Retinal Vessel Tortuosity Associated With Central Retinal Vein Occlusion: An Optical Coherence Tomography Study

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Conclusions. In eyes with CRVO, OCT can be used to visualize anteroposterior venous tortuosity and associated structural changes to the retinal parenchyma. Keywords: central retinal vein occlusion, retinal vessel tortuosity, optical coherence tomography

Central retinal vein occlusion (CRVO) is a vision-threatening retinal vascular disorder that occurs frequently in older individuals, and occasionally in the younger population.1–3 It is characterized by extensive flame-shaped retinal hemorrhages, venous engorgement and tortuosity, optic disc swelling, cotton wool spots, and macular edema. It has been proposed that CRVO is caused by a circulatory disturbance in the trunk of the central retinal vein at the level of the lamina cribrosa, or just posterior to it.4,5 Color Doppler flow imaging of eyes with CRVO has shown a marked reduction in venous flow rate in the central retinal vein.6–8 Fluorescein angiography (FA), an essential tool for the evaluation of disease severity, is used to visualize capillary nonperfusion and leakage from the macular capillaries.9,10 However, this technique, even when applied in stereoscopy, does not enable a three-dimensional evaluation of the retinal vessels in relation to the retinal neuronal tissues.

Technological advances in optical coherence tomography (OCT) image resolution and acquisition speed allow the retinal architecture to be visualized in great detail. These images have contributed to our understanding of the morphologic abnormalities that characterize various macular diseases.11–15 Extensive OCT investigations in eyes with retinal vein occlusion have identified various macular pathologies, that is, foveal cystoid spaces,12 serous retinal detachment,13 hyperreflective foci,16 and subretinal hemorrhage,17–19 that correlate with visual function.20,21 Moreover, sequential thin sectioning with OCT allows for three-dimensional evaluation of the morphologic changes to retinal vessels. For example, Muraoka et al.22 recently used this technique to obtain a hypothesis for the pathogenesis of branch retinal vein occlusion (BRVO).

The purpose of our study was to evaluate CRVO-associated vascular changes using OCT sequential thin sectioning and circumpapillary scanning. On the basis of our observations, we reported CRVO-associated retinal features that have not been described previously to our knowledge. We also have elucidated the association of these vascular changes with the associated retinal complications.

**Patients and Methods**

The Ethics Committee at Kyoto University Graduate School of Medicine approved this prospective study, which was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from each subject before any study procedures or examinations were performed. This prospective study consisted of 35 eyes of 35 consecutive patients with unilateral acute CRVO, who were...
examined at the Department of Ophthalmology of Kyoto University Hospital during the period from April 2011 to March 2013. In our study, only patients who had experienced symptoms for less than 3 months were included. The CRVO was diagnosed on the basis of a fundus examination and FA findings by two retina specialists (AT, TM). Of the 35 eyes included in our study, eight underwent pars plana vitrectomy for the treatment of macular edema. Eyes with hemi-CRVO, BRVO, or coexisting ocular disease (i.e., glaucoma or diabetic retinopathy), and eyes that had been treated previously for CRVO were excluded from our study.

At the initial examination, each patient underwent comprehensive ophthalmic examinations, including the measurement of best-corrected visual acuity (VA) using a Landolt chart, fundus biomicroscopy with a noncontact lens, and 45° digital fundus photographs (TRC-50LX, 3216 × 2136 pixels; Topcon, Tokyo, Japan) after pupil dilation. The FA in conjunction with a confocal laser scanning system (HRA-2; Heidelberg Engineering, Heidelberg, Germany) was performed to assess retinal perfusion status. The CRVO was classified as ischemic if the FA revealed more than 10 disc areas of nonperfusion.

At each visit, a comprehensive ophthalmologic examination was performed for each eye. The examination included the measurement of best-corrected VA, indirect ophthalmoscopy, slit-lamp biomicroscopy with a noncontact lens, and OCT using a Spectralis HRA+OCT (Heidelberg Engineering). The FA was performed if necessary. Of 27 eyes that did not undergo pars plana vitrectomy, three were treated with scatter laser photoagulation for the retinal nonperfusion.

The CRVO-associated major retinal vessels were assessed in detail using the Spectralis HRA+OCT. Each OCT A-scan had a depth of 2 mm and comprised 512 pixels, providing a depth transverse digital sampling of 3.87 × 7.50 μm per pixel. Longitudinal sections, along major retinal vessels, and cross-sections, vertical to the major retinal vessels, were sequentially and thinly imaged (minimally 25 sections of 5°, Fig. 1). Each sequential B-scan was the average of more than 20 scans of the same area. Circumpapillary OCT images were obtained in a 3.46-mm diameter annulus around the center of the optic disc. Each image represented the data derived from 100 B-scans of the same area.

