Change in subfoveal choroidal thickness after argon laser panretinal photocoagulation

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Abstract

• AIM: To evaluate changes in subfoveal choroidal thickness (SFCT) and macular thickness as measured by enhanced depth imaging spectral–domain optical coherence tomography (EDI–OCT) after argon laser panretinal photocoagulation (PRP) in patients with severe diabetic retinopathy.

• METHODS: This prospective, comparative case series included 21 patients (28 eyes) with severe diabetic retinopathy. All patients underwent three sessions of PRP. The SFCT and macular thickness were measured using EDI–OCT at baseline and one week after completion of 3 sessions of PRP.

• RESULTS: SFCT before PRP was (318.1 ± 96.5) µm and increased to (349.9 ± 108.3) µm (P = 0.001) after PRP. Macular thickness significantly increased at one week after PRP (from 273.1 ± 23.9 µm at baseline to 295.8 ± 25.3 µm at one week; P < 0.001). No significant relationship between the changes in macular thickness and SFCT was observed (r = −0.13, P = 0.52).

• CONCLUSION: PRP induced increases in both SFCT and macular thickness. Changes in SFCT did not correlate with changes in macular thickness.

• KEYWORDS: choroidal thickness; diabetic retinopathy; EDI-OCT; macular edema; panretinal photocoagulation

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INTRODUCTION

The Diabetic Retinopathy Study [1] demonstrated that argon laser panretinal photocoagulation (PRP) is beneficial in eyes with proliferative retinopathy and high risk characteristics and PRP is currently indicated for eyes with severe nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) [2,3]. However, visual field defects, choroidal detachment, cyclopia, myopia, increased intraocular pressure and macular edema have been reported as complications of PRP [4-8]. Likewise, there is a significant correlation between increased macular thickness and decreased visual acuity [9]. Many previous studies that have attempted to explain the underlying mechanism of macular edema after PRP have focused on ocular circulation and cytokines [10-12]. Recently, enhanced depth imaging optical coherence tomography (EDI-OCT), which is a simple method for cross-sectional visualization of the choroid, was introduced [13]. By placing the conventional spectral-domain OCT closer to the eye so that an inverted image is obtained, the acquired images have allowed for the visualization of the choroid with improved resolution and sensitivity. Among available spectral-domain OCTs, Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) provides good quality image by averaging 100 scans through automatic averaging and eye tracking features. Several studies have succeed in obtaining cross-sectional views of the choroid in numerous ophthalmic diseases. One study used EDI-OCT to evaluate a variety of choroidal tumors, including small choroidal tumors that cannot be detected by ultrasonography [14]. Another study used the same technique to measure alterations in the subfoveal choroidal thickness (SFCT) of central serous chorioretinopathy after treatment [15]. Here, we used EDI-OCT to evaluate the effect of PRP on SFCT in very severe NPDR and PDR.

SUBJECTS AND METHODS

Subjects The protocol was approved by the institutional review board (EMCT 11-3-11) and all patients gave written informed consent before all examinations. Patients were recruited for one year from March, 2011, after the approval from institutional review board. This study was conducted according to the principles of the 1975 Declaration of Helsinki, as revised in 1983. A total of 28 eyes from 21 patients with diabetes mellitus (7 women, 14 men; age 53.5 ± 505
7.8 years) with very severe NPDR (a=11) or PDR (a=17) were studied prospectively. All subjects underwent comprehensive ocular examination by one physician at an initial visit. All subjects underwent ocular examination, including best-corrected visual acuity (BCVA), slit lamp biomicroscopic exam, measurement of intraocular pressure with a non-contact tonometer, dilated fundus examination with a SuperField non-contact lens (Volk, Mentor, OH, USA) and intravenous fluorescein angiography (FA) was performed on 26 eyes for accurate staging. Other two eyes had definite new vessels at optic disc and preretal hemorrhage on fundus examination which suggested high risk PDR. Severity of retinopathy was graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) retinopathy severity scale [16], and the presence of clinically significant macular edema (CSME) was determined by the ETDRS protocol [17]. Patients with clinically significant macular edema, epiretinal membrane, tractional retinal detachment, vitreous hemorrhage, high ametropia (spherical equivalent worse than +6.0 diopters or -6.0 diopters), macular degeneration, and/or previous laser treatment were excluded from the study.

