USE OF CHOROIDAL VASCULARITY INDEX FOR CHOROIDAL STRUCTURAL EVALUATION IN CENTRAL SEROUS CHORIORETINOPATHY WITH CHOROIDAL NEOVASCULARIZATION

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Purpose: To evaluate choroidal vascular structure in eyes with central serous chorioretinopathy (CSC) by assessing the choroidal vascular index (CVI).

Methods: We retrospectively analyzed the medical records of 117 eyes with CSC. Subjects were divided into 4 groups according to clinical characteristics: 1) acute CSC (N = 29), 2) non-neovascularized chronic CSC without flat irregular pigment epithelial detachment (N = 49), 3) non-neovascularized chronic CSC with flat irregular pigment epithelial detachment (N = 21), and 4) chronic CSC with choroidal neovascularization (N = 18). Subfoveal choroidal area (1,500 mm) of swept source optical coherence tomography scans were divided into luminal and stromal areas by the image binarization technique. The CVI was defined as the ratio of the luminal to the total subfoveal choroidal area.

Results: The CVI was significantly lower in eyes of Group 4 than those of other groups (all P < 0.05). The subfoveal choroidal thickness was significantly lower in Group 4 than in Groups 1 and 2 (P < 0.05), but regression analysis showed no association with the CVI.

Conclusion: Decreased CVI may reflect choroidal vascular structure changes in eyes with choroidal neovascularization complicating CSC. These findings suggest that the CVI could be useful for evaluating choroidal vascular changes in eyes with CSC.

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Central serous chorioretinopathy (CSC) typically occurs in younger patients and is characterized by idiopathic serous sensory retinal detachment at the macular region.1,2 The current pathogenesis of CSC has suggested that choroidal changes, such as hyperpermeability of choroidal vessels on indocyanine green angiography (ICGA), increase hydrostatic pressure. This change induces retinal pigment epithelial detachment (PED) or atrophy of the retinal pigment epithelium (RPE).3–6

Pigment epithelial detachment is reported in 53% to 100% of patients with CSC, and various types of PED have been reported.7,8 For example, typical dome-shaped PEDs have a sharply demarcated and protruding appearance without signs of RPE hyperplasia. Flat irregular PEDs (FIPEDs) are more likely observed in chronic CSC than in acute CSC.8,9 A study on chronic CSC with FIPED reported that choroidal neovascularization (CNV) was detected in 18.9% of these patients by ICGA and fluorescein angiography (FA), and that most cases were relatively stable without progressing to active CNV during a mean of 14.6 years of follow-up.9

Bousquet et al7 found that one-third of FIPEDs in CSC contained CNV using optical coherence tomography angiography (OCTA). However, CNV prevalence in CSC has been variously reported,10–14 and
the results of these studies show discrepancies, originating from the definition of FIPED and patient selection. Considering the suggested pathogenesis of CNV until recently, choroidal vascular changes may be related to CNV occurrence. However, it is not well known how the choroidal structure changes in eyes with CNV complicating CSC.

Recent studies have assessed the choroidal vascularity index (CVI), defined as the proportion of the luminal area (LA) to the total choroidal area (TCA). Assessment of choroidal structure by the CVI has been conducted in various retinal diseases, especially in pachychoroid spectrum diseases and age-related macular degeneration (AMD). The CVI can be used to measure choroidal vascularity quantitatively, thus supplementing the limitations of using choroidal thickness (CT) alone.

In this study, we evaluated the choroidal structure using the CVI and analyzed differences among eyes with CSC with different characteristics.

Methods

Study Design

This study was conducted in the Department of Ophthalmology and Visual Science in Seoul St Mary’s Hospital and adhered to the tenets of the Declaration of Helsinki; all protocols were approved by the institutional review board of The Catholic University of Korea. Informed consent was waived because of the nature of this retrospective study. Ophthalmologic history, comprehensive medical records, and results of ocular examinations, including best-corrected visual acuity (BCVA) measurement, noncontact pneumatic tonometry, slit-lamp biomicroscopy, dilated fundus examination, OCT, and OCTA, were obtained for all subjects.