To quantify the anteroposterior venous tortuosity associated with CRVO, we selected randomly one of the temporal major retinal veins in each eye for OCT imaging. Quantitative OCT measurements were performed using the manufacturer’s built-in software (Spectralis Acquisition and Viewing Modules, version 4.0; Heidelberg Engineering). By reviewing the sequential OCT sections of a given vein, we identified the innermost (vitreous side) and the outermost (choroidal side) points of the vessel wall (Fig. 2). At both points, we measured the vertical distance from the RPE line to the center of the venous lumen. We defined the degree of anteroposterior venous tortuosity as the difference between these two measurements (Fig. 2). In most eyes, the innermost point...
Table 1. Baseline Characteristics of Patients With Acute Central Retinal Vein Occlusion

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>66.3 ± 15.4</td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>12/23</td>
</tr>
<tr>
<td>Hypertension, +/−</td>
<td>18/17</td>
</tr>
<tr>
<td>Diabetes mellitus, +/−</td>
<td>10/25</td>
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<tr>
<td>Duration of symptoms, wks</td>
<td>4.0 ± 4.3</td>
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<tr>
<td>Visual acuity, logMAR</td>
<td>0.31 ± 0.39</td>
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<td>Foveal thickness, μm</td>
<td>566.8 ± 228.7</td>
</tr>
<tr>
<td>Height of serous retinal detachment, μm</td>
<td>95.9 ± 110.4</td>
</tr>
<tr>
<td>Foveal cystoid spaces, eyes</td>
<td>27.77%</td>
</tr>
<tr>
<td>Foveal serous retinal detachment, eyes</td>
<td>21.60%</td>
</tr>
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<td>Retinal perfusion status, nonischemic/ischemic</td>
<td>30/5</td>
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</table>

RESULTS

OCT Imaging of Retinal Vessels in Physiologically Normal Eyes

To characterize the morphologic features of nondiseased retinal vessels, we first examined the major retinal vessels in the contralateral eyes. Cross-sectional OCT images (vertical-to-horizontal ratio, approximately 3:2) revealed major retinal vessels as oval-shaped configurations with heterogeneous reflectivity. These vessels were located primarily within the retinal nerve fiber layer (RNFL) and, occasionally, in the inner plexiform layer (IPL, Fig. 1). The primary location of major retinal vessels within the RNFL also was confirmed in circumpapillary OCT sections. In these OCT sections, vessels appeared as four distinctive hyperreflective entities in a given plane (Fig. 1). The tops and bottoms of the vessel walls depicted on these images represented the innermost (vitreous side) and outermost (choroidal side) hyperreflectivities, respectively. Paired areas of hyperreflectivity, typically hourglass-shaped, were observed within the vessel lumen as well. In longitudinal sections, four areas of vessel hyperreflectivity were band-shaped, with the inner- and outermost bands representing the vessel wall, and the two intermediate bands representing the bloodstream.

Abnormalities of the Retinal Vasculature in Eyes With CRVO

We examined 35 eyes with acute CRVO from 35 patients (12 women, 23 men, Table 1). Fundus examination at the initial visit revealed that all eyes had retinal hemorrhages, marked venous dilation, and tortuosity in all four quadrants. All eyes exhibited retinal thickening with a mean foveal thickness of 566.8 ± 228.7 μm, as measured by OCT. Late-phase FA photographs revealed filling delays in numerous large vessels in all eyes with CRVO. Broad areas of nonperfusion (>10 disc diameters) and modest areas of nonperfusion (≤10 disc diameters) were seen in five and 30 eyes, respectively.

During the acute phase, OCT was used successfully for three-dimensional visualization of the retinal vasculature in all eyes (86%). Similar to the contralateral nondiseased eyes, the major retinal arteries were located within the RNFL (Fig. 1). The major retinal veins were dilated and markedly elongated, traversing back and forth within the plane of the swollen neurosensory retina. Some vessels crossed from the inner retinal surface to the underlying RPE layer (Fig. 3). As shown in Figures 3 and 4, neurosensory retina thickening was more prominent near major retinal veins compared to other regions. The most thickened portions of the neurosensory retina had tortuous retinal veins nearby, which seemed to contribute to distention of the neurosensory retina.

