Relations Among Foveal Blood Flow, Retinal-Choroidal Structure, and Visual Function in Retinitis Pigmentosa


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PURPOSE. To investigate the relationships between foveal blood flow as measured by laser speckle flowgraphy (LSFG), the retinal-choroidal structure in enhanced depth imaging-optical coherence tomography (EDI-OCT), and central visual function in patients with retinitis pigmentosa (RP).

METHODS. We studied 52 consecutive typical RP patients ≤50 years old and 21 age- and sex-matched controls. The mean blur rate (MBR), which represents the blood flow volume, was calculated in a 2.4-mm² area centered on the fovea by LSFG. Subfoveal horizontal EDI-OCT images were recorded, and the choroidal area, choroidal hyporeflective area, and choroidal hyperreflective area were analyzed in the central 2.4-mm-wide region. The central foveal thickness (CFT), subfoveal choroidal thickness (SCT), and ellipsoid zone (EZ) width were also measured. Visual acuity (VA) and retinal sensitivity (Humphrey 10-2 program) were measured in the RP patients.

RESULTS. The MBR, choroidal area, hyporeflective area, hyperreflective area, and SCT were significantly decreased in the RP patients (all $P < 0.001$, versus controls). Spearman’s rank testing demonstrated no significant correlation between the MBR and the choroidal structural parameters in the RP patients. Decreased MBR was significantly associated with reductions in VA, retinal sensitivity, CFT, and EZ width (all $P < 0.05$). The choroidal structural parameters did not correlate with central visual function, and the choroidal area, hyperreflective area, and SCT were inversely associated with CFT (all $P < 0.05$).

CONCLUSIONS. These results demonstrated the divergence between the choroidal structure and blood function, and suggest that decreased choroidal flow, rather than the structural alteration, is closely associated with foveal degeneration in RP.

Keywords: retinitis pigmentosa, choroidal blood flow, choroidal structure, central visual function

Retinitis pigmentosa (RP) comprises a group of inherited retinal degeneration disorders that affects more than 1.5 million individuals globally.1 Although RP is a genetically and clinically heterogeneous disease, the affected individuals exhibit shared clinical phenotypes such as bone-spicule pigmentation and the attenuation of retinal vessels. In RP, primarily rods are affected owing to genetic defects; however, the bystander cells such as cones, retinal pigment epithelial cells, and vascular endothelial cells are also attenuated during the retinal remodeling following rod degeneration. Further characterization of these secondary changes in RP will be critical to better understand its common pathology.2–4

In addition to the attenuation of retinal vessels, decreased choroidal blood flow has been shown in RP patients by multimodal techniques, including measurement of the intraocular pressure pulse amplitude, laser Doppler flowmetry, and magnetic resonance imaging.5–7 Falsini et al.9 have reported that the decreased subfoveal blood flow, as measured by laser Doppler flowmetry, is correlated with the reduction of cone response in a focal electroretinogram.

Laser speckle flowgraphy (LSFG) is a US Food and Drug Administration-approved system used to noninvasively measure the blood flow in the ocular fundus.8 The mean blur ratio (MBR) of the fundus speckle pattern linearly correlates with the blood flow measured by conventional techniques such as the microsphere and hydrogas clearance methods,9–11 and the MBR shows a high level of intrasession reproducibility.12 Using LSFG, we have previously demonstrated that in RP patients the foveal MBR is decreased and correlates with central visual sensitivity.13 These findings are consistent with those reported by Falsini et al.,5 suggesting that the reduction of choroidal blood flow may be involved in the cone cell loss during retinal remodeling in RP.

