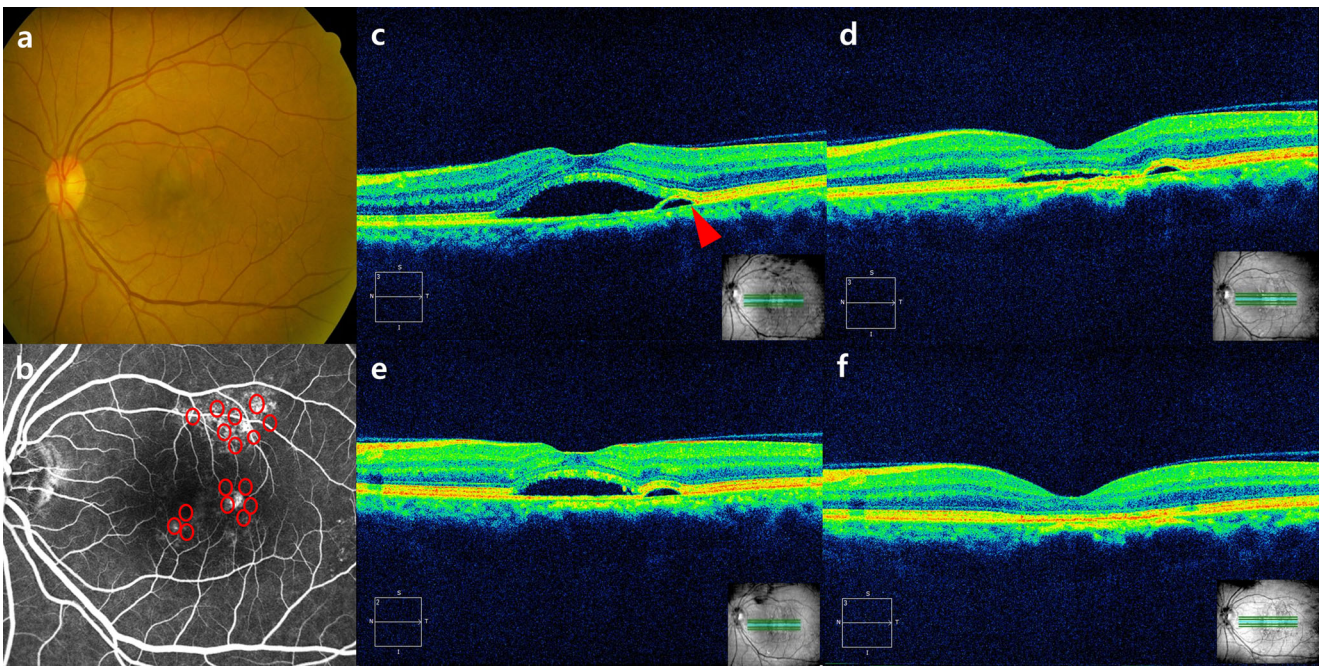

Fig. 5 Case 15. A 55-year-old man presented with a 6-month history of subretinal fluid (SRF) in the left eye. His left best-corrected visual acuity (BCVA) was 20/32. Selective retina therapy (SRT) was irradiated at the diffuse leaking area on FA and surrounding the pigment epithelial detachment (PED). (a) Initial color fundus photography. (b) Sixteen SRT spots (red circles) were applied at multiple leaking points on FA. (c) Subretinal fluid (SRF) with PED (red arrow head) on optical coherence tomography (OCT) was observed at initial presentation. (d) SRF was markedly decreased at 1 month after SRT. (e) A 2nd SRT treatment was performed because SRF was observed 2 months after SRT. (f) Complete resolution of SRF and PED was shown on OCT 3 months after SRT