Study Population

All participants were recruited between March 2017 and June 2018 at Seoul St. Mary’s Hospital in Korea, and a retrospective chart review was conducted. Patients diagnosed with CSC who underwent adequate ocular examination and had enough medical records were included in our study. Exclusion criteria were as follows: 1) drusen in the macular area; 2) high myopia with refractive errors of more than ±6 diopters (as spherical equivalent); 3) presence of other retinal diseases, including glaucoma, exudative AMD, pachychoroidal vasculopathy, retinal vein occlusion, or neurodegenerative disease; 4) previous vitrectomy; 5) any history of uveitis; 6) other systemic disease that could affect the eye; and 7) media opacity that could affect image quality. Eyes were also excluded on the basis of previous treatment with anti–vascular endothelial growth factor, photodynamic therapy, focal laser, or eplerenone therapy, which possibly affects the CVI.

Patients were divided into acute CSC, chronic CSC without FIPED, and chronic CSC with FIPED groups, according to their clinical characteristics. Patients with CSC with FIPED were further divided into FIPED with CNV (vascularized PED) and FIPED (nonvascularized PED) without CNV groups.

Study Protocol

We reviewed patients’ medical records, including sex, age, BCVA, and history of hypertension, and analyzed multimodal imaging findings, including FA and ICGA (Heidelberg Spectralis, Heidelberg, Germany), swept source OCT (SS-OCT), and OCTA.

Best-corrected visual acuity was measured by using Snellen chart and converted to the logarithm of the minimum angle of resolution scale for the purpose of statistical analysis.

The SS-OCT device (DRI Triton; Topcon, Tokyo, Japan), equipped with a 1,050-nm wavelength light source, is able to perform 100,000 A-scans/second. A six-line radial pattern scan (1,024 A-scans) centered on the fovea was obtained for each eye. To obtain OCTA images, Topcon OCTA device (Topcon Corporation) was used. The scanning area was captured in 3 mm × 3 mm sections centered on the fovea.

Image Analysis

Central serous chorioretinopathy was defined by its typical clinical manifestation and serous sensory retinal detachment at the macular region with or without PED, seen by OCT. Chronic CSC was defined when the symptom duration was >6 months or when having recurrent episodes. Acute CSC was defined when the symptom was self-resolved without treatment within 6 months. Flat irregular PED was defined as an irregular elevation appearance of the RPE allowing for distinct visualization of Bruch membrane on OCT as described by Bousquet et al. All assessments of OCT images were performed by two experienced independent retinal specialists (Y.-H.P. and M.K.) who were blinded to other imaging findings and patients’ clinical history. All assessments of OCTA images were performed by a different pair of experienced independent retinal specialists who were blinded to other imaging finding and patients’ clinical history. A combination of FA/ICGA and OCT images was assessed by another pair of retinal specialists who
were blinded to OCTA findings and other clinical history. Disagreements regarding the interpretation of images were resolved by open adjudication.

Choroidal thickness was measured using an automatic built-in software associated with the SS-OCT device. Subfoveal CT (SFCT) was measured by calculating the distance from the outer border of the RPE to the inner edge of the suprachoroidal space. Choroidal area was defined as the area between the outer border of the RPE to the inner edge of the suprachoroidal interface. We measured SFCT manually at the foveal center using digital calipers provided by the SS-OCT software. Next, two experienced independent observers measured SFCT, and the average value was used for analysis, to avoid interobserver variation.

Choroidal Vascularity Index Assessment

For image binarization to assess the CVI, the raster scan, which is passing through the fovea, was selected. The images were segmented as described by Agrawal et al. Image binarization was performed using ImageJ software (Version 1.51; https://imagej.nih.gov/ij/). To measure the TCA of the subfoveal region within a width of 1,500 μm (750 μm on either side of the fovea), the polygon selection tool in ImageJ software was used; selected polygonal regions were added to the regions of interest manager (Figure 1A). The image was converted to 8 bits, and a Niblack autolocal threshold tool giving the mean pixel value with the SD was applied for all points. After applying the color threshold tool, the stromal area (SA) was highlighted and subsequently added to the regions of interest manager. Both of the initially selected 1,500-μm polygonal TCA and highlighted SA were selected and merged through an “AND” operation in the regions of interest manager. This composition of areas was added to the regions of interest manager as a third area. The LA in the polygon was obtained by subtracting the SA from the total polygon area (Figure 1B). The TCA represented the total area of the selected SFC region, and the LA represented the vascular area. The ratio of LA to TCA was defined as the CVI.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows ver. 24.0 (SPSS, Inc, Chicago, IL). An exploratory analysis was conducted for all variables. The normality of data distribution was confirmed through the Kolmogorov–Smirnov test. The CVI, SFCT, and LA and SA corresponding to the choroid index satisfied normality. Differences between two groups were assessed using a T-test. Age and BCVA were not normally distributed. Nonparametric statistical methods, such as the Kruskal–Wallis test, were used. For categorical variables, the chi-square test was used. Univariate and multiple linear regression analyses were performed to analyze the effects of multiple factors associated with the CVI. Multivariate linear regression analysis of all factors was included in the univariate study. Two-sided P values < 0.05 were considered as significant.

