Longitudinal Changes of Retinal Thicknesses in Branch Retinal Artery Occlusion: Spectral-Domain Optical Coherence Tomography Study

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Retinal artery occlusion (RAO) can be classified as central retinal artery occlusion, branch retinal artery occlusion (BRAO), or cilioretinal artery occlusion on the basis of the obstructed site or range; BRAO accounts for 38% of all cases of RAO.1 Acute BRAO is clinically characterized by fundus examination as retinal whitening, with or without emboli around vascular occlusion sites. In patients with BRAO history, it can be difficult to make an accurate diagnosis because the retinal whitening fades and becomes similar to the normal fundus over time.

Spectral-domain optical coherence tomography (SD-OCT) produces high-resolution, high-speed images of the macula and optic nerve by using infrared wavelengths in the range of 800 nm; the technique is now used widely in different fields of ophthalmology.2,3 A histopathological study of BRAO revealed that retinal edema occurred in the acute phase because of hypoxic inner retinal ischemia, whereas atrophic retinal changes were observed in the chronic phase.4 SD-OCT has proven to be an important tool for diagnosing ophthalmic diseases, because it is able to noninvasively detect conformational changes corresponding to histopathological retinal changes at high resolution.

There have been several case reports of thickness changes in the overall macula, ganglion cell-inner plexiform layer (GC-IPL), and peripapillary retinal nerve fiber layer (pRNFL) over time in BRAO patients, as shown by optical coherence tomography (OCT).5–7 but no longitudinal study of retinal thickness changes in multiple patients has been reported. Therefore, this study analyzed longitudinal changes in the thicknesses of the overall macula, GC-IPL, and pRNFL in several BRAO patients using SD-OCT.

METHODS

This prospective study was approved by the Institutional Review Board of Chungnam National University Hospital (Daejeon, Republic of Korea). Informed consent was obtained from all patients, and the study adhered to the tenets of the Declaration of Helsinki.

Patients

This study included patients diagnosed with monocular BRAO at our retinal clinic from March 2012 to March 2016. We recorded their age, sex, laterality, presence/absence of diabetes or hypertension, prior history of intraocular surgery, uncorrected visual acuity, best-corrected visual acuity (at the initial
visit and after 12 months), spherical equivalent, IOP (using noncontact tonometry), and the sectors involved.

BRAO was diagnosed based on symptoms such as painless but sudden visual loss, and according to a clinical examination to detect retinal whitening in the involved areas. SD-OCT and fluorescein angiography were also used as auxiliary tools to detect retinal edema in the occluded areas, and to observe arterial filling delays.

Patients with retinal diseases and glaucoma, which might affect the OCT results, as well as those with a prior history of vitrectomy, vitreoretinal diseases in the fellow eye, or without follow-up data, were excluded from this study. Poor-quality OCT images (signal strength <7) were also excluded from the analysis. However, patients who had undergone cataract surgery without complications were included.

**OCT Measurements**

Both macular cube 512 × 128 scans and optic disc cube 200 × 200 scans were performed using a Cirrus HD OCT instrument (Carl Zeiss Meditec, Dublin, CA, USA), operated by a single experienced examiner. The patients visited the hospital at 1, 3, 6, and 12 months after the initial visit, and both eyes were examined at all visits.

Overall macular thickness measurements corresponding to the Early Treatment of Diabetic Retinopathy Study (ETDRS) areas were examined in the analyses. ETDRS areas were defined by three concentric rings (central, inner, and outer circles) centered on the fovea with diameters of 1, 3, and 6 mm, respectively, and with the two outer rings divided into quadrants by two intersecting orthogonal lines. The inner and outer circles were examined by subdividing into four quadrant sectors (superior, nasal, inferior, and temporal) consisting of nine subfields (Fig. 1, first column).

The ganglion cell analysis algorithm gains a GC-IPL thickness from sensing the outer boundaries of RNFL and inner plexiform layer (IPL) in the macula by using 3-dimensional information from the macular cube. GC-IPL thickness is measured as an oval, 3-dimensional annulus, which is compatible with an actual anatomic structure of the macula. The annulus comprised a vertical inner and outer diameter of 1.0 and 4.0 mm and horizontal inner and outer diameter of 1.2 and 4.8 mm, respectively. We determined the values for six sectors (the superior, superotemporal, superonasal, inferior, inferotemporal, and inferonasal areas) (Fig. 1, second column).

The optic disc cube 200 × 200 scan mode was used to image the optic disc and the pRNFL over a 6 × 6-mm optic nerve head. The pRNFL thickness was analyzed using a 12-hour thickness map of the optic disc cube 200 × 200 scan (Fig. 1, third column).