Methods
Panretinal photocoagulation (PRP) All patients were treated on an outpatient basis. A total of 17 out of 28 eyes had neovascularization at the disc or elsewhere while the remaining eleven eyes were categorized as very severe NDPR on biomicroscopy and fluorescein angiography. PRP was performed in three sessions and the order of treated areas was as follows: inferior, superonasal, and then superotemporal. For each session, spot-sizes of 200-300 μm and a pulse duration of 0.2s were used. A total of 1000-1600 burns were applied per eye with the panfundus contact lens (Superquad, Volk, Mentor, OH, USA) and argon green laser (Coherent Novus 2000, Lumenis, UT, USA) according to the ETDRS protocol [18]. PRP was performed weekly if only one eye was included in this study. If both eyes were included, PRP was performed weekly on one eye for three times and weekly on the other eye afterwards. Topical anesthetics was used in all cases before applying contact lens.

Choroidal thickness measurement The change in SFCT was measured by the EDI-OCT technique, in which the Heidelberg Spectralis OCT instrument was placed sufficiently close to the eye so as to obtain an inverted image. Each section was obtained using eye tracking and 100 scans were averaged to improve the signal-to-noise ratio. The choroidal thickness was measured using the manual caliper function in the Heidelberg Spectralis OCT software. The choroid was measured as a vertical distance, which is perpendicular to the center of fovea, from the outer portion of the hyperreflective line corresponding to the retinal pigment epithelium (RPE) to the sclerochoroidal interface (Figure 1). The choroidal thickness was measured from a vertical and a horizontal section under the center of the fovea from OCT data by two blinded, independent observers and averaged for analysis. The SFCT was measured at baseline and one week after final third PRP.

Retinal thickness measurement The average thickness of the central 1mm field of the ETDRS grid (central subfield) was used to evaluate changes in the central retinal thickness over time. Upper limit of normal central subfield thickness (CST) was defined as 315 μm and CST over 315 μm is considered to be clinically significant macular edema in this study as suggested by a previous report on normative data of SD-OCT[9].

Statistical Analysis Changes in the SFCT, CST and BCVA between baseline examination and the follow-up examination after the end of the PRP treatment were assessed using the Paired-Samples t-test. Pearson correlation analysis and Chi-square test were used to determine the relationship between clinical factors and changes in subfoveal choroidal thickness. All analyses were conducted using SPSS ver. 16.0 statistical software (SPSS Inc., Chicago, IL, USA). P values < 0.05 were considered statistically significant.

Figure 1 Retinal images of a 47-year-old man with bilateral proliferative diabetic retinopathy Enhanced depth imaging spectral-domain optical coherence tomography (EDI-OCT) images of the left eye at baseline (B) and one week after completion of PRP (C). Note that both subfoveal choroidal thickness and central subfield thickness increased from 322 μm to 360 μm and from 294 μm to 312 μm, respectively. 69mmx101mm (72x72 DPI).
RESULTS
A total of 28 eyes from 21 patients were included in the present study. The mean patient age was (53.5±7.8) years and 14 patients were male. There were 17 eyes diagnosed as PDR and 11 eyes as very severe NDPR. The mean duration of diabetes was (11.9±10.1) years. Seven patients had a history of hypertension and were taking oral systemic antihypertensive drugs. The hemoglobin A1c level was (8.1±1.2) mg/dL, measured during the PRP treatment (Table 1).

No history of ocular disease other than diabetic retinopathy and refractive errors was reported for any patient.

Change in subfoveal choroidal thickness Statistically significant increases in SFCT were detected after PRP treatment (Figures 1 and 2, Table 2). Twenty six out of 28 eyes showed increase of SFCT and the mean ±SD SFCT before PRP was (318.1±96.5) μm, which increased to (349.9±108.3) μm (P=0.001) after PRP. We also performed statistical analysis of the changes in SFCT induced by PRP with respect to baseline SFCT, age, gender, duration of diabetes, severity of diabetic retinopathy, HbA1c, number of laser spots, the presence of hypertension, and insulin treatment. There were neither significant nor independent risk factors for changes in SFCT.

