Retinal Hemodynamics Seen on Optical Coherence Tomography Angiography Before and After Treatment of Retinal Vein Occlusion

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Purpose. This study evaluates the retinal hemodynamics using optical coherence tomography angiography (OCTA) before and after anti–vascular endothelial growth factor (VEGF) therapy in patients with macular edema associated with retinal vein occlusion (RVO).

Methods. Twelve patients (23 eyes; mean age, 64 years) were included (eight eyes with branch RVO, four with central RVO, and 11 unaffected fellow eyes). The best-corrected visual acuity (BCVA) and central retinal thickness (CRT) were measured before and 6 months after treatment. The foveal avascular zone (FAZ), nonperfused areas (NPAs), and flow area were evaluated with OCTA before and after treatment.

Results. The BCVA and CRT improved significantly after treatment. In eyes with RVO, the baseline FAZ in the retinal deep capillary layer was larger than in fellow eyes and enlarged in the retinal superficial and deep capillary layers after therapy; NPAs decreased after therapy, especially in the retinal deep capillary layer; and the baseline flow area was smaller than in fellow eyes and improved after therapy, especially in the retinal deep capillary layer.

Conclusions. Optical coherence tomography angiography can evaluate the retinal hemodynamics in patients with RVOs. Anti-VEGF therapy reduced the NPA size and improved retinal blood flow, especially in the retinal deep layer. The current results suggested that anti-VEGF therapy might improve retinal deep ischemia in patients with RVO in the retinal deep layer, which is abundant in capillaries.

Keywords: optical coherence tomography angiography, foveal avascular zone, nonperfused area, retinal vein occlusion, anti–vascular endothelial growth factor therapy

A nti–vascular endothelial growth factor (VEGF) agents have revolutionized treatment of retinal diseases, such as exudative age-related macular degeneration, diabetic retinopathy, retinal vein occlusion (RVO). Recent prospective, randomized, and multicenter clinical trials have shown the effectiveness of intravitreal anti-VEGF agents in several retinal diseases. The side effects of blocking VEGF remain a concern, one of which is whether anti-VEGF therapy impairs retinal blood circulation and facilitates retinal vascular occlusion in eyes with diabetic retinopathy and RVO.

Recently developed noninvasive optical coherence tomography angiography (OCTA) enables mapping of several retinal and choroidal vascular layers. Moreover, OCTA has been used to measure the area of the foveal avascular zone (FAZ) and vascular density. We reported that OCTA can visualize nonperfused areas (NPAs) better than fluorescein angiography (FA) in branch retinal vein occlusion (BRVO). Considering these benefits of OCTA, the NPA and FAZ might be better measurable with OCTA than with FA.

In the current study, we quantified the retinal hemodynamics, that is, FAZs, NPAs, and flow areas in BRVO and central RVO (CRVO) using OCTA. We also evaluated the difference between the eyes with RVO and fellow eyes and the effect of anti-VEGF therapy on the retinal hemodynamics in patients with macular edema in RVOs during the follow-up period.

Methods

Study Design and Setting

This was a retrospective, observational, consecutive case series conducted in an institutional setting. The Institutional Review Board of Nagoya City University Graduate School of Medical Sciences approved the study protocol. The clinical trial was registered in University Hospital Medical Information Network Clinical Trials Registry (UMIN-ID: UMIN000015143). All patients provided written informed consent for participation in the study. The described research methods and analysis adhered to the tenets of the Declaration of Helsinki.

Patients

This study was conducted at Nagoya City University Hospital from November 2014 through May 2016. Twenty-three eyes of 12 patients (three men, nine women; mean age, 64 years; range, 42–78 years) were enrolled, including 12 eyes with macular edema associated with RVO (BRVO, eight eyes; CRVO, four eyes) and 11 unaffected fellow eyes. The patient characteristics are shown in Table 1. The fellow eye of patient 8 was excluded because the patient had BRVO bilaterally.
Interventional and Observational Procedure

All patients underwent an ophthalmic examination including measurement of the best-corrected visual acuity (BCVA), indirect ophthalmoscopy, fundus photography, OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Jena, Germany), OCTA (RTVue XR Avanti, AngioVue; Optovue, Inc., Fremont, CA), and FA (Optos 200Tx Imaging System; Optos PLC, Dunfermline, Scotland). Two masked retinal specialists determined the BRVO subtype (major or macular). Branch retinal vein occlusions with a NPA larger than 5 disc diameters and CRVOs with a NPA larger than 10 disc areas on FA were defined as an ischemic type.