Results

Demographics and Clinical Characteristics

A total of 116 eyes of 116 patients were included in this study. Thirty-nine patients were females. Subjects were divided into the following four groups: subjects with acute CSC not accompanied by FIPED (Group 1; N = 29), subjects with chronic CSC not accompanied by FIPED (Group 2; N = 49), subjects with CSC accompanied by FIPED but no evidence of CNV on OCTA (Group 3; N = 21), and subjects with CSC accompanied by FIPED and CNV on OCTA (Group 4; N = 18; Figure 2). The demographic and systemic
characteristics, as well as BCVA of the subjects, are shown in Table 1.

Sex and age were significantly different in each group (P < 0.001 for both, Kruskal–Wallis test). The proportion of female sex in Group 4 was significantly higher than in other groups (P = 0.001 vs. Group 1 and Group 2; P = 0.008 vs. Group 3). There was no significant difference in sex among Groups 1, 2, and 3. All groups showed significant differences in age. The mean age was higher in Group 4, followed by Groups 3, 2, and 1 (P < 0.001, Mann–Whitney test). The groups did not significantly differ in terms of BCVA (P = 0.063) and presence of hypertension (P = 0.277).

**Choroidal Vascular Structure**

Indicators for choroidal structure characteristics in each group are shown in Table 2. The mean SFCT was 486.00 ± 21.50, 453.22 ± 19.19, 449.57 ± 25.67, and

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**Table 1. Demographic and Clinical Characteristics of All Subjects**

<table>
<thead>
<tr>
<th>Group 1 (N = 29)</th>
<th>Group 2 (N = 49)</th>
<th>Group 3 (N = 21)</th>
<th>Group 4 (N = 18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of eyes</td>
<td>29</td>
<td>49</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>13</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
<td>36</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>42.0 ± 7.0</td>
<td>46.7 ± 7.4</td>
<td>50.3 ± 7.4</td>
<td>53.7 ± 7.4</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>3 (10.34%)</td>
<td>7 (14.28%)</td>
<td>0 (0%)</td>
<td>1 (5.55%)</td>
</tr>
<tr>
<td>BCVA, logMAR (mean ± SD)</td>
<td>0.07 ± 0.09</td>
<td>0.13 ± 0.17</td>
<td>0.23 ± 0.18</td>
<td>0.13 ± 0.15</td>
</tr>
<tr>
<td>Snellen equivalent (mean)</td>
<td>20/25</td>
<td>20/25</td>
<td>20/30</td>
<td>20/25</td>
</tr>
</tbody>
</table>

Group 1, acute CSC without FIPED; Group 2, chronic CSC without FIPED; Group 3, CSC with FIPED and no CNV; Group 4, CSC with FIPED and CNV. Statistically significant P values are highlighted in bold (Kruskal–Wallis test). Results are presented as mean ± SD as indicated.

HTN, hypertension; logMAR, logarithm of the minimum angle of resolution.
378.06 ± 26.46 μm in Groups 1, 2, 3, and 4, respectively. The SFCT was significantly lower in Group 4 than in Groups 1 and 2 (P < 0.05), but no significant difference was found compared with Group 3 (P = 0.06). There were no differences in SFCT among Groups 1, 2, and 3 (Student’s t-test). The respective mean CVIs in Groups 1 to 4 were 71.49 ± 4.39, 70.85 ± 3.65, 72.25 ± 4.57, and 67.18 ± 6.73%, respectively. Notably, the CVI was significantly lower in Group 4 than in Groups 1 (P = 0.01), 2 (P = 0.04), and 3 (P < 0.01; Figure 3). No difference in the CVI was observed among the other three groups (1, 2, and 3).