We defined the occluded area in the right inferotemporal BRAO (Fig. 2A) as the inner and outer inferior areas of the ETDRS subfields in the macular analyses (Fig. 2B), as the inferior segment of the GC-IPL map in the GC-IPL analyses (Fig. 2C), and as the inferotemporal area (from 6–9 o’clock) of the 12-hour thickness map in the pRNFL analyses (Fig. 2D). In the macular and GC-IPL analyses, nonoccluded area in the right inferotemporal BRAO was the inner and outer superior areas of the ETDRS subfields and the superior segment of the GC-IPL map, respectively (Figs. 2B, 2C). In the 12-hour thickness map in the pRNFL analyses, nonoccluded area in the right inferotemporal BRAO was divided into the following three areas: the superonasal area (from 12–3 o’clock, farthest away from occluded area), the superotemporal area (from 9–12 o’clock, horizontal mirror area), and the inferonasal area (from 3–6 o’clock, vertical mirror area) (Fig. 2D). We also defined the occluded and nonoccluded area in the left normal fellow eyes in the same manner as the right affected eyes (Figs. 2B–D). The mean values of the occluded and nonoccluded areas were used for the analyses.

The differences in the occluded areas between affected and normal fellow eyes were assessed at the initial examination, 1 month, 3 months, 6 months, and 12 months. The nonoccluded areas (opposite site of the occluded area) were also evaluated in both the affected eyes normal fellow eyes.

**Statistical Analysis**

SPSS for Windows statistical software (version 18.0; SPSS Inc., Chicago, IL, USA) was used to analyze all the data. The Wilcoxon signed-rank test was used to compare the mean thicknesses of the overall macula, GC-IPL, and pRNFL between affected and normal fellow eyes. The Friedman test and post hoc Wilcoxon signed-rank test was used to analyze changes in mean thickness of the overall macula, GC-IPL, and pRNFL over the follow-up period, relative to baseline, in affected and normal fellow eyes. A value of $P < 0.05$ was considered statistically significant.

**RESULTS**

**Demographics**

Five patients who were not followed-up after the initial visit were excluded from the study. Also, two patients who visited our clinic on schedule, but did not have five complete measured values for SD-OCT, were excluded. In addition, two patients diagnosed with epiretinal membrane and melanoctoma rupture, a patient who had pars plana vitrectomy because of rhegmatogenous retinal detachment, and a patient with branch retinal vein occlusion in the fellow eye, were ruled out. Finally, 11 of a total of 28 patients were excluded, with 17 patients being included in the study. These patients included 12 males and 5 females, and their average age was 60 ± 5 years. Diabetes and hypertension were detected in three and four patients, respectively, and prior ophthalmic histories of phacoemulsification and intraocular lens implantation were found in four patients before the diagnosis of BRAO. Based on the occluded sites, 7 and 10 eyes were shown to have superotemporal and inferotemporal BRAO, respectively (Table 1).

**OCT Measurements**

Changes in **Overall Macular, GC-IPL, and pRNFL Thicknesses in the Occluded Areas**. As shown in Tables 2 and 3, changes in the overall macular, GC-IPL, and pRNFL thicknesses in the occluded areas of affected eyes were statistically significant (all, $P < 0.01$); however, there was no significant difference in the occluded areas of normal fellow eyes (all $P > 0.05$; Friedman test).

The overall macular thickness in the occluded areas of affected eyes was 354 ± 50 μm at the initial visit. The overall macular thickness in the occluded areas of affected eyes decreased significantly at 1, 3, 6, and 12 months when compared with the initial visit, being 293 ± 45 μm, 244 ± 57 μm, 231 ± 40 μm, and 217 ± 46 μm, respectively ($P = 0.04$, $P < 0.01$, $P < 0.01$, and $P < 0.01$, respectively) (Fig. 3A). At the initial visit, the overall macular thickness in the occluded areas of affected eyes was significantly thicker than that of the normal fellow eyes ($P < 0.01$). However, a significant difference between the two eye groups was not found at 1 month ($P = 0.58$). Subsequently, the overall macular thickness in the occluded areas of affected eyes was thinner than in the
normal fellow eyes at 3, 6, and 12 months ($P = 0.01$, $P < 0.01$, and $P < 0.01$, respectively) (Table 2).

