Association between Optical Coherence Tomography Angiographic Findings and Visual Acuity in Retinal Vein Occlusion

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Purpose: To describe optical coherence tomography angiography (OCTA) findings in retinal vein occlusion and to analyze their correlation with visual functions.

Methods: Fluorescein angiography, optical coherence tomography and OCTA (RTVue XR Avanti with AngioVue, Optovue, Fremont, CA, USA) were performed. Qualitative analysis of the imaging data was performed.

Results: Twenty-one eyes from 20 patients were included. On OCTA, characteristic findings of the involved areas were noted in the superficial plexus and the deep plexus. In the superficial plexus, telangiectasias were found in 2 out of 21 eyes (9.5%) and capillary dropout in 9 (42.8%). In the deep plexus, telangiectasias were found in 13 (61.9%) eyes, and capillary dropout in 13 (61.9%). All composites were found to be more common in the deep plexus than in the superficial plexus. Eyes with capillary dropout in the superficial plexus, which indicates ischemia, showed lower visual acuity compared with those without capillary dropout (p = 0.049).

Conclusions: We were able to demonstrate that OCTA could visualize telangiectasias and capillary dropout in each retinal capillary layer. In particular, capillary dropout in the superficial capillary plexus was associated with visual impairment.

Keywords: Deep capillary plexus; Optical coherence tomography angiography; Retinal vein occlusion; Superficial capillary plexus

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder following diabetic retinopathy [1-5], and it can result in visual impairment due to macular edema, macular ischemia or proliferative changes such as vitreous hemorrhage or, neovascular glaucoma in more advanced stages.
Currently, fluorescein angiography (FA) is the most reliable method to detect retinal non-perfusion and analyze vascular status; however, the possible side effects of FA include mild allergic reactions, such as nausea and skin rash, and rare but life-threatening reaction like anaphylactic shock [6]. Therefore, noninvasive methods of recognizing vascular status have been highly sought after.

Optical coherence tomography (OCT) reveals in detail the retinal anatomic status, including intraretinal fluid and macula edema. Recently, new imaging technologies have been developed that allow for new insights into visualizing normal and pathologic vascularization. OCT angiography (OCTA) allows for visualization of both the superficial and deep retinal vascular plexus without the need for dye injection [7,8]. It is typically difficult to visualize these vascular complexes with FA, but this technique enables noninvasive visualization of vessels in the posterior part of the eye, including segmenting different layers, using the “En-face” OCTA modality. OCTA is thus thought to be able to demonstrate the relationship between changes in each retinal layer and visual functions.

Few studies have investigated the correlation between OCTA findings and visual function in RVO. Therefore, the purpose of this study is to describe OCTA findings in RVO and to analyze their correlation with visual functions.

**Materials and Methods**

This retrospective case series adhered to the ethical standards of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

The study participants were those with RVO who were seen in Nune Eye Hospital (Seoul, Korea) between November 2014 and July 2015. Each patient underwent a complete ophthalmic examination that included the following: a best corrected visual acuity measurement using the Snellen visual acuity chart, anterior segment examination, intraocular pressure measurement, and dilated fundus biomicroscopy. FA (Spectralis HRA, Heidelberg engineering, Heidelberg, Germany), spectral domain OCT (SD-OCT, Spectralis, Heidelberg engineering, Heidelberg, Germany), and OCTA were also performed. The instrument used in the OCTA was based on the OptovueRTVue XR Avanti (Optovue, Inc., Freemont, CA, USA) and was used to obtain amplitude-decorrelated angiography images. This instrument has an A-scan rate of 70,000 scans per second and uses a light source that is centered at 840 nm and a bandwidth of 50 nm. Each OCTA volume contained $304 \times 304$ A-scans with two consecutive B-scans that were captured at each fixed position before proceeding to the next sampling location. Split spectrum amplitude decorrelation angiography (SSADA) was used to extract OCTA information. Each OCTA volume was acquired over 3 seconds, and two orthogonal OCTA volumes were acquired to perform motion correction to minimize motion artifacts that might have arisen from microsaccades and fixation changes. The angiography information is displayed as the average of the decorrelation values when viewed perpendicularly through the thickness being evaluated. The modifications in reflectivity are directly linked to blood flow. The horizontal and vertical scans were combined with an algorithm that compensates for the motion of the patients’ eyes (i.e., motion correction technology) to create a 3D volume of the retinal vascularization. To delineate the plane to visualize the vascular pattern of the macular area, the automated segmentation lines were adjusted to the inner and outer margins of the lesion. The reference planes of the outer retina and the inner retina were primarily used for the evaluation of the deep vascular plexus and the superficial vascular plexus. An artifact removal function was used to eliminate retinal vessel shadowing.