Advances in optical coherence tomography (OCT) imaging techniques have revealed a significant alteration of choroidal structure in various retinal disorders.14 In RP patients, choroidal thickness is decreased.15–17 In addition, Kawano et al.18 have recently reported that their use of a binarization method to differentiate the hyper- and hyporeflective areas of the choroid reveals that the hyporeflective luminal area is
significant relationship was observed between the structural choroidal changes and foveal blood flow and central visual function. We also compared the images of enhanced depth imaging (EDI)–OCT and the choroidal area, showing that the choroidal area was significantly reduced in RP patients. However, the relationships among the structural retinal-choroidal changes, foveal blood flow, and central visual function have not been fully elucidated. We addressed this question in the present study by comparing the images of enhanced depth imaging (EDI)–OCT to the LSFG data, and by examining the association of the above-cited factors with central visual parameters.

### Patients and Methods

#### Ethics Statement

This clinical study was approved by the Institutional Review Board of Kyushu University Hospital (Fukuoka, Japan) and was conducted in accordance with the tenets of the Declaration of Helsinki on biomedical research involving human subjects. Written informed consent was obtained from all subjects after a thorough explanation of the nature of the study and its possible consequences.

#### Participants

RP patients ≤50 years of age were consecutively recruited from the Kyushu University Hospital in 2016. Fifty-four patients with a diagnosis of typical RP and 21 age- and sex-matched healthy control subjects were examined. Two RP patients were excluded from the study because of the insufficient quality of their OCT images. The baseline characteristics of subjects are summarized in Table 1. The examination results of the right eye of each subject were used for analysis.

The diagnosis of typical RP was based on the patient’s history of night blindness, visual field constriction and/or ring scotoma, and markedly reduced or nonrecordable a- and b-wave amplitudes on electroretinography testing, in addition to ophthalmoscopic findings (e.g., bone spicule–like pigment clumping in the mid-peripheral and peripheral retina and attenuation of retinal vessels).

Excluded from the study were patients with cone-rod or cone dystrophy, choroideremia, Bietti crystalline retinopathy, uveitis, and suspected cancer-associated retinopathy. Patients who had a history of intraocular surgery, those who received treatment with a calcium blocker or topical antiglaucoma treatment, and those who had refractive errors (spherical equivalent) greater than –6 diopters were also excluded.

The control subjects had undergone a health screening including vision, hearing, height, weight, blood pressure, urinary strip test, chest X-ray, and physician examination within the past 1 year, and had results without specific abnormal findings. Subjects who had a history of ocular disease or who had refractive errors (spherical equivalent) greater than –6 diopters were also excluded.

### Laser Speckle Flowgraphy

The principles and methods of the LSFG measurement have been described in detail previously. The subject’s pupil was dilated with 0.5% tropicamide and 0.5% phenylephrine (Santen, Osaka, Japan) before examination. The subject’s pupils were dilated with 0.5% tropicamide and 0.5% phenylephrine (Santen, Osaka, Japan) before examination. After switching to a diode laser (830 nm), a speckle pattern from the illuminated fundus was recorded by a CCD (charge-coupled device) camera (750 × 360 pixels) at a frequency of 1/30 second for 4 seconds.

The MBR of the speckle images was calculated in a 2.4-mm² area centered on the fovea by an LSFG analyzer software package (version 3.043.0) as described previously. Three consecutive measurements were taken for each subject, and the averaged value for each subject was used for the statistical analyses. The subject’s systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded after the measurement of LSFG. The ocular perfusion pressure (OPP) was calculated as follows: OPP = diastolic pressure – intraocular pressure.

### Optical Coherence Tomography

The choroidal tomographic images were obtained by EDI using a Spectralis HRA+OCT device (Heidelberg Engineering, Heidelberg, Germany). The horizontal scans through the center of the fovea (6 mm) were recorded by using the eye tracking system, and 100 scans were averaged for each subject. Because there are diurnal fluctuations of the choroidal thickness and structure, all examinations were performed between 9:00 AM and 1:00 PM. The quality of the OCT image was examined by three graders (SN, YK, TT). If two or more graders determined that the choroidal image was clearly distinguishable, the image was deemed acceptable and subjected to the following analyses.