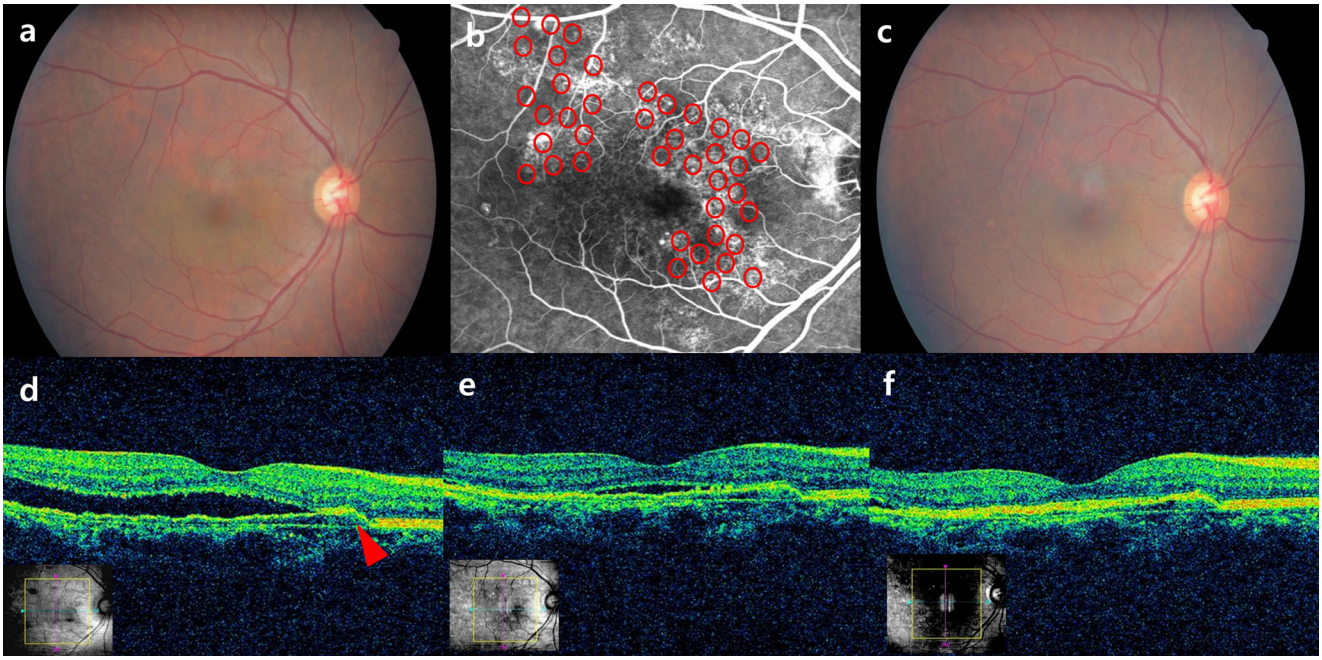

Fig. 6 Case 20. A 57-year-old woman presented with a 6-month history of subretinal fluid (SRF) in the right eye. Her right best-corrected visual acuity (BCVA) was 20/50. Selective retina therapy (SRT) was irradiated at the diffuse leaking area on fundus fluorescein angiography (FFA). (a) Initial color fundus photography. (b) Forty SRT spots (red circles) were applied at multiple leaking points on FFA. (c) No SRT spots were observed at 3 months after SRT. (d) SRF with flat pigment epithelial detachment (PED; red arrow head) was observed at baseline OCT. (e) SRF was markedly decreased at 1 month after SRT. (f) Complete resolution of SRF was shown on OCT 3 months after SRT

undertreatment but also to avoid inadvertent retinal damage in Asians who have more pigmented eyes compared to Caucasians. However, the signal from RFD could be variable among the same pulse energy due to various factors such as intrapersonal melanin variance at irradiated areas, focal RPE hyperpigmentation, SRF, and defocusing error. FFA-invisible spots above the therapeutic threshold were detected due to blocked fluorescence of hyperpigmentation when test SRT spots were applied at the hyperpigmented lesion in patients with congenital retinal pigment epithelial hypertrophy (CHRPE). Detection of RPE damage on the lesion was difficult due to hyperpigmentation; however, no overtreatment, like whitening burn, was observed. All of the automatic stops in hyperpigmented lesion were on the 1st micropulse due to immediate feedback signal which was above the therapeutic threshold. Even though the automatic stop in the RPE hyperpigmented area occurred at the 1st micropulse, invisibility of SRT spots on fundus photo indicates no overtreatment. While one FFA-visible SRT spot below the therapeutic threshold was noted, the spot was also invisible on the fundus photo (Fig. 3).