Qualitative analysis and comparisons of the entire imaging data were conducted. Two retinal specialists read OCTA images to determine the presence of telangiectasias, and capillary dropout. If the interpretation between two readers was different, a senior reader interpreted the results. When the image results of automated segmentation were poor, manual delineation of the superficial and deep retinal capillary plexus was performed. Telangiectasia was defined as an abnormal extension of the retinal capillary image on OCTA ($3 \times 3 \ mm^2$ mode, macular area). Capillary dropout was defined as an abnormal non-perfusion area to the boundary of the foveal avascular zone.

Statistical analyses were performed with a commercially available software package (PASW Statistics v. 18.0; SPSS Inc., Chicago, IL, USA). The Snellen visual acuity was converted to the Logarithm of the minimum angle of resolution (LogMAR) visual acuity and the Mann-Whitney test was used to compare the LogMAR visual acuity for the group.
Results

Demographics
Twenty-one eyes from 20 patients (16 women and 4 men) were included. The patients ranged in age from 30 to 79 years with a mean age of 62.4 years. All patients were Asian. The diagnoses of RVO were already established in all patients based on clinical history and fundus and angiographic features (3 CRVO and 18 BRVO). All patients presented with a long history (>3 months) of clinical treatment and minimal changes in their macular edema during the follow-up periods. The Early Treatment Diabetic Retinopathy Study best-corrected visual acuities ranged from 20/500 to 20/20 (mean 20/30). The anterior segment examinations did not show any relevant features. The biomicroscopic fundus examinations revealed retinal hemorrhage, exudate, tortuosity, and retinal edema at the posterior pole, particularly in the macular area. All eyes presented features that were consistent with RVO on the FA, and Spectral Domain Optical Coherence Tomography (SD-OCT) examinations.

FA and SD-OCT findings
On FA, blocked fluorescence from intraretinal hemorrhage was common. Telangiectatic vessels that formed collaterals, capillary non-perfusion and edema across the horizontal raphe were found. Hyperfluorescent leakage in the early phase (5 eyes, 23.8%) and hyperfluorescent staining in the late phase (19 eyes, 90.4%) were visible.

The SD-OCT examinations demonstrated the presence of cystoid macular edema (12 eyes, 57.2%), intraretinal fluid (14 eyes, 66.6%), and subretinal fluids (2 eyes, 9.6%). The mean subfoveal retinal thickness was 329.2 μm (range 207-544 μm).

OCTA findings
OCTA enables close observation of both the superficial and deep capillary plexus, which is not possible with FA. Where FA shows vessel walls stained with fluorescein, OCT angiography instead shows a very weak flow surrounded by a dark shadow (Fig. 1).

OCT angiography revealed 2 composites: (1) telangiectasias, and (2) capillary dropout (Fig. 2, 3).

Telangiectasias was observed in 2 (9.5%) and 13 eyes (61.9%), in the superficial and deep plexuses, respectively. Capillary dropout was observed in 9 (42.8%) and 13 eyes (61.9%), in the superficial and deep plexus, respectively (Table 1).

Association with visual acuity
We investigated the association between visual acuity and each composite (Table 2). In the superficial plexus, the LogMAR visual acuity for the group with telangiectasias (0.747, n = 2 eyes) was poorer than that of the group without telangiectasias (0.261, n = 19 eyes) but this finding was not significant (p = 0.467). In the deep plexus, the visual acuity for the group with telangiectasias (0.448, n = 13 eyes) was poorer than that of the group without telangiectasias (0.079,
In the superficial plexus, the LogMAR visual acuity for the group with capillary dropout (0.542, \(n = 9\) eyes) was significantly poorer than that of the group without capillary dropout (0.131, \(n = 12\) eyes) \((p = 0.049)\). In the deep plexus, the visual acuity for the group with capillary dropout (0.448, \(n = 13\) eyes) was poorer than that of the group without capillary dropout (0.079, \(n = 8\) eyes) but this finding was not significant \((p = 0.370)\).

Figure 2. fluorescein angiography (FA) and optical coherence tomo- graphy angiography (OCTA) showed vascular engorgement and capillary dropout in the case of a branch retinal vein occlusion (62-year-old man). (A) Early phase FA shows extensive non-perfused retinal areas. (B) Magnified view of early-phase FA within a blue square. Though normal capillaries can be found, only dilated capillaries are noted. (C) OCTA of the superficial vascular plexus. The superior half of the image presents vascular engorgement and congestion. The blue lined area indicates a capillary dropout area. (D) OCTA of the deep vascular plexus. More distinct vascular engorgement and congestion are found. The yellow-lined area indicates a capillary dropout area. (E) The OCTA of the superficial plexus was automatically segmented with an inner retinal reference plane. (F) The OCTA of the deep plexus was automatically segmented with outer retinal reference plane.