In our patients, 21 eyes (60%) had localized serous retinal detachments at the fovea. In addition, circumpapillary OCT images revealed localized retinal detachments around the optic disc in four eyes (temporal detachments in two eyes, nasal detachments in two eyes, Fig. 4). In these eyes, adjacent major retinal veins showed marked anteroposterior tortuosity within
The swollen retina. The venous tortuosity seemed to induce the adjacent localized retinal detachment (Figs. 3, 4). The OCT cross-sections also showed intraretinal spaces adjacent to tortuous retinal veins in 14 eyes (40%, Fig. 5). In these eyes, elongated major retinal veins ran within the swollen neurosensory retina in a zigzag manner and protruded from the RNFL toward the vitreous cavity. This anteroposterior venous tortuosity seemed to disrupt the boundary between the retinal vasculature and parenchyma, resulting in localized juxta-venous splitting of the inner retina (from the RNFL to the IPL, Fig. 5).

To quantify the degree of anteroposterior venous tortuosity, we examined longitudinal OCT images of retinal veins (Fig. 2). During the acute phase, the degree of anteroposterior venous tortuosity was 389.2 ± 176.3 μm. Table 2 shows the association of anteroposterior venous tortuosity with various other characteristics. Anteroposterior venous tortuosity was correlated positively with logMAR VA ($r = 0.457$, $P = 0.017$), mean foveal thickness ($r = 0.671$, $P < 0.001$), and the height of foveal detachment ($r = 0.414$, $P = 0.032$). The degree of anteroposterior venous tortuosity in ischemic CRVO was significantly larger than that in nonischemic CRVO (530.8 ± 79.6 μm and 357.0 ± 171.4 μm, respectively, unpaired $t$-test, $P = 0.038$).

At the final examination (8.2 ± 8.3 months after the initial visit), the retinal hemorrhages had resolved completely in 13 eyes (37%) in association with reductions in venous dilation and tortuosity (219.8 ± 151.9 μm). However, OCT images revealed that most eyes still had marked anteroposterior venous tortuosity. Despite the substantial reduction in retinal edema, the retinal veins remained displaced from the inner retinal layers. The deepest edges of major retinal veins were located in the outer retina, sometimes extending to the RPE (Fig. 3).

**DISCUSSION**

Few reports have examined the appearance of retinal vessels on OCT images. To study the morphologic features of normal retinal vessels, we first examined major retinal vessels in nondiseased contralateral eyes. Cross-sectional and longitudinal OCT images of the vasculature confirmed that major retinal arteries and veins ran straight, primarily within the RNFL, except at sites of arteriovenous crossing. Venous tortuosity unexpectedly was prominent in the anteroposterior (sagittal) direction. In eyes with acute CRVO, tortuous veins...
intriguingly ran anteroposteriorly, in a zigzag manner, from the inner retinal surface to the RPE layer at the bottom of the swollen retina. While venous tortuosity is a typical characteristic of CRVO, it has been reported only as parallel rather than perpendicular to the retinal plane. This tortuosity may be explained by the following: Müller cells spread their cell bodies from the internal limiting membrane to the external limiting membrane and support the retinal architecture, and dilated veins decrease the mobility at arteriovenous crossing sites, where veins and arteries share a common sheath.

The reason why CRVO results in marked venous tortuosity is uncertain. In previous histologic studies, Green et al. described the clinical and histopathologic features of CRVO in 29 eyes. The findings highlighted the role of thrombosis formation within the central retinal vein trunk. The circulatory disturbance induced by central retinal vein thrombosis likely increases intravascular pressure within the retinal veins, which could lead to marked venous dilation and tortuosity. This hypothesis is supported by the fact that venous tortuosity is seen occasionally in eyes with hypotony (decreased intraocular pressure would lead to an increased perfusion pressure) after trabeculectomy. Unfortunately, previous histologic reports have not examined comprehensively the characteristics of tortuous retinal veins in the context of CRVO.

The VEGF levels are increased substantially in eyes with CRVO, particularly in eyes with ischemic CRVO, and have been associated with venous tortuosity. Tolentino et al. showed that intravitreal injections of VEGF induced CRVO-like features, including venous tortuosity, in primate eyes. In eyes with acute CRVO, an intravitreal injection of an anti-VEGF agent often triggers an immediate reduction in macular edema, venous dilation, and tortuosity. It may be that CRVO induces retinal ischemia, which can upregulate VEGF and contribute to the development of venous tortuosity. In most eyes, even after the complete regression of retinal hemorrhages and edema, anteroposterior venous tortuosity persisted. Vessel tortuosity appears to be irreversible, even after the underlying cause has been addressed effectively.

