Optical Coherence Tomography Angiography Assessment of Macular Choriocapillaris and Choroid Following Panretinal Photocoagulation in a Diverse Population With Advanced Diabetic Retinopathy

Tong Zhao, MD†‡, Yi Chen, MD†§, Dongwei Liu, MD†¶, and Jay M. Stewart, MD†

Purpose: The aim of this study was to evaluate choroidal and retinal microvasculature with optical coherence tomography angiography (OCTA) after panretinal photocoagulation (PRP) for diabetic retinopathy in a primarily Hispanic and Asian population.

Design: Retrospective study.

Methods: Eyes were examined by OCTA in the macula (3 × 3 mm) just before PRP treatment and 1 to 3 months afterwards. Choroidal thickness (CT) and central retinal thickness (CRT) were measured. Choroidal flow signal voids (CFSV) and choriocapillaris flow signal voids (CCFSV) were acquired. Retinal microvasculature parameters, including superficial and deep vessel density, superficial and deeper perfusion density, foveal avascular zone area, perimeter and circularity, were calculated. Ocular examinations and demographic information were analyzed.

Results: CT at a location 1000 μm temporal to the fovea increased significantly after PRP (from 278.64 μm to 313.44 μm, P = 0.026). CCFSV increased slightly from (46.72 ± 8.52)% to (47.07 ± 10.77)%, but the difference was not statistically significant (P = 0.782). A similar finding was observed in CFSV (increase from 35.81% to 36.64%, P = 0.165). The change in all retinal microvasculature parameters was also not significant. Best-corrected visual acuity (BCVA) decreased from 0.218 ± 0.153 to 0.262 ± 0.147 (P = 0.034). Increased CRT (from 245.41 ± 33.18 μm to 251.14 ± 38.97 μm, P = 0.007) was observed. The change in CRT positively correlated with pre-PRP CRT (r = 0.434, P = 0.019) and BCVA reduction (r = 0.418, P = 0.024). Neither BCVA reduction nor CRT increase correlated with OCTA metrics.

Conclusions: OCTA demonstrates redistribution of choroidal circulation from the periphery to the macula after PRP, with increased macular CT and stable choroidal blood flow density. Eyes with greater macular thickness are more likely to experience an increase in CRT.

Key Words: diabetic retinopathy, optical coherence tomography angiography, panretinal photocoagulation


INTRODUCTION

Panretinal photocoagulation (PRP) is a standard treatment option for eyes with proliferative diabetic retinopathy (PDR) and severe nonproliferative diabetic retinopathy (SNPDR), especially when regular follow-up cannot be guaranteed.1 PRP is believed to work through disrupting the outer-layer retina, lowering oxygen consumption, and reducing the intravitreal vascular endothelial growth factor (VEGF) levels.2 Numerous studies have focused on how the retinal blood flow changes after PRP,3–6 showing a decreasing trend of overall retinal flow. However, studies on choroidal flow with angiography and laser speckle flowgraphy have yielded inconsistent results.7–10 Either increased or decreased perfusion of choroidal circulation could be found as a result of different laser types, follow-up time, and examining methods.

Optical coherence tomography angiography (OCTA) provides detailed information about the choroidal and retinal microvasculature using a noninvasive imaging method, which provides new methods to evaluate changes in macular choroidal perfusion under various conditions. In this study, we address this question by evaluating a range of OCTA-derived metrics to quantify the change of both choroidal and retinal flow in the macula after PRP.

METHODS

The study is a retrospective review of a consecutive series of laser-treatment-naive patients who received PRP treatment for PDR or SNPDR associated with diabetes mellitus (DM) in the Department of Ophthalmology, at Zuckerberg San Francisco General Hospital between January and June 2019 and underwent OCTA imaging as part of the standard imaging protocol at all visits. The study was approved by the Human Research Protection Program at the University of California, San Francisco. The University of California and San Francisco Human Research Protection Program granted a waiver of consent, affirming that patient welfare would not be adversely affected by waiving informed consent. All research adhered to the tenets of the Declaration of Helsinki.
PDR and SNPDR were defined based on the Early Treatment Diabetic Retinopathy Study. Exclusion criteria included: (1) any history of ocular injury, other retinal diseases, laser treatment or vitrectomy; (2) diabetic macular edema, defined as central retinal thickness (CRT) ≥ 300 μm at any time during the study course; (3) history of intravitreal injection within 3 months before PRP; (4) low quality OCTA images: signal strength less than 6 or presence of significant motion artifacts, defocus, or blur.