All patients received intravitreally injected anti-VEGF agents to treat macular edema associated with RVO. Ranibizumab (Lucentis; Novartis International AG, Basel, Switzerland) was used to treat BRVO, and aflibercept (Eylea; Bayer HealthCare Pharmaceuticals, Berlin, Germany) was used to treat CRVO. All patients were followed monthly from the initial visit through 6 months after the initial treatment. Additional injections of both anti-VEGF agents were administered if a patient had macular edema that exceeded 250 μm of central retinal thickness (CRT) and/or exudative change at the macula. The ophthalmic examination included measurement of the BCVA, OCT, and OCTA, which were performed before treatment and month 6 after the initial treatment. The CRT was measured on OCT. Optical coherence tomography angiography images were obtained using RTVue XR Avanti, AngioVue with a split-spectrum amplitude decorrelation angiography algorithm as described previously. Optical coherence tomography angiography images 3 × 3 mm in area centered on the fovea were used for data analysis (Figs. 1–3). The FAZ, NPA, and flow area were measured using the software in the OCTA system. Fluorescein angiography was performed before treatment and months 3 or 6 after surgery to determine the type of RVO and/or determine the need for laser photocoagulation. Retinal scatter laser photocoagulation was applied to the peripheral ischemic retina to prevent retinal neovascularization and/or vitreous hemorrhages.

Statistical Analysis

The visual acuity (VA) was measured using Landolt C charts and converted to the logarithm of the minimal angle of resolution (logMAR) for statistical analyses. The paired t-test was used to compare the logMAR VA and CRT before and 6 months after anti-VEGF therapy. The FAZ and flow area in the
eyes with RVO and the fellow eyes were compared using the paired t-test. The significance level was \( P < 0.05 \).

**RESULTS**

**Retinal Vein Occlusion Subtypes and Intervention**

Patient characteristics are shown in Table 1. Six major BRVOs and two macular BRVOs were identified. All six major BRVOs were ischemic, and two macular BRVOs were nonischemic. One ischemic CRVO and three nonischemic CRVOs were identified. Treatment for each patient is shown in Table 2. The mean numbers of anti-VEGF injections were 3.8 ± 1.6 (mean ± standard deviation) in eyes with BRVO and 2.8 ± 1.0 in eyes with CRVO. Retinal scatter laser photocoagulation was performed to treat NPAs in only one eye (patient 6) of eight eyes with BRVO because of retinal neovascularization. No eyes with CRVO were treated with laser photocoagulation during the follow-up period.

**Best-Corrected Visual Acuity**

The decimal BCVAs are shown in Table 3. In five of the eight eyes with BRVO and two of the four eyes with CRVO, the BCVAs improved over 1.0 decimal unit after treatment. The mean logMAR VAs in the eyes with RVO improved significantly \( (P = 0.0092) \) 6 months after the treatment (Table 3).

**Central Retinal Thickness**

The CRT values are shown in Table 3. The CRTs in the eyes with RVO decreased significantly \( (P < 0.0001) \) 6 months after anti-VEGF therapy.

**Central Avascular Zone**

In eyes with RVO, the FAZs enlarged significantly compared with that in the fellow eyes in the retinal deep layer but not in the retinal superficial layer (Fig. 4). Moreover, the FAZ areas in eyes with RVO were enlarged 6 months after anti-VEGF therapy, especially in the retinal superficial capillary layer (Fig. 5). Interestingly, in eyes treated with fewer injections of anti-VEGF agents, the FAZ size of both the layers was much enlarged compared with that in eyes treated with more frequent injections (Fig. 5). Figure 1 shows the FAZ in a representative patient.