The GC-IPL thickness in the occluded areas of affected eyes was 91 ± 18 μm at the initial visit, and 67 ± 14 μm, 51 ± 21 μm, 45 ± 24 μm, and 40 ± 25 μm at 1, 3, 6, and 12 months, respectively. All measurements were significantly thinner compared with those at the initial visit (all, $P < 0.01$) (Fig. 3A). At the initial visit, the GC-IPL thickness in the occluded areas of affected eyes was thicker than that of the normal fellow eyes, but the difference between the two groups was not significant ($P = 0.24$). However, the GC-IPL thickness was significantly reduced compared with the normal fellow eyes at 1, 3, 6, and 12 months (all, $P < 0.01$) (Fig. 2).

The pRNFL thickness in the occluded areas of affected eyes was 96 ± 13 μm at the initial visit, and 94 ± 7 μm, 76 ± 11 μm, 66 ± 11 μm, and 60 ± 16 μm at 1, 3, 6, and 12 months, respectively. At 1 month, the pRNFL thickness was reduced compared with the initial visit, but there was no significant difference ($P = 0.65$). However, it decreased significantly at 3, 6, and 12 months when compared with the initial visit (all, $P < 0.01$) (Fig. 4). There was no significant difference in the pRNFL thickness between the affected eyes and the normal eyes at the initial visit or 1 month later ($P = 0.72$ and $P = 0.24$, respectively). However, pRNFL thickness in the occluded areas of affected eyes was significantly reduced at 3, 6, and 12 months compared with normal fellow eyes ($P = 0.01$, $P < 0.01$, and $P < 0.01$, respectively) (Table 3).

**Changes in Overall Macular, GC-IPL, and pRNFL Thicknesses in the Nonoccluded Areas.** In the nonoccluded areas of the overall macula and GC-IPL (Fig. 3B)

### Table 1. Baseline Characteristics of Patients With BRAO

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean or Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>17</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>60 ± 5</td>
</tr>
<tr>
<td>Sex, n, male:female</td>
<td>12:5</td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>4</td>
</tr>
<tr>
<td>Laterality, n, R.L</td>
<td>9:8</td>
</tr>
<tr>
<td>BCVA at initial visit, mean ± SD, logMAR</td>
<td>0.27 ± 0.47</td>
</tr>
<tr>
<td>BCVA at 12 mo, mean ± SD, logMAR</td>
<td>−0.08 ± 0.04</td>
</tr>
<tr>
<td>IOP at initial visit, mm Hg, mean ± SD</td>
<td>16 ± 4</td>
</tr>
<tr>
<td>Involved area</td>
<td></td>
</tr>
<tr>
<td>Superotemporal, n</td>
<td>7</td>
</tr>
<tr>
<td>Inferotemporal, n</td>
<td>10</td>
</tr>
</tbody>
</table>

BCVA, best-corrected visual acuity.
There was no significant difference in the pRNFL thickness between the affected eyes and the normal fellow eyes at the initial visit, and at 1 and 3 months (P = 0.96, P = 0.87, and P = 0.13, respectively), whereas pRNFL thickness in the non-occluded vertical mirror areas of affected eyes was significantly reduced at 6 and 12 months compared with normal fellow eyes (P = 0.02, P < 0.01, respectively) (Table 3).

**DISCUSSION**

The present study prospectively characterized changes in retinal thickness in BRAO patients over 12 months. The overall macular thickness in the occluded areas of affected eyes increased significantly compared with that in normal fellow eyes at the initial visit, and it was significantly reduced gradually at 1, 3, 6, and 12 months compared with the initial visit.

Our findings are consistent with those of other previous studies that reported overall macular thickening in acute BRAO patients and overall macular thinning in patients with BRAO history. However, except for one report, most of the studies reporting changes in retinal thickness after acute BRAO were case reports. Ritter et al. analyzed the SD-OCT B-scans of the macular region in eight acute BRAO patients, and reported that total retinal thickness in occluded areas was significantly thickened compared with topographically corresponding nonoccluded areas in the same eyes at baseline and gradually thinned during the next 3 months. This is similar to our results. But, our study used macular cube scans to analyze the overall macular thickness for 12 months. Also, there is a

### Table 2. Longitudinal Changes in the Thicknesses of the Overall Macula, GC-IPL in the Occluded and Nonoccluded Areas, and a Comparison Between the Affected and Normal Fellow Eyes