Best-corrected visual acuity (BCVA) was assessed using the Snellen Chart and then converted into the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Pneumonometry, slit-lamp biomicroscopy, and ultra-widefield fundus imaging (Optos Daytona, Optos Plc, Dunfermline, United Kingdom) were also performed at every visit. CRT was measured using HRA + OCT Spectralis (Heidelberg Engineering GmbH, Germany). The Heidelberg Spectralis spectral-domain OCT (SD-OCT) at 870 nm with enhanced depth imaging was used to measure CRT and choroidal thickness (CT). CT at 2000 μm (SD-OCT) at 870 nm with enhanced depth imaging was used to measure CRT and choroidal thickness (CT). CT at 2000 μm, 1000 μm from the temporal and nasal to the fovea as well as at the fovea, were measured (Fig. 1). The demographics of all subjects including gender, age, and race, and the most recent hemoglobin A1c (HbA1c) were recorded.

OCTA imaging was performed with a Cirrus HD-OCT 5000 with AngioPlex OCT Angiography (Carl Zeiss Meditec, Dublin, CA) on the day of PRP, just before treatment, and again at a follow-up visit within 1 to 3 months after the laser treatment. The resulting OCT volume scan had dimensions of 3 × 3 × 2 mm centered at the fovea. Motion-related artifacts were minimized with the help of the tracking algorithm on the Cirrus device.

According to Cirrus segmentation algorithms, the inner retina, identified as the layer between the inner limiting membrane and an offset 110 μm from the retinal pigment epithelium layer, was further divided into the superficial retinal layer (superficial 70%) and deeper retinal layer (the deeper 30% remaining). The vascular density and perfusion density of the superficial retinal layer were generated automatically in the Cirrus analysis software. The foveal avascular zone was also identified automatically in the Cirrus, followed by manual checking and adjusting as needed. Foveal avascular zone (FAZ) area, FAZ perimeter, and FAZ circularity were generated subsequently. Circularity was calculated with the formula: 4π × FAZ area / FAZ perimeter.\(^2\)\(^,\)\(^12\) The images of the deeper retinal layer were analyzed with ImageJ software (1.8.0_112, http://imagej.nih.gov/ij/; National Institutes of Health, Bethesda, Maryland, USA) to acquire the deep vascular density (DVD) and deep perfusion density (DPD).\(^13\) The choriocapillaris slab was defined as the layer between 29 μm and 49 μm beneath the RPE, and the choroidal slab was between 64 μm and 115 μm. Dark areas of absent or decreased signal were considered as flow voids of the choriocapillaris. The percent of flow signal voids area of choriocapillaris flow signal voids (CCFSV) and choroidal flow signal voids (CFSV) were calculated following the procedure described previously:\(^14\) automatic local thresholding was performed using the Phansalkar method, and inversion of grayscale was done; “Analyze Particles” was used to detect flow signal voids.

Patterned scanning laser (PASCAL, Topcon, Japan) treatment was performed through a wide-field contact lens (Volk SuperQuad 160). Laser spots were applied in a typical PRP fashion outside the major vascular arcades, with the spot size of 200 μm, duration of 20 ms, and power of 300 to 1200 mW per spot. PRP was completed at 1 sitting or in 2 sessions with an interval of a week.

Statistical analyses were conducted using IBM SPSS (Version 22.0, Chicago, IL, USA). Continuous variables are presented as means ± standard deviations. The one-sample Kolmogorov–Smirnov test was used to determine whether the OCTA metrics followed a normal distribution. Paired sample \(t\) tests were used for before-after comparisons. Multivariate analyses were performed to determine whether age and HbA1c were independent factors for CCFSV and CFSV. The correlations between the change of BCVA or CRT and other factors were analyzed via Pearson correlation tests. Statistical significance was defined as \(P < 0.05\) (2-tailed).