Change in retinal thickness CST significantly increased at one week after PRP (from 273.1±23.9μm at baseline to 295.8±25.3μm at one week; P<0.001) (Figures 1 and 2). In seven eyes, CST increased to a degree of significant macular edema without a loss of visual acuity. There was no significant linear correlation between changes in SFCT and CST induced by PRP (r=-0.13, P=0.52) (Figures 3, 4).

DISCUSSION
In the present study we demonstrated that argon laser PRP causes a significant increase in both SFCT and CST in eyes

<p>| Table 1  Demographic and clinical characteristics of patients |</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>21 (28)</td>
</tr>
<tr>
<td>Age, mean±SD (a)</td>
<td>53.5±7.8</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>14/7</td>
</tr>
<tr>
<td>Severity, very severe NDPR/PDR</td>
<td>11/17</td>
</tr>
<tr>
<td>Refractive error, mean±SD (diopters)</td>
<td>-0.27±1.6</td>
</tr>
<tr>
<td>Hypertension, number</td>
<td>7</td>
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<tr>
<td>Duration of Diabetes, mean±SD (a)</td>
<td>11.9±10.1</td>
</tr>
<tr>
<td>Hemoglobin A1c, mean±SD (mg/dL)</td>
<td>8.1±1.2</td>
</tr>
<tr>
<td>Insulin, number</td>
<td>16</td>
</tr>
</tbody>
</table>

NPDR: Nonproliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy.

<p>| Table 2  Change in SFCT and CST |</p>
<table>
<thead>
<tr>
<th>Parameters</th>
<th>At baseline</th>
<th>One week after PRP</th>
<th>P (95%CI of difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horizontal SFCT, (μm)</td>
<td>317.0</td>
<td>349.4</td>
<td>0.001 (14.5-50.2)</td>
</tr>
<tr>
<td>Vertical SFCT, (μm)</td>
<td>319.2</td>
<td>350.4</td>
<td>0.003 (11.6-50.7)</td>
</tr>
<tr>
<td>Mean SFCT, (μm)</td>
<td>318.1</td>
<td>349.9</td>
<td>0.001 (14.7-49.8)</td>
</tr>
<tr>
<td>CST (μm)</td>
<td>273.1</td>
<td>295.8</td>
<td>&lt;0.001 (17.1-28.1)</td>
</tr>
</tbody>
</table>

*Analysis performed by the Paired-Samples t-test; CI: Confidence interval; Note that both SFCT and CST increased significantly after PRP.

Figure 2 SFCT and CST measurements at baseline and one week after PRP. OCT revealed a statistically significant increase in SFCT and CST one week after PRP.

Figure 3 Change of SFCT observed in individual subjects.

Figure 4 Scatter plot showing changes in SFCT and CST. A significant linear correlation between changes in SFCT and CST was not noted (r=-0.13, P=0.52). 69mm×62mm (72×72 DPI).

Change in visual acuity No significant difference in best-corrected visual acuity was observed between baseline (0.02±0.07)logMAR and one week (0.09±0.24)logMAR after PRP, as analyzed by Paired-Samples t-test (P=0.18).

