

# Observation of Retinal Neovascularization using Optical Coherence Tomography Angiography after Panretinal Photocoagulation for Proliferative Diabetic Retinopathy

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## Research Article

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# Abstract

**Background:** To describe the longitudinal changes of retinal neovascularization elsewhere (NVE) on optical coherence tomography angiography (OCTA) in proliferative diabetic retinopathy (PDR) treated by panretinal photocoagulation (PRP).

**Methods:** Each patient included in this prospective clinical study was newly diagnosed PDR and NVE on both fundus fluorescein angiography (FFA) and OCTA. They received PRP of 4 sessions using multi-wavelength laser. Best-corrected visual acuity (BCVA) and OCTA images encompassing NVE were obtained before each PRP session and at 1 month, 3 months, and 6 months. Paired sample *t*-test was used to investigate differences between BCVA and NVE area before and after PRP.

**Results:** Thirty-two eyes of 32 patients with a mean age of  $50.56 \pm 7.05$  years were included. We found statistically significant reduction in the NVE size at all timepoints compared with the baseline except at 6 months (all  $P < 0.05$ ). Further analysis demonstrated no statistically significant change of NVE size between two adjacent timepoints except from baseline to post-1<sup>st</sup> PRP and from 3 months to 6 months (both  $P < 0.05$ ). BCVA at 3 months showed a statistically significant improvement compared with baseline ( $P < 0.05$ ), but no significant changes of BCVA were observed during other visits.

**Conclusions:** Using OCTA we found an overall regression in the NVE size following PRP starting as early as 1 week after 1<sup>st</sup> session and lasting until 3 months. OCTA provides quantitative information of vascular changes and could be a practical method for the longitudinal evaluation of neovascularization.

## Background

Diabetic retinopathy (DR) is the leading cause of visual impairment and blindness in the working population. DR was responsible for vision loss in 12.6% of diabetic patients and tended to occur in patients much younger than that in western countries<sup>[1]</sup>, and proliferative diabetic retinopathy (PDR) characterized by retinal neovascularization at the disc (NVD) or elsewhere in the retina (NVE) is the most common form<sup>[2]</sup>. Panretinal photocoagulation (PRP) has been the standard treatment for PDR during the past several decades. Although anti-VEGF agents demonstrated a positive effect in regressing retinal neovascularization in recent years, PRP is still recommended by 98% of retina specialists as primary management of PDR<sup>[3]</sup>. In China, the treatment of repeated injections of anti-VEGF agents was impractical in many patients because they are not covered by medical insurance, but the cost-effectiveness and relatively long duration make PRP a sound and sensible choice for these patients.

The goal of PRP is to modify the natural history of PDR by regressing neovascularization (NV) and destroying areas of peripheral retina to reduce the drive for NV formation. According to the ETDRS, 60% of PDR patients responded to PRP with regression of NV within 3 months<sup>[4]</sup>, but the temporal profile of NV changes has not been addressed in a detailed fashion. The introduction of optical coherence tomography angiography (OCTA) has provided clinicians with a non-invasive tool to study the morphological details of retinal neovascular complex. The quantitative information on NVE can be

regularly obtained with OCTA without concern for the intravenous dye-related adverse outcomes related with fundus fluorescein angiography (FFA). Furthermore, the absence of leakage in OCTA facilitates a precise delineation of NV area, which enables the frequent and repeated evaluation of NV changes before and after PRP sessions.

In the present study, we sought to explore the short-term and long-term effect of PRP in regressing retinal NV, and OCTA was performed to quantify and monitor the NVE changes over time in response to PRP treatment.

## Methods

This was a prospective analysis of case series including the patients diagnosed as PDR in the Department of Ophthalmology at Peking Union Medical College Hospital between December 2017 and February 2019. The study was approved by the Ethics Committee of Peking Union Medical College Hospital. All procedures were carried in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants. Inclusion criteria included patients with newly diagnosed PDR and NVE on both FFA and OCTA, and those who had not underwent any treatment. Exclusion criteria included other causes of NVE like retinal vein occlusion; fibrovascular proliferation with retinal traction; fibrosis, scarring, atrophy and hard exudates with central involvement; diabetic macular edema (DME) involving central macula; and previous history of vitrectomy, optic neuropathy and uncontrolled glaucoma.