Although RFD-v1.0 showed high accuracy in detecting RPE cell damages in this study, for considering various factors affecting feedback signal, the RFD signal from test spots should be evaluated carefully to determine the adequate range of pulse energy before applying a treatment spot.

Our study had several limitations, including it being a retrospective case series, short-term follow-up period and nonrandomized study design. Nevertheless, SRT treatment with RFD for chronic CSC improved visual acuity and resulted in complete resolution of serous retinal fluid within 3 months in 74.0% of patients in this study. Although we performed FFA in all patients before irradiating treatment spots, absence of overtreatment in this study may indicate a practical SRT treatment without FFA which could be performed with an automatic adjustment by RFD after evaluating test spots. These favorable clinical outcomes support that SRT treatment with RFD could be beneficial treatment option in chronic CSC patients. However, there may be limitation in confirmation of RPE damage since FFA was not used for evaluation of treatment spots. Further randomized prospective studies are necessary to determine the safety and efficacy of SRT with RFD and confirm the validity of the FFA-free procedure.

Compliance with ethical standards

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Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Financial interest None of the authors has any financial interest in any of the products described.

References

1. Nicholson B, Noble J, Forooghian F, Meyerle C (2013) Central serous chorioretinopathy: update on pathophysiology and treatment. Surv Ophthalmol 58:103–126
2. Wang M, Munch IC, Hasler PW, Prunte C, Larsen M (2008) Central serous chorioretinopathy. Acta Ophthalmol 86:126–145
3. Spaide RF, Campeas L, Haas A, Yannuzzi LA, Fisher YL, Guyer DR, Slakter JS, Sorenson JA, Orlock DA (1996) Central serous chorioretinopathy in younger and older adults. Ophthalmology 103:2070–2079 **discussion 2079-2080**
4. Guyer DR, Yannuzzi LA, Slakter JS, Sorenson JA, Ho A, Orlock D (1994) Digital indocyanine green videoangiography of central serous chorioretinopathy. Arch Ophthalmol 112:1057–1062
5. Spaide RF, Goldbaum M, Wong DW, Tang KC, Iida T (2003) Serous detachment of the retina. Retina 23:820–846 **quiz 895-826**
6. Spitznas M (1986) Pathogenesis of central serous retinopathy: a new working hypothesis. Graefes Arch Clin Exp Ophthalmol 224:321–324
7. Klein ML, Van Buskirk EM, Friedman E, Gragoudas E, Chandra S (1974) Experience with nontreatment of central serous choroidopathy. Arch Ophthalmol 91:247–250
8. Gilbert CM, Owens SL, Smith PD, Fine SL (1984) Long-term follow-up of central serous chorioretinopathy. Br J Ophthalmol 68:815–820
9. Bujarborua D (2001) Long-term follow-up of idiopathic central serous chorioretinopathy without laser. Acta Ophthalmol Scand 79:417–421
10. Koskela P, Laatikainen L, von Dickhoff K (1994) Contrast sensitivity after resolution of central serous retinopathy. Graefes Arch Clin Exp Ophthalmol 232:473–476
11. Moon JW, Yu HG, Kim TW, Kim HC, Chung H (2009) Prognostic factors related to photodynamic therapy for central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol 247:1315–1323
12. Reibaldi M, Cardascia N, Longo A, Furino C, Avitabile T, Faro S, Sanfilippo M, Russo A, Uva MG, Munno F, Cannemi V, Zagari M, Boscia F (2010) Standard-fluence versus low-fluence photodynamic therapy in chronic central serous chorioretinopathy: a nonrandomized clinical trial. Am J Ophthalmol 149(307–315):e302