RESULTS

A consecutive 30 subjects (41 eyes) receiving PRP treatment were initially recruited. After exclusion due to poor-quality images (11 eyes), inadequate follow-up (6 eyes), or the development of diabetic macular edema after PRP (3 eyes), a total of 28 eyes of 21 patients remained. All patients were initially diagnosed as type 2 DM. Their ages ranged from 41 to 78 years, with a mean of 55.4 ± 8.4 years. Seven patients were female (31.8%). According to the patients self-identified race and ethnicity, half of the subjects were Hispanic (52.4%), followed by Asian (28.6%), non-Hispanic Black (9.5%), and others (9.5%). The mean HbA1c was 8.5% ± 2.1% (range: 5.5–12.7). Fifteen patients (71.4%) had hypertension. Three eyes (10.3%) were graded as NPDR whereas 25 (89.3%) had PDR. Twelve eyes (42.9%) had a history of intravitreal injections more than 3 months before their PRP treatment. Two eyes (7.1%) were pseudophakic, and the remainder of eyes were phakic. Nine eyes (32.1%) had neovascularization of the disc, and 10 eyes (35.7%) had neovascularization elsewhere.

The mean number of laser spots was 2065 ± 414. The mean follow-up period was 6.2 ± 3.0 weeks with a range of 3 to 12 weeks. The BCVA decreased after PRP to 0.262 ± 0.147 compared with before (0.218 ± 0.153, \(P = 0.034\)). Intraocular pressure showed no significant difference between before (16.9 ± 2.4 mm Hg) and after PRP (16.6 ± 3.0 mm Hg). The CRT increased significantly from 245.41 ± 33.18 μm to 251.14 ± 38.97 μm (\(P = 0.007\)). [At baseline, the CT of the Hispanic population at the fovea was 337.77 ± 85.52 μm, which was thicker than that of the Asian population (320.22 ± 34.09 μm), but the difference was not statistically significant (\(P = 0.568\)).] Increased CT was found...
after PRP at all 5 measurement locations, although only at the site 1000 μm temporal to the fovea was the increase statistically significant (from 278.64 μm to 313.44 μm, \( P = 0.026 \)) (Table 1).

As for OCTA parameters, all were consistent with a normal distribution (\( P > 0.05 \)). CCFSV increased slightly from (46.72%/C6 8.52%) to (47.07%/C6 10.77%), but the difference was not statistically significant (\( P = 0.782 \)). A similar finding was observed in CFSV (from 35.81% to 36.64%, \( P = 0.165 \)) (Fig. 2). DVD increased slightly after PRP (116.66/C6 19.60 mm–1) compared before (118.04/C6 21.48 mm–1), but the difference was not significant (\( P = 0.709 \)). Otherwise, all other retinal vessel metrics (SVD, SPD, and DPD) decreased without significance (Table 2). Trends of enlarged area (0.34/C6 0.11 mm² to 0.36/C6 0.12, \( P = 0.376 \)) and reduced circularity (0.52/C6 0.08 to 0.50/C6 0.08, \( P = 0.396 \)) were observed in the FAZ, but none of these differences was found to be significant.

Multivariate analyses showed that CCFSV at baseline was not dependent upon age (\( P = 0.858 \)) or HbA1c (\( P = 0.871 \)). The change in CCFSV was also not dependent upon age (\( P = 0.146 \)) or HbA1c (\( P = 0.107 \)). Similar findings could be seen as for CFSV (all \( P > 0.05 \) either for age or HbA1c).

The change of BCVA negatively correlated with pre-PRP BCVA (\( r = -0.379, P = 0.043 \)) and positively correlated with the change of CRT (\( r = 0.418, P = 0.024 \)). The change of CRT positively correlated with pre-PRP CRT (\( r = 0.434, P = 0.019 \)). No correlation was found between number of laser spots and change of BCVA or change of CRT. HbA1c did not correlate with a change in BCVA or CRT. The change of all OCTA metrics did not correlate with change of BCVA or CRT. In addition, no correlation was found between change of BCVA or CRT and previous neovascularization of the disc, neovascularization elsewhere, or lens status.