To analyze factors affecting CVI values, we conducted a univariate analysis. Univariate regression analysis revealed that age, sex, BCVA, hypertension, or SFCT did not significantly correlate with the CVI. Multivariate linear regression analysis of all factors included in the univariate study showed that no factor was significantly associated with the CVI (Table 3).

**Discussion**

Type 1 CNV can occur, although rarely, in eyes with long-term CSC,20 with an incidence between 2% and 9%.21–23 It is known that CNV is more common in patients with CSC with certain characteristics, such as a history of laser photocoagulation, old age, or diffuse RPE atrophy.24,25 Irregular PED is one of the most common OCT findings of Type 1 CNV in AMD.26 A current study suggested that CSC with FIPED presents more frequently with CNV than does CSC with typical dome-shaped PEDs.9 However, when CNV is present in CSC, the diagnosis is challenging, as the clinical presentation and features overlap and coexist in both.10

In the current study, we investigated differences in the choroidal vascular structure depending on the characteristics of CSC by measuring a quantitative parameter, CVI. The most important finding of our study was that eyes with CNV complicating CSC exhibited significantly lower choroidal vascular component compared to those with CSC without CNV. Our results suggest that changes in the choroidal structure may be associated with CNV in CSC. However, there were no significant differences in the CVI between patients with chronic or acute CSC and those with FIPED. This suggests that changes in the CVI are particularly relevant to the presence of CNV, rather than reflecting clinical characteristics of CSC. Reduction of the CVI in eyes with CNV may suggest secondary choroidal changes due to CNV or underlying choroidal ischemia, which are related to the development of...
CNV. However, it is difficult to determine a cause and effect relationship based on this in vivo study without pathologic confirmation.

Wei et al\(^2\) previously studied choroidal vascular changes in eyes with exudative AMD using the CVI. The authors found a low CVI in these patients compared with healthy individuals, and this decrease in the CVI was considered to correlate with choroidal ischemia, observed in previous pathology studies.\(^2\) These authors suggested the CVI as a novel parameter to monitor choroidal changes in exudative AMD. Recent studies have also reported decreased CVI in eyes with AMD.\(^1\)\(^7\),\(^2\)\(^7\),\(^3\)\(^0\) By contrast, it was also reported that eyes with acute CSC show higher CVI compared with their fellow eyes or control healthy eyes. This result was explained by the possible dilatation of choroidal vessels and fluid accumulation.\(^1\)\(^5\),\(^1\)\(^6\) In our study, the mean CVI in eyes with CSC with CNV was 67.18 ± 6.73, which was significantly lower than that in eyes of other CSC groups without CNV. However, it was relatively higher than the values reported in studies involving AMD.\(^1\)\(^7\),\(^2\)\(^7\),\(^3\)\(^0\) This might be due to the mixed characteristics of CSC and CNV.

The ability of OCTA to detect CNV in CSC eyes has been reported to differ among studies, and there are discrepancies in the rate of CNV detection, ranging from 24% to 42%.\(^7\),\(^1\)\(^0\),\(^1\)\(^3\),\(^1\)\(^4\) Previous studies are not comparable because of differences in the definition of FIPED. In the current study, we used the same definition as Bousquet et al\(^7\) who reported a higher CNV detection rate of 35.6% by OCTA than by FA/ICGA in eyes with CSC and FIPED. In the study by Bousquet et al,\(^7\) the rate of visible choroidal neovascular network by OCTA in the early phase of ICGA was 57.9% in CSC with CNV, whereas no eye without CNV was detected by OCTA. Moreover, poorly defined late staining in FA was more frequent in eyes with CNV than those without. Similar to a previous report, we did not find any case positive for CNV by FA/ICGA in patients without CNV, as detected by OCTA. However, it is possible that we included patients who were not diagnosed with CNV during the examination or were judged not to have CNV and could be positive for the actual CNV components, thus influencing our results.