13. Lai TY, Chan WM, Li H, Lai RY, Liu DT, Lam DS (2006) Safety enhanced photodynamic therapy with half dose verteporfin for chronic central serous chorioretinopathy: a short term pilot study. Br J Ophthalmol 90:869–874
14. Ruiz-Moreno JM, Lugo FL, Armada F, Silva R, Montero JA, Arevalo JF, Arias L, Gomez-Ulla F (2010) Photodynamic therapy for chronic central serous chorioretinopathy. Acta Ophthalmol 88:371–376
15. Khosla PK, Rana SS, Tewari HK, Azad RU, Talwar D (1997) Evaluation of visual function following argon laser photocoagulation in central serous retinopathy. Ophthalmic Surg Lasers 28:693–697
16. Little HL (1976) Complications of argon laser retinal photocoagulation: a five-year study. Int Ophthalmol Clin 16:145–159
17. Brinkmann R, Roider J, Birngruber R (2006) Selective retina therapy (SRT): a review on methods, techniques, preclinical and first clinical results. Bull Soc Belge Ophtalmol 302:51–69
18. Schuele G, Elsner H, Framme C, Roider J, Birngruber R, Brinkmann R (2005) Optoacoustic real-time dosimetry for selective retina treatment. J Biomed Opt 10:064022
19. Park YG, Seifert E, Roh YJ, Theisen-Kunde D, Kang S, Brinkmann R (2014) Tissue response of selective retina therapy by means of a feedback-controlled energy ramping mode. Clin Exp Ophthalmol 42:846–855
20. Kim HD, Han JW, Ohn YH, Brinkmann R, Park TK (2014) Functional evaluation using multifocal electroretinogram after selective retina therapy with a microsecond-pulsed laser. Invest Ophthalmol Vis Sci 56:122–131
21. Roider J, Liew SH, Klatt C, Elsner H, Poerksen E, Hillenkamp J, Brinkmann R, Birngruber R (2010) Selective retina therapy (SRT) for clinically significant diabetic macular edema. Graefes Arch Clin Exp Ophthalmol 248:1263–1272
22. Kang S, Park YG, Kim JR, Seifert E, Dirk TK, Ralf B, Roh YJ (2016) Selective retina therapy in patients with chronic central serous Chorioretinopathy: a pilot study. Medicine (Baltimore) 95:e2524
23. Park YG, Kim JR, Kang S, Seifert E, Theisen-Kunde D, Brinkmann R, Roh YJ (2016) Safety and efficacy of selective retina therapy (SRT) for the treatment of diabetic macular edema in Korean patients. Graefes Arch Clin Exp Ophthalmol 254:1703–1713. doi:10.1007/s00417-015-3262-1
24. Roider J, Brinkmann R, Wirbelauer C, Laqua H, Birngruber R (2000) Subthreshold (retinal pigment epithelium) photocoagulation in macular diseases: a pilot study. Br J Ophthalmol 84:40–47
25. Klatt C, Saeger M, Oppermann T, Porksen E, Treumer F, Hillenkamp J, Fritzer E, Brinkmann R, Birngruber R, Roider J (2011) Selective retina therapy for acute central serous chorioretinopathy. Br J Ophthalmol 95:83–88
26. Elsner H, Porksen E, Klatt C, Bunse A, Theisen-Kunde D, Brinkmann R, Birngruber R, Laqua H, Roider J (2006) Selective retina therapy in patients with central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol 244:1638–1645
27. Klatt C, Elsner H, Porksen E, Brinkmann R, Bunse A, Birngruber R, Roider J (2006) Selective retina therapy in central serous chorioretinopathy with detachment of the pigmentary epithelium. Ophthalmologe 103:850–855
28. Yasui A, Yamamoto M, Hirayama K, Shiraki K, Theisen-Kunde D, Brinkmann R, Miura Y, Kohno T (2016) Retinal sensitivity after selective retina therapy (SRT) on patients with central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol. doi:10.1007/s00417-016-3441-8