**DISCUSSION**

The choriocapillaris is especially important for macular oxygen and nutrition supply because of the absence of the retinal vasculature in the foveal area. It is believed that the perfusion of choroidal circulation is altered as diabetic retinopathy progresses. Nesper et al demonstrated significant reduction of choriocapillaris flow in PDR groups. \(^{13}\) Conti et al revealed that choroidal vascular density of NPDR and PDR eyes was decreased compared with...
BCVA (logMAR) 0.218

Greater reduction of choroidal vascular density than NPDR eyes.

Comprehensive evaluation of choroidal changes following laser parameters. Further studies are warranted to provide a more comprehensive understanding.

The results of previously published studies provide some indirect evidence of reperfusion of choroidal vessels. This is the first study to use OCTA to measure macular choroidal blood flow: Okamoto et al. believed that the reduction of CT after PRP is related to a CRT increase, and a CRT increase was positively related to a decrease of CT. This phenomenon suggests that deeper retinal vessels might also contribute to the increase in DVD after PRP, resulting in a decrease of the vessel diameter and the area density on OCTA (DPD). The better perfusion of the deeper vasculature was thereby reflected in the elongated vessels or higher number of branches. That could be an explanation for the distinctive change in OCTA compared with other parameters, even though the increase in DVD was not significant.

Another important area of investigation is the decrease in BCVA after PRP. Our findings were that a BCVA reduction was related to a CRT increase, and a CRT increase was positively related to pre-PRP CRT; namely, eyes with thicker pre-PRP CRT tended to have more significant CRT increase. Some previous studies have reported an increase in CRT after PRP. Notably, increased CRT after PRP does not mean PRP directly caused foveal thickening. It may also be a result of the natural process of the disease. Shimura et al. suggested that injection treatment before PRP might be beneficial.

Our study excluded eyes with recent injections in the 3 months before laser treatment in order to eliminate the potential influence of injections. It would be useful to explore the change in OCTA metrics after the combination of PRP and anti-VEGF injections or injections alone.

This study included a mainly Hispanic and Asian population, with absence of Whites, which is notable compared with other studies. Karapetyan et al. found that Whites had the greatest foveal CT, followed by Asians and Africans, but the difference was not significant. Similarly, we found a greater CT in Hispanic patients than Asian patients, with no statistically significant difference. We are unaware of previous reports on CRT at the fovea in diabetic Hispanic subjects. However, as for Asian subjects, our result of subfoveal CT (320 μm) is consistent with that reported by Okamoto et al. (327 μm). The number is smaller than in healthy Asian subjects (Karapetyan et al., 384 μm, and Ikuno et al., 354 μm). Although a previous study showed no significant difference between races/ethnicities, this potential confounding factor should be considered in studies reporting CT.

There were some limitations of this study. The wide distribution of age and HbA1c in the study population were potential confounding factors. Multivariate analyses showed that age and HbA1c were not dependent factors, but the small sample size reduced the reliability of the multivariate analyses, making the conclusion less generalizable. Further large-sample studies controlled for age and HbA1c are warranted. Second, only 1 follow-up visit was included, and the time point had a relatively large deviation. However, Lorusso et al. found that there were no significant differences in vessel density of both superficial and deep retinal capillary plexus between 1 month and 6 months after PRP, so we expect that our results regarding retinal vasculature are reliable even though the OCTA scans were not all collected at the same visit.