Our OCT analyses revealed two new characteristics of CRVO to correlate with anteroposterior venous tortuosity. Sequential OCT thin-section images showed that elongated retinal veins commonly ran in a zigzag manner throughout the entire retina, and often accompanied intraretinal spaces (retinoschisis-like changes), or localized retinal splitting around the tortuous vein. Shimada et al. previously reported the...
existence of paravascular cysts in highly myopic eyes. The cysts were thought to result from a combination of persistent vitreoretinal traction on retinal vessels and scleral stretching. Obviously, the pathogenesis of these retinal splits was quite different from the juxtavenous splitting observed here in eyes with CRVO.

In addition, circumpapillary OCT images revealed localized retinal detachments around the optic disc in four eyes. The adjacent major retinal veins showed marked tortuosity. These vessels likely produced traction within the outer retina, contributing to the formation of localized retinal detachments.

The distending force of tortuous retinal veins is strong enough to split the retina. Ikuno et al. reported that an inward tractional force along retinal arterioles in highly myopic eyes was closely related to that which causes myopic foveoschisis or retinal detachment. Therefore, we speculated that morphologic changes in the retinal parenchyma might be induced not only by changes in retinal vascular function (e.g., hyperpermeability), but also by changes in retinal vein morphology (e.g., tortuosity, elongation).

Based on the above-mentioned observations, we hypothesized that the degree of venous tortuosity would correlate with CRVO severity. In our study, we quantified the degree of anteroposterior tortuosity in a major retinal vein based on the analysis of longitudinal OCT images (Fig. 2). The degree of anteroposterior venous tortuosity was found to correlate significantly with poor VA, foveal pathomorphology (mean foveal thickness and height of foveal detachment), and the degree of CRVO ischemia at baseline (Table 2).

The OCT revealed intraretinal spaces (retinoschisis-like changes) adjacent to tortuous retinal veins in 40% of CRVO eyes (Fig. 5). In eyes with CRVO, elongated major retinal veins sometimes protrude from the RNFL toward the vitreous cavity.

**Figure 5.** Juxtavenous splitting of the neurosensory retina induced by tortuous retinal veins associated with acute CRVO. (A–F) Case 1. Fundus photograph (A) of an eye with acute CRVO showing the location (white arrows) of OCT scans. The OCT scans obtained along white arrows b to d in the upper area, and along white arrows e and f in the lower area show juxtavenous retinal splitting (white arrowbeads) adjacent to the tortuous, elongated veins (blue arrowbeads). (G–K) Cases 2 and 3. Cross-sectional OCT images obtained along arrows b and i (Case 2), and circumpapillary OCT sections (Case 5) show tortuous elongated veins (blue arrowbeads) rising steeply and protruding toward the vitreous. Juxtavenous retinal splitting has developed beneath tortuous veins (white arrowbeads).

**Table 2.** Association of Anteroposterior Venous Tortuosity With Factors Related to Acute Central Retinal Vein Occlusion

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Age</td>
<td>-0.280</td>
<td>0.158</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>0.153</td>
<td>0.566</td>
</tr>
<tr>
<td>Visual acuity, logMAR</td>
<td>0.457</td>
<td>0.017</td>
</tr>
<tr>
<td>Mean foveal thickness</td>
<td>0.671</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height of foveal detachment</td>
<td>0.414</td>
<td>0.032</td>
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</table>
Tortuous Retinal Vessels in CRVO

Therefore, we believed that anteroposterior venous tortuosity disrupts the boundary between the retinal vasculature and parenchyma, inducing localized juxtafenous splitting of the neurosensory retina. Retinal ganglion cells and the axons (retinal nerve fibers) proximal to this retinal splitting could be damaged considerably by the associated mechanical force. The effects on visual function as well as the reversibility of these changes remain to be investigated.

The limitations of our study include our small sample size and the limited nature of our follow-up examinations. The reader should note that retinal hemorrhage or edema due to acute CRVO can make it difficult to analyze retinal structures. In our study, even sequential thin OCT sections did not allow us to visualize the retinal vasculature in 14% of patients seen at the initial visit. Additionally, scan depth limits prevented examination of the primary occlusion site (near the lamina cribrosa), even after the resolution of any retinal hemorrhage. Finally, although we randomly selected one of the major temporal veins in each eye to quantify anteroposterior venous tortuosity, the evaluation of all major retinal veins may be more appropriate.

Although some of our findings were based on descriptive and qualitative evaluations, we successfully demonstrated the existence of morphologic changes to the retinal vasculature following CRVO. This report presented a novel clinical perspective on anteroposterior venous tortuosity in the context of CRVO. The OCT-derived measurements of venous tortuosity also correlated with VA and retinal perfusion status. Further prospective studies with larger samples and longer follow-up periods are necessary to confirm the current findings.

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