**Nonperfused Area**

In eyes with RVO, the NPAs decreased 6 months after anti-VEGF therapy in both the superficial and deep capillary layer (Fig. 5). Interestingly, more frequent injections of anti-VEGF injections resulted in more reduction of NPAs in both layers compared with fewer injections. In addition, the effect was more notable in retinal deep layer (Fig. 5). Figure 2 shows the NPA in a representative patient.

**Flow Area**

In eyes with RVO, the flow area was smaller than in the fellow eyes in both the superficial and deep capillary layers (Fig. 4). Moreover, more frequent injections of anti-VEGF agents improved the flow areas in both layers compared with fewer injections, which suggested that continual blockade of VEGF might result in reperfusion of the NPAs (Fig. 5). Similar to the result in the NPAs, the effect was more notable in the retinal
deep layer (Fig. 5). Figure 3 shows the flow area in a representative patient.

**DISCUSSION**

In the current study, we evaluated the retinal hemodynamics, including the FAZ, NPA, and flow area using OCTA; the differences between the eyes with RVO and the fellow eyes; and the changes in retinal hemodynamics before and after anti-VEGF therapy in RVOs.

The first finding was that the FAZ area in eyes with RVO was larger than in the fellow eyes and was enlarged 6 months after anti-VEGF therapy, especially in the retinal superficial capillary layer. A previous report using FA showed that the FAZ in eyes with BRVO was larger than in the fellow eyes. However, the FAZ itself and its border on the FA images were obscured. Therefore, quantitative analysis of the FAZ is difficult on FA. In addition, using FA, it is impossible to perform differential layer analysis in the retinal superficial and deep layers. Samara et al. reported enlargement of the FAZ area using OCTA and showed that the FAZ was enlarged only in the deep layer in eyes with BRVO compared with the fellow eyes. Our current result was the same. We also found that the FAZ area in eyes with BRVO or CRVO was enlarged, especially in the deep capillary layer. Furthermore, the FAZ area was larger in eyes with CRVO than in those with BRVO (Fig. 6). The average intraocular VEGF levels are higher in eyes with CRVO than in BRVO. Even in patients without retinopathy who are diabetic, the intraocular VEGF levels increased and the FAZ area was enlarged. Enlargement of the FAZ area might be related to the intraocular VEGF levels. In fact, in eyes with fewer injections of anti-VEGF agents, the FAZ size in both the layers was much enlarged compared with that in eyes with more frequent injections (Fig. 5). Therefore, more frequent injections of anti-VEGF agents might suppress enlargement of the FAZ. Samara et al. reported that the size of the FAZ area in the deep layer was correlated positively with the logMAR VA. However, in the current study, the VA improved after therapy, although the FAZ enlarged gradually. Future studies with a large sample size are needed to determine a relation between FAZ size and VA. The FAZ size was larger in retinal deep layer than...
in retinal superficial layer (Fig. 5). On the other hand, the ratio of FAZ enlargement was bigger in retinal superficial layer than in retinal deep layer (Fig. 5).

Our second finding was that the NPAs in eyes with RVOs decreased 6 months after therapy, especially in the retinal deep capillary layer. Interestingly, more frequent injections of anti-VEGF agents resulted in smaller NPAs and improved flow area, while fewer injections did not do so, suggesting that frequent blockade of VEGF might result in reperfusion of NPAs and improved retinal vessel flow. It has been recognized for many years that in some patients with RVOs the NPAs increase in size over time.22 Therefore, the current result was surprising. Also, it is still controversial whether VEGF inhibition worsens retinal ischemia.23 Because VEGF is a survival factor for vascular endothelial cells, its blockade might result in worse progression of the retinal ischemia.23 In fact, several studies have reported such an effect.9–11 However, Campochiaro et al.22 reported that blockade of VEGF not only prevented worsening of NPAs but also might have improved the retinal perfusion status. That report supports our current results. However, in the study of Campochiaro et al., the NPAs were assessed on FA images and the size was expressed in disc areas. In addition,

### Table 3. Changes in VA and CRT in Each Patient

<table>
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<th>Patient</th>
<th>VA, Decimal Units</th>
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<tr>
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Average 0.346 ± 0.302 0.0357 ± 0.0758 569 ± 130 285 ± 42.7

P value 0.0092* <0.0001*

* Significant difference.