Figure 3. optical coherence tomography angiography (OCTA) showing telangiectasias in a case of branch retinal vein occlusion (62-year-old man). (A) OCTA of the superficial vascular plexus. Compared with the deep vascular plexus, relatively minimal changes are indicated without capillary dropout. (B) OCTA of the deep vascular plexus. Yellow circles indicate telangiectasias.

Table 1. Characteristic findings of optical coherence angiography in retinal vein occlusion

|                     | Superficial plexus | Deep plexus |
|---------------------|--------------------|-------------|
| Telangiectasia      | 2 (9.5)            | 13 (61.9)   |
| Capillary dropout   | 9 (42.8)           | 13 (61.9)   |

Values are presented as n (%).

Discussion

RVO is an occlusive retinopathy, and the presence of edema or ischemia in the central macula determines the disease’s progress and visual function. However, FA, the standard technique for analyzing vascular status cannot evaluate the deep vascular plexus; in contrast OCTA, a new imaging technique, allows for detailed observation of the vascular state of the deep vascular plexus regardless of hemorrhage or edema.

Few studies have reported OCTA findings in retinopathies. Detailed images have been published of choroidal neovascularization [7]; quantitative analysis for microaneurysms and retinal non-perfused areas in eyes with diabetic retinopathy [9]; alternations of the inner and outer retinal vascular plexus; and invasion in the outer and subretinal spaces in eyes with macular telangiectasia type 2 [10].

OCTA revealed vascular dilatation, telangiectasias, and capillary dropout not only in the superficial but also in the deep vascular plexus; in addition, an association was found between the presence of capillary dropout and visual impairment. RVO apparently affects the deep capillary plexus, which was evidenced by the more frequent involvement of
the 3 composites (vascular dilatation, telangiectasia, and capillary dropout) in the deep compared with the superficial vascular plexus. However, when the superficial plexus was involved in more severe ischemic damage, visual impairment could be expected. In fact, in this study, capillary dropout in the superficial capillary plexus was associated with visual impairment. However, eight of the nine cases of capillary dropout in the superficial capillary plexus were also accompanied by capillary dropout in the deep capillary plexus. Nevertheless, the results when comparing the visual acuity between 4 cases of capillary dropout in deep capillary plexus only and 8 cases of simultaneous capillary dropout in the deep and superficial capillary plexuses, showed relatively great differences in LogMAR visual acuity (0.135 and 0.599 respectively), although this was not statistically significant ($p = 0.061$). Based on these results, capillary dropout in the superficial capillary plexus primarily occurs with capillary dropout in the deep capillary plexus especially in the severe form of RVO. This may be an indicator that represents a more severe form of ischemia in the retina, especially in the macula area. In this respect, it is believed that OCTA can be a very useful device: additional prospective studies using OCTA to evaluate these factors to determine the prognosis of visual acuity are needed.

Angiographichypo-fluorescent areas that indicate capillary occlusion or capillary dropout are regarded as areas of retina ischemia [11], that is, retinal non-perfusion. We determined non-perfusion status by observing capillary dropout in the macular area ($3 \times 3 \text{ mm}^2$). The microvascular network in the deep plexus near the macula has been reported to be well developed in the inner and outer borders of the inner nuclear layer [12,13]. Therefore, in DM retinopathy, the deep plexus is considered to be more protective against microthrombosis than the superficial plexus; however, in our study, ischemic signs such as capillary dropout and telangiectasias were more common in the deep plexus compared with the superficial plexus. A larger study is required to study this phenomenon in detail.

The deep capillary plexus is not observed by FA, and media opacity or leakage such as hemorrhage distort vascular images. OCTA has the advantage of observing changes in the deep capillary plexus, even in the early stages of disease, and it can distinguish between vascular changes of the deep capillary plexus and the superficial capillary plexus. Additionally, because of the noninvasive nature of OCTA, the risk of fluorescent side-effects is eliminated, and frequent application is possible. This enables observing changes over short time periods and evaluating the effects of treatment.

This study had several limitations. First, it was a small retrospective cross-sectional study. Second, the case group was heterogeneous, as each patient had undergone different treatments. Third, OCTA still has several technical problems. Fixation is required for several seconds, and the imaging is limited to a relatively small area ($3.0 \times 3.0 \text{ mm}$). In addition, vascular permeability malfunctions such as leakage and staining cannot be measured and the artery vein is hard to detect. These technical limitations of OCTA need to be improved.

This study reports OCTA findings in patients with RVO. With this imaging technique, we were able to demonstrate that OCTA could visualize telangiectasias, and capillary dropout in each retinal capillary layer. In particular, capillary dropout in the superficial capillary layer is associated with visual impairment. A prospective, large-scale study is required to evaluate the clinical value of OCTA for RVO imaging.

**Conflicts of interest**

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial
interest (such as honoraria; educational grants; participation in speakers’ bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interests (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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