The eligible patients received PRP in 4 sessions with an interval of 1 week between sessions. PRP was performed in the order of the nasal, inferior, superior, and temporal sides with 300 ~ 400 scatter laser burns per session by a retina specialist (Feng H.) using VISULAS® Trion multi-wavelength laser (Carl Zeiss Meditec Inc., Dublin, CA) and was completed with a total of 1200 ~ 1600 spots. During the treatment, laser parameters were individually adjusted to obtain mild white spots, with a 300-micron spot size and separated 1 spot apart between them.

Patients underwent comprehensive ophthalmic examinations that included best-corrected visual acuity (BCVA) (Snellen visual acuity ratios), intraocular pressure, slit-lamp biomicroscopy, indirect ophthalmoscopy and OCTA examination. Data was collected at 7 timepoints: at baseline on the same day they underwent the first PRP session; at each visit before second, third, and fourth PRP session; then at 1 month, 3 months, and 6 months after the last PRP session. The primary outcome was NVE changes from baseline to 6 months, and secondary outcome was BCVA changes over time.

OCTA images were acquired by a retina specialist (Feng H.) using the RTVue-XR Avanti spectral-domain OCT with AngioVue software 2.0 (Optovue Inc., Fremont, California, USA). The “HD Angio Retina 6 × 6mm” mode was used to encompass the NVE area also visible on the corresponding FFA. Images with low scan quality (SSI less than 40) or significant motion artifact were discarded, and the best images for the detection of new vessel structures were selected for analysis. To ensure the validity and repeatability of the results, the images were analyzed by two independent retina specialists who were masked to the

clinical status of the patients (Weihong Y. and Fangtian D.). B-scan OCT images with overlaying flow signal were used to confirm the presence of new vessels, which were structures with positive flow signals existing on the surface of retina or protruding into the vitreous cavity. Segmentation of the inner boundary of the B-scan was manually moved at the vitreous cavity above the new vessels, and the outer boundary was manually adjusted just below the internal limiting membrane to minimize the depiction of superficial vascular plexus [5]. A region of interest was manually outlined by the retina specialists to encompassing the new vessels, then the flow area was automatically calculated by multiplying the number of pixels for which the decorrelation value was above that of the background with the pixel size using the Angiovue software (Fig. 1). Measurements of NVE area represent the average value obtained by the two observers. Before statistical analysis, the images obtained by OCTA were corrected according to the Littman formula and Sampson DM et al's conclusion[6, 7].

We used generalized estimating equations (GEE) to take into account the correlation of changes over time by assuming an autoregressive(1) correlation structure of the responses from subjects. Multiple comparisons were adjusted by using Tukey's method. Intraclass correlation coefficients (ICC) was calculated to assess the agreement between the observers. A *P* value of less than 0.05 was considered statistically significant.

## Results

OCTA images from 6 patients were discarded because of low scan quality or significant motion artifact, and a total of 32 patients (32 eyes) with a mean age of  $50.56 \pm 7.05$  years were enrolled in this study. The mean baseline NVE area was  $1.448 \pm 1.101 \text{ mm}^2$ , and mean baseline BCVA on logMAR was  $0.286 \pm 0.164$ . None of the patients underwent additional PRP or other treatment procedures during the follow-up period.

There was excellent agreement between the two observers with respect to NVE size. The mean NVE before and after PRP sessions along with the corresponding intra-class correlation coefficients (ICC) between observers are summarized in Table 1. Compared with baseline, a statistically significant reduction in NVE size was observed at all time points ( $P < 0.05$ ) excluding that at 6 months (Fig. 2). On further analysis, the change in NVE size was statistically significant from baseline to post-1st PRP ( $P = 0.0004$ ; Table 1). There was no statistically significant difference in NVE size between other adjacent timepoints. BCVA at 3 months showed a statistically significant improvement compared with baseline ( $P < 0.05$ ), but no significant changes of BCVA were observed during other visits.

Table 1

The difference of mean NVE area in comparison with previous timepoint

	mean NVE area	ICC between observers	<i>P</i>
Baseline	1.448 ± 1.101	0.927	-
Post-1st PRP	1.297 ± 0.942	0.912	0.0004
Post-2nd PRP	1.268 ± 0.897	0.938	0.9906
Post-3rd PRP	1.206 ± 0.880	0.918	0.4447
1 months	1.172 ± 0.842	0.963	0.9685
3 months	1.121 ± 0.790	0.921	0.3384
6 months	1.155 ± 0.769	0.931	0.7951

## Discussion

In this study, we used OCTA to study the evolution of neovascularization in PDR after PRP therapy throughout 6-month follow-up period. It was demonstrated that the NVE regression started as early as 1 week following the first PRP session and lasted at least for 3 months.