The OCT images were analyzed by two independent analyzers (YM, JF) using ImageJ software (version 1.47, http://image.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA), as described previously. The choroidal area between the
retinal pigment epithelium (RPE) line and the choriocapillaris border in the 2.4-mm-wide region centered on the fovea was set with the ImageJ ROI Manager. The brightness of the images was adjusted by setting the average reflectivity of the hyporeflective luminal areas of three choroidal vessels with lumens >100 μm as the minimum value. The image was then converted to 8 bits and adjusted by the Niblack Auto Local Threshold (in ImageJ). The binarized image was converted to an RGB (red, green, blue) image, and the hyporeflective luminal area was determined by using the Threshold Tool (in ImageJ). After the data for the distance of each x and y pixels were added, the ImageJ program automatically calculated the choroidal area, hyporeflective luminal area (dark pixels), and hyperreflective interstitial area (light pixels).

The central foveal thickness (CFT), subfoveal choroidal thickness (SCT), and ellipsoid zone (EZ) width were also measured by using ImageJ software. CFT was defined as the distance between the inner edge of outer nuclear layer and the inner border of the RPE at the foveal center. SCT was defined as the distance between the outer border of the RPE and the inner border of the RPE at the foveal center. SCT was defined as the distance between the inner edge of outer nuclear layer and the outer border of the RPE. EZ was defined as the points where the thickness of the outer segment layer became zero (the nasal borders of EZ were defined as the points where the distance between the outer border of the RPE and the inner border of the RPE at the fovea was 3 mm eccentricity from the fovea), the temporal and/or nasal edges of images were set as EZ borders. The EZ width was defined as the horizontal distance between these two points. The OCT images were opened in the ImageJ software, and the length of each parameter was manually measured (by YM) after the data for the distance of each x and y pixels were entered.

Clinical Examinations

Each subject’s best-corrected visual acuity (VA), static perimetry, and intraocular pressure (pneumotonometer NT-530; NIDEK, Aichi, Japan) were measured before obtaining the LSFG and OCT measurements on the same visit. The axial length was measured with an IOLMaster non-contact optical device (Carl Zeiss, Dublin, CA, USA).

VA was measured with a Landolt decimal VA chart (CV-6000, Tomey, Nagoya, Japan; or AVC-36, Kowa, Nagoya, Japan) at 5 m or by single Landolt test cards (HP-1258; Handaya, Tokyo, Japan). The refractive error was measured by an auto-kerato-refractometer (ARK-1a; NIDEK). The best-corrected VA values were obtained from the minimum Landolt C letter that the subject was able to correctly identify on >60% (3/5) of trials, and converted to the logarithm of the minimum angle of resolution (logMAR) units.

Automated static perimetry tests were performed with a Humphrey Field Analyzer (HFA) (Carl Zeiss) using the central 10-2 Swedish Interactive Thresholding Algorithm Standard Program. The lens was corrected as appropriate for the test distance. If the test reliability was not satisfactory (fixation loss >20%, false positive >15%, or false negative >33%), the visual field testing results were excluded from the study. Visual sensitivity parameters including the mean deviation (MD) and the averaged retinal sensitivity at the central 4 points (foveal sensitivity [FS]) and that at the central 16 points (foveal-parfoveal sensitivity [F-PFS]) were calculated as described previously.25-27 The 16 points topographically match the 2.4-mm-wide region examined by LSFG.

Statistical Analysis

The data are presented as the arithmetic mean ± standard deviation (SD). Statistically significant differences in the mean values between the groups were analyzed by Wilcoxon rank sum test, and the differences of frequency were tested by χ² tests. We performed a multiple group comparison by an analysis of variance followed by Dunnett’s adjustment. The relationships among choroidal structure, MBR, and visual parameters were examined by using Spearman’s rank correlation coefficient. The abovementioned statistical analyses were performed with SAS software (version 9.3; SAS Institute, Cary, NC, USA). The interobserver correlation coefficients (ICCs) were calculated by using a two-way mixed-effects model for measurements of absolute agreement. SPSS software (version 23; IBM, Somers, NY, USA) was used for the ICC analysis. Two-sided values of P < 0.05 were considered significant.