To date, the pathogenesis of CNV complicating CSC has not been elucidated. Fung et al\(^2\) previously suggested that long-standing PED associated with CSC could lead to splits of Bruch membrane and loss of its barrier function against CNV. Our findings suggest that, in addition to these changes in Bruch membrane and RPE, the choroidal vascular change is also associated with the development of CNV. Moreover, decreased vascular structure in CNV indicated reduced choroidal vascular perfusion. In general, CSC is known to cause choroidal hyperperfusion. A study using laser interferometry showed higher pulsation amplitude in eyes with CSC than control eyes, suggesting choroidal hyperperfusion in patients with

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### Table 3. Univariate and Multivariate Analysis Results

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th>Multivariate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standardized (\beta)</td>
<td>(P)</td>
</tr>
<tr>
<td>Age, years</td>
<td>-0.047</td>
<td>0.385</td>
</tr>
<tr>
<td>Sex, female</td>
<td>-1.576</td>
<td>0.093</td>
</tr>
<tr>
<td>BCVA, LogMAR</td>
<td>1.092</td>
<td>0.676</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>0.627</td>
<td>0.681</td>
</tr>
<tr>
<td>SFCT, (\mu\text{m})</td>
<td>0.084</td>
<td>0.372</td>
</tr>
</tbody>
</table>

Linear regression analysis of factors associated with the CVI. \(\beta\), regression coefficient. Statistically significant \(P\) values are highlighted in bold.

*Multivariate analysis adjusted for all variables from univariate analysis.

logMAR, logarithm of the minimum angle of resolution.
CSC.\textsuperscript{31} By contrast, a previous study using FA, ICGA, and laser Doppler flowmetry demonstrated that blood volume and flow in the choroid is reduced in AMD and that this was associated with increased risk of CNV.\textsuperscript{32,33} Another study using Doppler flowmetry also showed decreased foveal choroidal blood flow in CSC eyes, possibly correlated with the localized, nonperfused areas of the choriocapillaris that are frequently seen during ICGA.\textsuperscript{34} Doppler flowmetry uses a shorter wavelength than laser interferometry and detects blood flow in choriocapillaris rather than in deeper large choroidal vessels. These discrepancies in perfusion might reflect the variability of blood flow in the different choroid layers.\textsuperscript{8} As in AMD, focal hypoperfusion of the choriocapillaris is considered to be associated with the development of CNV. To verify this hypothesis, further pathological studies need to be conducted.

We also found that a higher proportion of patients were females and the average age was also higher in the CSC with CNV than without CNV group, suggesting that age and female sex are associated with the development of CNV at CSC. Regarding the clinical features of CSC with Type 1 CNV, Shiragami et al.\textsuperscript{35} reported that neovascular CSC was associated with chronic CSC, female sex, and poor BCVA. Although it is not well understood why females show more susceptibility to CNV than males, female hormones may play a role in this aspect.\textsuperscript{35} An older age could also be a risk factor for neovascular CSC like CNV in AMD.

Our study has some limitations. The study included a few patients in each subgroup, and we only measured a width of 1,500 μm in a single scan through the fovea, as a representative image. A larger area or a volume scan over the macular area could provide more information on the disease profile. Some authors have reported the possible effects of diurnal variation on CT obtained through OCT.\textsuperscript{36} It is not known how circadian changes may affect choroidal vascularity, but this might have influenced our study results. Previous studies have also reported that the CVI is not significantly affected by axial length,\textsuperscript{16} which we did not incorporate; this might have also affected our results. These limitations should be addressed in future studies.

The advantage of our study is that we could observe choroidal vascular changes from quantitative measurements obtained using SS-OCT. To the best of our knowledge, this is the first report showing choroidal structural changes in CNV complicating CSC using the CVI.

Because the eyes with CSC and CNV exhibited a significantly lower CVI than those of non-neovascularized CSC, further studies and data collection are necessary to assess the longitudinal changes in the CVI from simple chronic CSC to development of CNV. Future research is needed; however, we suspect that choroidal changes, such as ischemia, occur in patients with low CVI. This could be a risk of CNV. Therefore, the CVI may be a useful tool for evaluating the risk of CNV in CSC. It is more valuable in assessing the choroid, as it is not limited to the CT parameter. Although the CVI is not currently included in the commercial OCT software, it is a validated method and easily accessible. Therefore, it could be a widely used tool in daily clinical practice if it is added to the commercial OCT software. In conclusion, the CVI is a useful quantitative parameter for choroidal evaluation in patients with CSC.

Key words: central serous chorioretinopathy, choroidal neovascularization, choroidal vascularity index, choroidal vasculature, choroidal thickness.

References