PRP has been recommended in the latest Diabetic Retinopathy Clinical Guidelines released by American Academy of Ophthalmology in 2017[8] as the primary treatment of PDR. However, this destructive treatment may be associated with side effects such as pain, transient blurring, macular edema and loss of peripheral or night vision. Although it has been recommended by ETDRS to repeat PRP sessions from 3 months on in PDR patients[4], treatment regimens including interval between sessions and timing of additional laser varied across different studies. In this context, precise quantification of retinal NV area may be crucial for evaluating the efficacy of treatment regimens. Several authors have used FFA to investigate NV changes at 1 ~ 12 months after PRP, but the invasive nature and dye leakage related with FFA hindered frequent and accurate measurement of NV area[9–11]. With the recent availability of OCTA, retinal NV could be regularly followed up at short intervals. Russell JF et al imaged the NV in PDR patients from 1 week to 3 months after PRP with both FFA and OCTA, supporting the use of OCTA for longitudinal evaluation of NV[12]. In the current study, NVE size was serially measured at 7 timepoints, and to our knowledge, this is the first study that has used OCTA to describe in detail the evolution of retinal NV during and after PRP sessions.

Our findings suggest an early and relatively durable response of retinal NV to PRP therapy in treatment-naïve PDR patients, that is, a significant regression of NVE can be detected as early as 1 week after the first PRP session and lasted until 3 months, and significant changes of NVE occurred from baseline to post-1st PRP. Therefore, if one wants to decide whether a retinal NV is responsive to PRP therapy, one could make this determination as early as 1 week after the first session. In addition, if one wants to re-

treat retinal NV with additional laser when the therapeutic response is starting to wear off, one may need to wait for at least 3 months, which is consistent with the recommendations by ETDRS. If local intensive laser treatment for NVE was added to these patients as ETDRS prescribed, more significant NVE regression could be anticipated. Unlike the significant regression of NVE, BCVA in our patients showed no evident improvement except at 3 months, which may be due to the inevitable side effects related with laser. However, BCVA in these patients was not significantly worsening during PRP sessions, and BCVA at 6 months was still comparable with baseline, suggesting that laser regimen in this study was reasonable and effective in regressing NV and avoiding side effects as well.

Previous studies of FFA evaluating the response of retinal NV to PRP observed that anti-NV effect of PRP could last no more than 6 months[9–11], which is in line with the current study and suggests a relatively durable response of retinal NV to PRP treatment. As OCTA is a new imaging modality, it has been used by few authors to observe NV changes after PRP treatment. Russell JF et al imaged the NV in 20 eyes from 1 week to 3 months after PRP using both FFA and OCTA and reported similar progression or regression of NV with both methods[12]. Fawzi AA et al found that PRP has increased macular blood flow which could be measured by several OCTA parameters[13]. Our study firstly evaluated the NV changes during PRP sessions and demonstrated a very quick response of NV to PRP in treatment-naïve patients, supporting the use of PRP as primary treatment in such patients. Moreover, the comparison between two adjacent timepoints further demonstrated the short-term and long-term effect of PRP. Laser was administered on the nasal side during the 1st PRP session, which might cover more NV around the optic disc and should be the reason why more significant NVE regression was observed after this session. On the contrary, the increase of NVE area between 3 months and 6 months suggested that additional laser should be considered during this period.

OCTA was used in this study to establish the changes of NVE over time following PRP treatment. We found that NVE area could be rapidly quantified on OCTA, and it was feasible to follow up patients at short intervals without concern for potential FFA-related adverse events. Therefore, OCTA could be a useful imaging modality in monitoring the efficacy of treatment regimens in PDR patients, which reinforces the results obtained by Russel JF et al[12]. Since it was reported that 60% of patients with PDR responded to PRP treatment with NV regression within 3 months[11], OCTA could be potentially used in the irresponsive cases to monitor the changes of NV for the reference of treatment regimens such as timing of additional laser and combination of other treatment.