DISCUSSION
In the present study we demonstrated that argon laser PRP causes a significant increase in both SFCT and CST in eyes
with severe diabetic retinopathy without macular edema. Visualization of the choroid behind the RPE before and after PRP was achieved in earlier studies using ultrasonography, which has relatively low spatial resolution, and ultrasound biomicroscopy (UBM), which has a limited ability to evaluate the anterior choroid beyond 7mm from the limbus. However, EDI-OCT, employed in present study, enabled direct visualization of the choroidal structures in the foveal region with higher resolution. Increases in SFCT can be interpreted as either an increase in choroidal blood flow due to vasodilation or choroidal effusion induced by possible choroidal vascular obstruction from laser photoocoagulation. Takahashi et al. measured alterations in choroidal blood flow in the foveal area one month after PRP using a laser doppler flowmetry technique. They reported that PRP induces an increase in both choroidal blood flow and choroidal blood volume and interpreted this as vasodilation of the choriocapillaris. The observed increases in SFCT in our study corresponded well with increased choroidal blood flow in subfoveal areas reported by Takahashi et al. A recent histologic study of feline choriocapillaris under the retinal photoocoagulated lesion explained the mechanism underlying the increase in local choroidal blood flow. In their study, feline choriocapillaris under the photoocoagulated lesion were found to exhibit a filling defect and lack of ICG fluorescence. Even in lesions with normal angiograms, the microsphere count, which was injected intra-vascularly, was much lower than that in the control area, implying damage to the choriocapillaris and a subsequent decrease in choroidal blood flow. This decrease in choroidal circulation in the peripheral photoocoagulated lesion may redistribute the blood supply and result in an increase in choroidal blood flow in the foveal area. The other study reported that the PRP-treated group had significantly lower pulsatile ocular blood flow compared to the NPDR group, as measured by a computerized pneumotonometer. Considering that 85% of pulsatile ocular blood flow is known to reflect total choroidal circulation, these findings appear to be contradictory to our results. However, in terms of redistribution of choroidal blood supply, it supports the assumption that even though the total choroidal circulation was decreased, local circulation in the foveal region increased as a result of a redistribution mechanism. Conversely, thickening of the subfoveal choroid may indicate choroidal effusion produced by a disruption of the choriocapillaris caused by laser photoocoagulation. Two studies that used ultrasonography and UBM found that damage to the choroid induced transudation in 59%-90% eyes after PRP, with the associated ciliochoroidal effusion resolving completely in 7-14 days. PRP was performed in three sessions and SFCT was measured one week after the final session of PRP in the present study. Choroidal effusion was likely present and accumulated from the repeated PRP and therefore, may have affected the results. CST was significantly increased one week after the final session of PRP, and CSME developed in seven eyes without a corresponding change in visual acuity. Specifically, three eyes showed signs of retinal swelling type of macular edema while four eyes exhibited cystoid macular edema on OCT findings. The observed increased macular thickness is consistent with other studies that have reported increased macular thickness after PRP in eyes with severe diabetic retinopathy without macular edema. Nagaoka et al. reported that choroidal circulation decreased significantly in NPDR patients with macular edema compared to those without macular edema. They suggested that retinal hypoxia resulting from insufficient blood flow is a possible cause of macular edema. However, in this study, a significant correlation between increased SFCT and CST was not observed (Figure 3). Although the sample size was small, no difference in SFCT change was found between eyes that developed CSME after PRP and eyes that did not. This lack of correlation between changes in SFCT and changes in CST is consistent with the results of a previous study that reported no significant relationship between changes in choroidal blood flow and macular thickness and suggests that neither choroidal circulation nor effusion is responsible for inducing macular edema.

Thus, factors independent of choroidal circulation, such as inflammatory cytokines and breakdown of the blood-retinal barrier, may contribute to the pathogenesis of PRP-induced macular edema in eyes with severe diabetic retinopathy. Previous studies showed that eyes with PDR that had received PRP had higher MCP-1 and IP-10 levels compared to PDR eyes that did not undergo PRP treatment and foveal thickness was strongly correlated with the vitreous levels of IL-6 and RANTES in PRP-treated eyes. In addition, immediate BRB breakdown induced by retinal photocoagulation has been demonstrated using real-time magnetic resonance imaging. This prospective study had several limitations, including a small sample size and a short-term follow-up period. Thus, long-term follow-up of SFCT may identify differences between the short-term effects described here. Indeed, Takahashi reported that choroidal blood flow was increased six months after PRP compared with baseline choroidal flow, suggesting long-term effects of PRP on choroidal circulation. However, taking into account the fact that ciliochoroidal effusion was completely absorbed in two weeks, recovery from impairment of the choriocapillaris after PRP might have affected choroidal thickness as measured during the long-term follow-up period. Likewise, a previous study...
found that macular thickness at 12 months after PRP was decreased so that it was not significantly different from the baseline macular thickness. Taken together, the results of the present study are limited to the immediate response of the choroid and macula to PRP. In addition, a study is needed to investigate the direct relationship between choroidal thickness and choroidal blood flow parameters. Such a study would require a larger number of patients than was examined in the present study because of known interactions between choroidal thickness, age, and refractive error.

In conclusion, SFCT which was successfully measured by EDI-OCT, increased significantly after PRP. Increases in macular thickness were observed after PRP but were not associated with changes in SFCT. This suggests that changes in choroidal circulation may not be the primary factor causing PRP-induced macular edema.

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