### Table 2: Change in Clinical and OCTA Parameters Before and After PRP Laser Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before PRP</th>
<th>After PRP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA (logMAR)</td>
<td>0.218 ± 0.153</td>
<td>0.262 ± 0.147</td>
<td>0.034</td>
</tr>
<tr>
<td>IOP (mm Hg)</td>
<td>16.9 ± 2.4</td>
<td>16.6 ± 3.0</td>
<td>0.554</td>
</tr>
<tr>
<td>CRT (μm)</td>
<td>245.41 ± 33.18</td>
<td>251.14 ± 38.97</td>
<td>0.007</td>
</tr>
<tr>
<td>CCFSV (%)</td>
<td>46.72 ± 8.52</td>
<td>47.07 ± 10.77</td>
<td>0.782</td>
</tr>
<tr>
<td>CFSV (%)</td>
<td>35.81 ± 4.45</td>
<td>36.64 ± 5.27</td>
<td>0.603</td>
</tr>
<tr>
<td>SVD (mm⁻¹)</td>
<td>15.99 ± 1.84</td>
<td>15.43 ± 1.77</td>
<td>0.175</td>
</tr>
<tr>
<td>SPD (%)</td>
<td>31.02 ± 1.77</td>
<td>30.01 ± 3.19</td>
<td>0.238</td>
</tr>
<tr>
<td>DVD (mm⁻¹)</td>
<td>116.66 ± 19.60</td>
<td>118.04 ± 21.48</td>
<td>0.709</td>
</tr>
<tr>
<td>DPD (%)</td>
<td>25.30 ± 3.43</td>
<td>25.01 ± 4.48</td>
<td>0.719</td>
</tr>
<tr>
<td>FAZA (mm²)</td>
<td>0.34 ± 0.11</td>
<td>0.36 ± 0.12</td>
<td>0.376</td>
</tr>
<tr>
<td>FAZP (mm)</td>
<td>2.88 ± 0.57</td>
<td>2.99 ± 0.64</td>
<td>0.163</td>
</tr>
<tr>
<td>FAZC</td>
<td>0.52 ± 0.08</td>
<td>0.50 ± 0.08</td>
<td>0.396</td>
</tr>
</tbody>
</table>

BCVA indicates best-corrected visual acuity; CCFSV, choriocapillaris flow signal voids; CFSV, choroidal flow signal voids; CRT, central retinal thickness; DPD, deeper perfusion density; DVD, deep vessel density; FAZA, foveal avascular zone area; FAZC, foveal avascular zone circularity; FAZP, foveal avascular zone perimeter; IOP, intraocular pressure; OCTA, optical coherence tomography angiography; PRP, panretinal photocoagulation; SPD, superficial perfusion density; SVD, superficial vessel density.

nondiabetic controls. Wang et al reported that PDR eyes had a greater reduction of choroidal vascular density than NPDR eyes compared with controls.

Li et al found that the vascular density of the choroid capillary plexus in DM without retinopathy was decreased significantly compared with controls, and that the reduction occurred even earlier than in the retinal vasculature, indicating that microvascular ischemia originated in choroid layer and extended inward, affecting the deep and then superficial layers.

In this study, we found stable flow signal voids in both macular choriocapillaris and choroidal layer after PRP. To our knowledge, this is the first study to use OCTA to measure macular choroidal circulation after PRP. Several technologies have been used before: indocyanine green angiography, laser Doppler flowmetry, laser speckle flowgraphy, and color Doppler imaging, but the results have been variable. Some studies presumed that there was a choroidal blood redistribution from obliterated choriocapillaris in the peripheral area to the macular region, resulting in increased choroidal flow in macula.

However, other studies found that PRP reduced choroidal blood flow: Okamoto et al believed that the reduction of CT and choroidal flow was secondary to reduction of VEGF production, although Mikoshiba et al demonstrated that choroidal flow increased transiently but decreased at a later time, as the redistribution of the blood could not compensate for the overall reduction of choroidal flow due to destroyed peripheral choriocapillaris. Interestingly, sustained nonperfusion of choriocapillaris has been confirmed with the use of OCTA to directly detect the laser scar from an early stage through years after PRP, indicating that PRP can cause permanent CC damage.