This pilot study has several limitations. First, the small sample size and relatively short follow-up period did not allow a comprehensive evaluation of NVE changes following PRP treatment. Further studies to analyze larger datasets are needed to reinforce our results. A second limitation is that the observation of NVE was restricted within a narrow field of view and peripheral NVE could not be visualized. The development of OCTA imaging such as wide-angle display should address this concern. Third, OCTA images may be also affected by several types of artifacts. Although images with severe artifacts affecting the measurement have been excluded, the potential effect of some artifacts should be carefully evaluated. Some authors have adjusted the image size according to individual axial length[7]. Axial

length correction was not performed in this study because all included cases had a refractive error less than  $\pm 3.0D$ , but this might have an impact on the area calculation of new vessel area. NVE area in this study was automatically calculated using the Angiovue software through multiplying the number of pixels for which the decorrelation value was above that of the background. This was dependent on the image quality and might influence the repeatability of measurements in some cases. The leakage of new vessel could not be identified with OCTA as with FFA, thus the activity of NV could be not being directly evaluated, and the presence of residual vessels on OCTA may or may not correlate with activity or risk of vision loss. Therefore, in cases with persistent NV on OCTA, FFA is warranted to assess its activity, and the prognosis of such blood vessels needs further investigation. In one of our cases, shrinking NVE was present on OCTA image of one year after PRP, but no fluorescein leakage was observed on FFA at the same time (Fig. 3), suggesting that endothelial cells of these residual blood vessels may have improved even normal function. However, the prognosis of such blood vessels is still unclear and needs further observation.

## Conclusion

We observed in the patients with PDR an overall regression of NVE area following PRP treatment which started 1 week after the first session and lasted until 3 months. OCTA provided quantitative information on vascular changes and may have an important role in monitoring the efficacy of treatment regimens in these patients.

## List Of Abbreviations

DR	diabetic retinopathy
PDR	proliferative diabetic retinopathy
NVD	retinal neovascularization at the disc
NVE	retinal neovascularization elsewhere
PRP	panretinal photocoagulation
NV	neovascularization
OCTA	optical coherence tomography angiography
FFA	fundus fluorescein angiography
DME	diabetic macular edema
BCVA	best-corrected visual acuity
GEE	generalized estimating equations
ICC	intraclass correlation coefficients

## **Declarations**

### **Ethics approval and consent to participate**

The study was approved by the Ethics Committee of Peking Union Medical College Hospital. All procedures were carried in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants.

### **Consent for publication**

All authors have approved the manuscript and agree with submission.

### **Availability of data and materials**

The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis as well as the decision to submit for publication.

### **Competing interests**

The authors have no conflicts of interest to declare.

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### **Authors' contributions**

The authors have contributed to this manuscript as follows: Feng He carried out the study, follow-up the cases, analyzed the results, and wrote the manuscript. Weihong Yu designed the study, and reviewed the manuscript. Fangtian Dong designed the study.