<table>
<thead>
<tr>
<th>Overall Macular Thickness</th>
<th>GC-IPL Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Affected Eyes</strong></td>
<td><strong>Nonoccluded Area</strong></td>
</tr>
<tr>
<td><strong>Fellow Eyes</strong></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td>First visit</td>
<td>354 ± 50</td>
</tr>
<tr>
<td>1 mo</td>
<td>293 ± 45</td>
</tr>
<tr>
<td>3 mo</td>
<td>244 ± 37</td>
</tr>
<tr>
<td>6 mo</td>
<td>231 ± 40</td>
</tr>
<tr>
<td>12 mo</td>
<td>217 ± 46</td>
</tr>
</tbody>
</table>

### Table 3. Longitudinal Changes in the Thicknesses of the pRNFL in the Occluded and Nonoccluded Areas, and a Comparison Between the Affected and Normal Fellow Eyes

<table>
<thead>
<tr>
<th>Nonoccluded Area</th>
<th><strong>Farthest Away From Occluded Area</strong></th>
<th><strong>Horizontal Mirror</strong></th>
<th><strong>Vertical Mirror</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Affected Eyes</strong></td>
<td><strong>Fellow Eyes</strong></td>
<td><strong>P</strong></td>
<td><strong>Affected Eyes</strong></td>
</tr>
<tr>
<td>First visit</td>
<td>96 ± 13</td>
<td>97 ± 9</td>
<td>0.72</td>
</tr>
<tr>
<td>1 mo</td>
<td>94 ± 7</td>
<td>98 ± 10</td>
<td>0.24</td>
</tr>
<tr>
<td>3 mo</td>
<td>76 ± 11</td>
<td>98 ± 10</td>
<td>0.01</td>
</tr>
<tr>
<td>6 mo</td>
<td>66 ± 11</td>
<td>99 ± 10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>12 mo</td>
<td>60 ± 16</td>
<td>98 ± 8</td>
<td>0.01</td>
</tr>
</tbody>
</table>

| **P** | **0.01** | **0.97** | **<0.01** | **0.61** | **0.48** | **<0.01** | **0.22** | **<0.01** | **0.51** |

*P value, Wilcoxon signed-rank test was used to compare the affected eyes and normal fellow eyes.
†P value by Friedman test.
methodological difference in that our study compared the retinal thickness in the occluded areas of affected eyes to that of the normal fellow eyes.

The etiologies of these changes in the overall macular thickness after RAO can be seen in several previously reported histopathologic studies.4,12,13 A mouse model of histopathological changes in the retinal layer after RAO showed pyknotic nuclei, vacuolated spaces, and degenerative changes in the ganglion cell layer (GCL) and inner nuclear layer (INL); furthermore, the retinal layer was thickened because of swelling in the INL 3 to 24 hours after RAO. However, the retinal layer was thinner at 21 days after RAO because of nuclear loss in the inner retina.4 In addition, histopathological findings of the human retina after RAO have been reported. Zimmerman12 investigated the retinas of patients who died 62 hours after being blinded in one eye, and demonstrated that the inner retina was greatly swollen in general, and pyknosis was found in the GCL and INL.

**FIGURE 3.** Changes in the mean thicknesses of the overall macula, GC-IPL over the follow-up period, relative to baseline, in the occluded and nonoccluded areas of the affected eyes. (A) In the occluded areas of the affected eyes, the thicknesses of the overall macula and GC-IPL significantly decreased throughout the follow-up period (overall macula: \( P = 0.04 \) at 1 month, all \( P < 0.01 \) at 3, 6, and 12 months; GC-IPL: all \( P < 0.01 \) at 1, 3, 6, and 12 months) (post hoc Wilcoxon signed-rank test). (B) In the nonoccluded areas of affected eyes, there was no significant difference when compared with the initial examination. \( *P < 0.05 \) compared with the baseline value.

**FIGURE 4.** Changes in the mean thicknesses of the pRNFL over the follow-up period, relative to baseline, in the occluded and nonoccluded areas of the affected eyes. In the occluded areas of the affected eyes, the thickness of the pRNFL significantly decreased at 3, 6, and 12 months (\( P = 0.65 \) at 1 month, all \( P < 0.01 \) at 3, 6, and 12 months) (post hoc Wilcoxon signed-rank test). In the nonoccluded areas of affected eyes, the thickness of the pRNFL farthest away from the occluded area had no significant difference when compared with the initial examination. However, in the nonoccluded horizontal and vertical mirror area, the thickness of the pRNFL significantly decreased at 3, 6, and 12 months compared with initial visit (all, \( P < 0.04 \) in horizontal mirror area, and \( P = 0.02, P < 0.01, \) and \( P < 0.01 \) in the vertical mirror area, respectively; post hoc Wilcoxon signed-rank test). \( *P < 0.05 \) compared with the baseline value.
There have been a few previous studies reporting SD-OCT measurements of the GC-IPL and pRNFL thicknesses during acute BRAO. Nolan et al. performed OCT measurements in one patient with acute BRAO, and reported that the GC-IPL thickness was within normal limits at the initial visit, and decreased initially at the 3-week follow-up, and this decrease had progressed by the 1-year follow-up. On the other hand, the pRNFL was still within normal limits at 3 weeks, but was thinner than that of the normal fellow eye at 1 year. These results are similar to those reported presently, with the exception that the thickness of the GC-IPL, and pRNFL in the affected and normal fellow eyes were accurately and objectively measured using macular cube and optic disc cube scans in our study, and then statistically analyzed in a large number of patients.