Although that study did not focus on the macula, its findings provide some indirect evidence of reperfusion of choroidal blood flow from periphery to macula. This reperfusion might exist in the form of increased macular CT but not significant blood flow density change, as was found in our study. The results of previously reported studies most likely varied because of different methods, instruments, regions of interest, disease severity, and laser types and parameters. Further studies are warranted to provide a more comprehensive evaluation of choroidal changes following laser treatment. There may be value in longitudinal evaluation of choroidal flow parameters in specific patients to see whether flow voids demonstrate change over time. As for retinal microvasculature, the findings showed no significant change of vessel density after PRP, which was similar to the conclusion from the study by Lorusso et al., but inconsistent with Fawzi et al., whose study indicated that macular blood flow increased after PRP. Interestingly, we found a slightly increased DVD after PRP, which supports Fawzi et al’s hypothesis of a “steal phenomenon.” That is, as the reduction of dilated superficial vessels occurs after PRP, the deeper vessels can improve perfusion. In our study, the DVD (vessel length density) increased whereas DPD (vessel area density) decreased. This phenomenon suggests that deeper retinal vessels might also contribute after PRP, resulting in a decrease of the vessel diameter and the area density on OCTA (DPD). The better perfusion of the deeper vasculature was thereby reflected in the elongated vessels or higher number of branches. That could be an explanation for the distinctive change in OCTA compared with other parameters, even though the increase in DVD was not significant.

Another important area of investigation is the decrease in BCVA after PRP. Our findings were that a BCVA reduction was related to a CRT increase, and a CRT increase was positively related to pre-PRP CRT; namely, eyes with thicker pre-PRP CRT tended to have more significant CRT increase. Some previous studies have reported an increase in CRT after PRP. Notably, increased CRT after PRP does not mean PRP directly caused foveal thickening. It may also be a result of the natural process of the disease. Shimura et al. suggested that injection treatment before PRP might be beneficial.

Our study excluded eyes with recent injections in the 3 months before laser treatment in order to eliminate the potential influence of injections. It would be useful to explore the change in OCTA metrics after the combination of PRP and anti-VEGF injections or injections alone.

This study included a mainly Hispanic and Asian population, with absence of Whites, which is notable compared with other studies. Karapetyan et al. found that Whites had the greatest foveal CT, followed by Asians and Africans, but the difference was not significant. Similarly, we found a greater CT in Hispanic patients than Asian patients, with no statistically significant difference. We are unaware of previous reports on CT at the fovea in diabetic Hispanic subjects. However, as for Asian subjects, our result of subfoveal CT (320 μm) is consistent with that reported by Okamoto et al (327 μm). The number is smaller than in healthy Asian subjects (Karapetyan et al., 384 μm, and Ikuno et al., 354 μm). Although a previous study showed no significant difference between races/ethnicities, this potential confounding factor should be considered in studies reporting CT.

There were some limitations of this study. The wide distribution of age and HbA1c in the study population were potential confounding factors. Multivariate analyses showed that age and HbA1c were not dependent factors, but the small sample size reduced the reliability of the multivariate analyses, making the conclusion less generalizable. Further large-sample studies controlled for age and HbA1c are warranted. Second, only 1 follow-up visit was included, and the time point had a relatively large deviation. However, Lorusso et al. found that there were no significant differences in vessel density of both superficial and deep retinal capillary plexus between 1 month and 6 months after PRP, so we expect that our results regarding retinal vasculature are reliable even though the OCTA scans were not all collected at the same visit.
the same time point following treatment. Third, as this was an observational study of patients undergoing PRP laser, no control group was included. It is possible that in this population of eyes with severe diabetic retinopathy, the natural course could be toward a significant decrease in vessel density without treatment, with a slowing of this effect by PRP. Our study would not detect such an impact of laser treatment. Finally, we utilized 3 × 3 mm scans in order to maximize details at the fovea and perifoveal area, but including 6 × 6 mm scans would allow a more comprehensive evaluation of the entire macular area.

In summary, in this study we found no significant change in choriocapillaris and choroidal blood flow signal voids after PRP, whereas CT increased to some extent, indicating redistribution of choroidal circulation to the macula from the periphery. No change of retinal vessel density or FAZ size after PRP laser treatment was observed. Eyes of greater macular thickness at baseline were more likely to be associated with CRT increase. Further controlled, long-term studies are needed to evaluate the impact of laser treatment more thoroughly.

REFERENCES