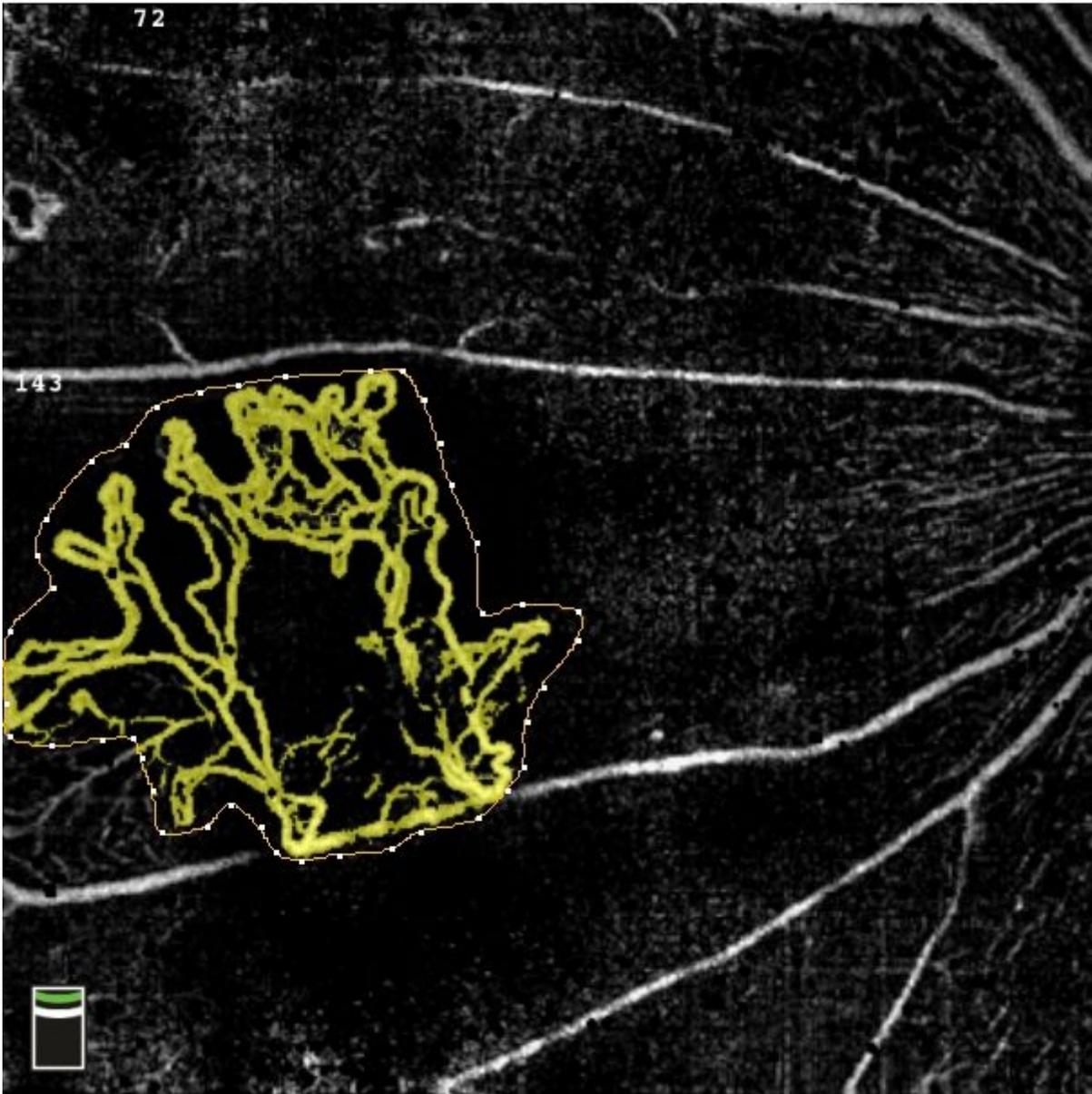
### **Acknowledgements**

Not applicable

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## Figures



**Figure 1**

The measurement of neovascularization area on OCTA. A select area of 0.998 mm<sup>2</sup> (highlighted) was manually outlined by the retina specialist, and the flow area of 0.653 mm<sup>2</sup> was automatically calculated by Angiovue software.