### Figure 4. Mean value of FAZs and flow areas in fellow eyes and eyes with RVO. Error bars represent standard error. In eyes with RVO, the FAZs enlarged significantly compared with those in the fellow eyes in the retinal deep layer but not in the retinal superficial layer. The flow areas in eyes with RVO were smaller than in the fellow eyes in both the superficial and deep capillary layers, although the differences were not significant. *Significant difference. Superficial indicates retinal superficial capillary layer; deep indicates retinal deep capillary layer.

### Figure 5. Mean value of FAZs, NPAs, and flow areas. Error bars represent standard error. (A) Mean value of FAZ, NPA, and flow area in eyes with retinal vein occlusion at baseline and 6 months after treatment. (B) Mean percentages 6 months after anti-VEGF therapy compared with baseline. Red indicates over 20% increase; Blue indicates over 20% reduction. Superficial indicates retinal superficial capillary layer; deep indicates retinal deep capillary layer.
retinal hemorrhages usually result in hypofluorescence on FA images because both excitation and emission lights are blocked but minimally impair the OCTA images obtained using a longer wavelength light (840 nanometers). We previously reported that OCTA visualizes NPAs better than FA. Moreover, OCTA enables quantification of the size as an absolute value. Taken together, OCTA is superior for evaluating NPA size compared with FA. Intraocular injections of VEGF drugs in primates resulted in leukostasis and progressing NPAs. Miyamoto et al. also reported that VEGF-induced capillary nonperfusion occurred downstream from the area of leukocyte adhesion. Later, after the disappearance of the leukocytes, the capillaries reopened because neutrophil and monocyte diameters can exceed those of retinal capillary lumens. Vascular endothelial growth factor blockade might halt leukocyte adhesion and lead to retinal reperfusion. If VEGF inhibition actually reduces the size of the NPA in RVOs, it might suppress the incidence of retinal and iris neovascularization and neovascular complications. In fact, in the current study, only one eye (patient 6 with BRVO) underwent laser photocoagulation because of retinal neovascularization, although the follow-up period was just 6 months.

In eyes with RVOs, venous obstruction leads to turbulent blood flow, elevated venous pressure, and overload of drainage capacity that might cause dilation of retinal vessels and capillaries. In the current study, the retinal flow area in the eyes with RVO was smaller than in fellow eyes, especially in the retinal deep capillary layer; this occurred despite retinal vessel dilation in the eyes with RVO, possibly because those eyes have NPAs. Therefore, the flow area in the eyes with RVO might improve after anti-VEGF therapy, accompanied by decreased NPAs. Furthermore, more frequent injections of anti-VEGF agents improved the flow area, while fewer injections did not do so, which was the same result as with the NPAs. That also supports the relation between the NPAs and retinal flow.

Anti-VEGF therapy reduced the NPA size and improved retinal flow, especially in retinal deep capillary layer. A previous analysis of the human retina showed that the densities of the capillaries were much greater in the deep capillary layer than in the superficial layer. Therefore, the deep retinal layer might be more susceptible than the superficial layer. However, it is unclear why the FAZ enlargement was more notable in the retinal superficial layer than in the deep layer. The resolution of macular edema might affect the enlargement of FAZ size on OCTA in the retinal superficial layer.

The current study had several limitations. First, there were no controls. Untreated control subjects are needed to evaluate the effect of anti-VEGF therapy. Second, the sample size was limited, and the study design was retrospective. Third, the eyes with BRVO and those with CRVO were treated with different intravitreal drugs. The number of injections also differed among the patients. Fourth, the area in which we evaluated the retinal hemodynamics was too small, that is, within only a 3 × 3-mm area of the posterior pole. This is because the image quality in a 3 × 3-mm area is much better than in a 6 × 6-mm area. Wide-field OCTA with high-quality images is eagerly awaited for evaluating the entire scope of the retinal hemodynamics.

In conclusion, our current results showed that OCTA can evaluate the retinal hemodynamics noninvasively. Using this system, we found that anti-VEGF therapy improved the retinal deep ischemia in RVOs. A future prospective, randomized, controlled study with a large sample size is needed to confirm the current results.

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