We have considered the reason for the differences between previous reports in terms of the GC-IPL and pRNFL of acute BRAO patients. Yu et al. analyzed the SD-OCT findings of superficial and deep capillary ischemia after RAO. The superficial capillary network is located in the GCL and the NFL, and the deep capillary network is between the INL and the OPL. They reported that 31 of 40 eyes showed hyperreflectivity of the inner retinal layer, in the form of superficial and deep capillary ischemia, with the other 9 eyes showing paracentral middle maculopathy in the INL in the form of isolated deep capillary ischemia (with sparing of the superficial capillary ischemia), thereby indicating that changes varied by retinal layer after RAO. They explained that these results were caused by differences in ischemic susceptibility, and emphasized that the deep capillary plexus located in the watershed zone may have been more vulnerable to ischemia. Accordingly, it was expected that the GCL and NFL, having superficial capillary plexuses, and the INL and OPL, with deep capillary plexuses, would show different changes depending on the ischemic conditions. In addition, Coady et al. reported that retinal ischemic changes could differ according to the degree of ischemia, time course of the disease, and anatomical factors. Also, we thought that pRNFL was initially unaffected in disc-sparing retina artery occlusion in acute BRAO, and that subsequent thinning of the pRNFL occurred because of macular GC-IPL damage. Therefore, early measurements of the GC-IPL and pRNFL differed depending on the condition of the patients, and it suggested that further studies should be conducted using a greater number of patients.

In addition, the nonoccluded horizontal and vertical mirror areas of affected eyes in pRNFL showed significant thickness changes from 3 months after the initial visit, which is similar to the results of occluded areas. However, in the nonoccluded horizontal mirror areas, there was no significant difference between the affected eyes and the normal fellow eyes, whereas the nonoccluded vertical mirror areas showed a significant difference between the affected eyes and the normal fellow eyes at 6 and 12 months. From these results, we considered that nonoccluded vertical and horizontal mirror areas, especially in vertical mirror areas of affected eyes, may be influenced by occluded area in pRNFL changes after acute BRAO.

This study has some limitations. First is the limited resolution in the initial visit and first month of follow-up. If there were retinal contour changes, such as retinal edema or atrophy, segmentation errors may occur and manual correction may be needed. We considered that it usually occurs in severe retinal edema or atrophy, especially in lesions such as exudate and cyst. However, in this study, no such lesions or severe edema were found, so that the segmentation error is expected to be relatively low. Therefore, we did not perform manual correction, and used the measured values by auto-segmentation. Second, we analyzed the pRNFL, not macular RNFL in the BRAO affected area. It would have been better to obtain other retinal layers as well as the macular RNFL to show the effect of BRAO on various retinal layers in macula. However, the analysis software used in this study did not provide the above information. For the above two limitations, further studies are needed to examine longitudinal changes of each retinal layer using advanced software with higher resolution. Finally, this study included a small sample size of 17 patients, so it could not represent various BRAO eyes. A larger sample size is needed to include diverse BRAO eyes.

Despite these limitations, to our knowledge, this is the first prospective study analyzing longitudinal changes in the thicknesses of the overall macula, GC-IPL, and pRNFL in multiple BRAO patients using SD-OCT. In addition, this study was conducted in a unique way to compare the mean thickness of the topographically corresponding area in the both eyes. We think that this method can provide more accurate and objective results and it can be applied to longitudinal studies on other retinal diseases.

In conclusion, this study showed that the pattern of thickness changes up to 3 months after initial BRAO was different in overall macula, GC-IPL, pRNFL. In particular, when the patient with BRAO visits the hospital for the first time at 1 month when only thickness of the GC-IPL is significantly reduced, it is important for the ophthalmologist to make a careful diagnosis using other additional examinations. This detailed analysis of retinal thicknesses in BRAO can be useful for clinicians to understand the changes in each thickness after initial visit in patients with BRAO.

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References