## Mean NVE area before and after PRP sessions in comparison with baseline

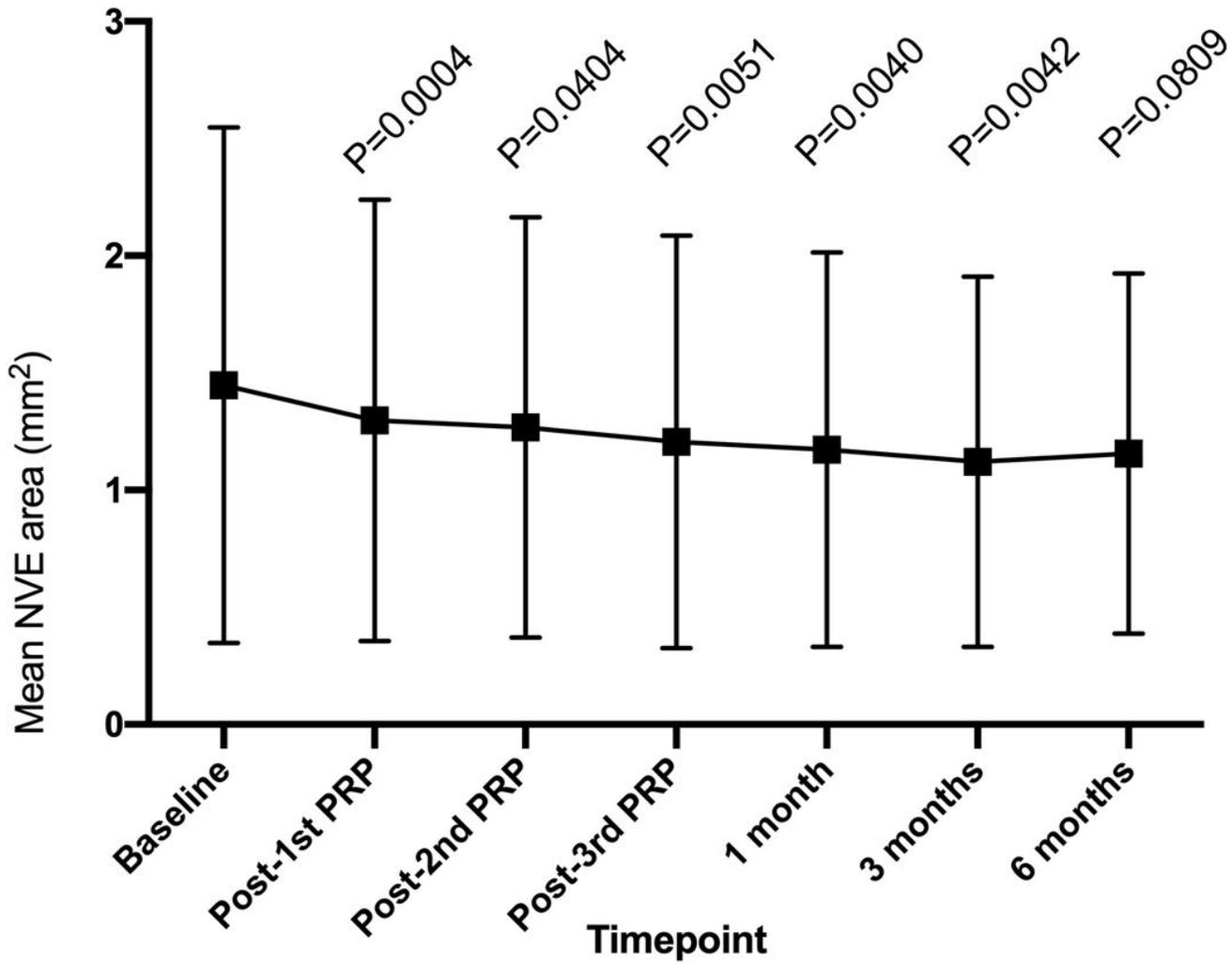


Figure 2

Mean NVE areas(mm2) before and after PRP sessions in comparison with baseline.

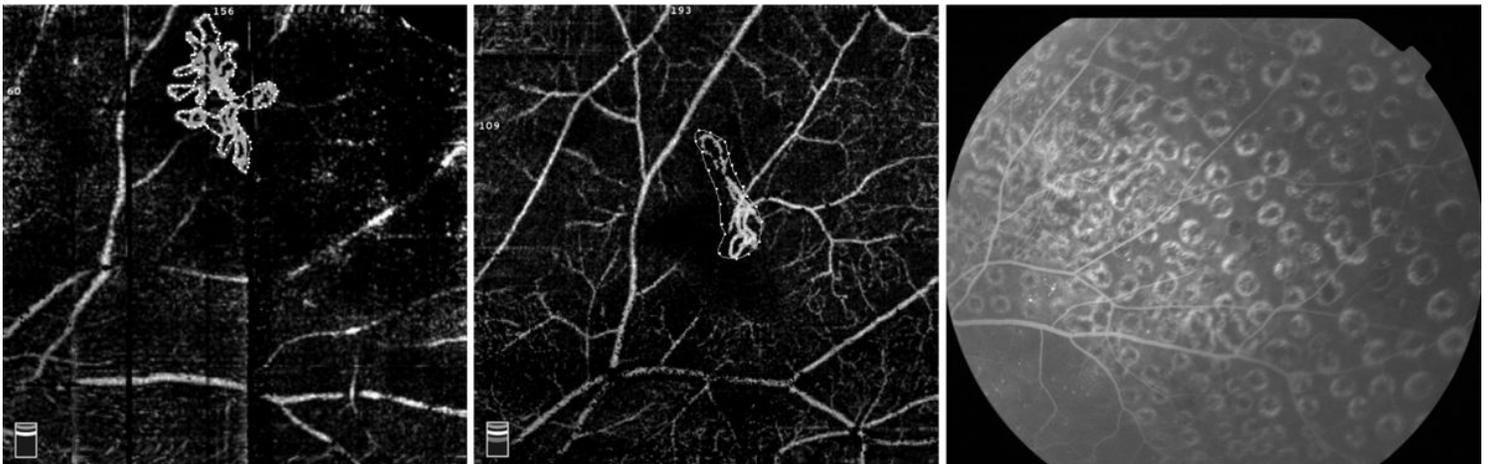


Figure 3

Neovascularization at baseline OCTA with a select area of 0.998 mm<sup>2</sup> (highlighted), and a flow area of 0.653 mm<sup>2</sup> (left); OCTA still showed abnormal vascular shape at an interval of 1 year after PRP, with a select area of 0.675 mm<sup>2</sup> (highlighted), and a flow area of 0.272 mm<sup>2</sup> (middle), and no evidence of fluorescein leakage was seen at the FFA (right).