RESULTS

Alterations of Foveal Blood Flow and Choroidal Structure in the RP Patients

The demographic data of the study population are summarized in Table 1. There were no significant differences in age, sex distribution, IOP, SBP, DBP, or OPP between the patient and control groups. The MBR in the 2.4-mm² area was significantly decreased in the RP patients (7.2 ± 2.3 AU) compared to that in the controls (11.2 ± 3.2 AU, P < 0.0001; Fig. 1; Table 1).

The choroidal area, hyporeflective luminal area, and hyperreflective interstitial area, and the ratio of the hyporeflective area to the total choroidal area were measured in the EDI-OCT images by two analyzers (YM, JF). The interobserver agreement rate was high, as based on the ICCs of 0.970 (coefficient of variation [CV]: 0.928–0.988) for the measurements of the choroidal area, 0.957 (CV: 0.899–0.982) for the choroidal hyporeflective area, 0.925 (CV: 0.828–0.969) for the choroidal hyperreflective area, and 0.805 (CV: 0.578–0.916) for the percentage hyporeflective area in the control subjects, and the ICCs of 0.985 (CV: 0.973–0.991) for the measurements of the choroidal area, 0.979 (CV: 0.964–0.988) for the choroidal hyporeflective area, 0.869 (CV: 0.782–0.923) for the choroidal hyperreflective area, and 0.829 (CV: 0.719–0.898) for the percentage hyporeflective area in RP patients. The averaged values between the two observers’ measurements were used in the following analyses.
The choroidal area in the 2.4-mm-wide region of the horizontal scan was significantly smaller in the RP patients (0.62 ± 0.18 mm²) than the controls (0.87 ± 0.19 mm²; P < 0.0001; Table 1). The binarization analysis demonstrated that both the choroidal hyporeflective luminal area and the hyperreflective interstitial area were significantly decreased in the RP patients (P < 0.001, respectively), whereas the percentage hyporeflective area to the total choroidal area was not significantly different between the RP patients and controls (P = 0.1964; Table 1). The SCT and EZ width were significantly decreased in RP patients (P < 0.001, respectively), while the CFT was comparable between RP patients and controls (P = 0.0677).

We next performed a subgroup analysis by F-PFS, in which the central 16 points of the HFA10-2 program topographically matched the 2.4-mm-wide region measured by LSFG. The MBR was significantly reduced in the RP patients with F-PFS < 30 dB (8.0 ± 6.0 AU; P = 0.0006 versus controls) and showed a trend of further decrease in the RP patients with F-PFS < 30 dB (6.3 ± 1.9 AU; P = 0.0001 versus controls, and P = 0.0677 versus the RP patients with F-PFS ≥ 30 dB; Table 2). The choroidal structural parameters (i.e., choroidal area, hyporeflective area, hyperreflective area, and SCT) in the RP patients with F-PFS ≥ 30 dB were significantly decreased as compared to the controls (all P < 0.01); there were no differences in the choroidal structural parameters between the patients with F-PFS ≥ 30 dB and those with F-PFS < 30 dB (Table 2). The EZ width of patients with F-PFS ≥ 30 dB was decreased to 3.5 ± 1.5 mm; however, they had preserved CFT (245.6 ± 26.0 µm) comparable to the controls (231.5 ± 19.0 µm; Table 2), suggesting that the choroidal thinning may precede the foveal retinal thinning in RP patients.

The representative findings of the LSFG, EDI-OCT, binarized analysis of the choroid, and visual function are shown in Figure 2.

### TABLE 2. Subgroup Analysis of RP Patients by F-PFS

<table>
<thead>
<tr>
<th>RP F-PFS ≥ 30 dB (n = 28)</th>
<th>P Value vs. Control</th>
<th>RP F-PFS &lt; 30 dB (n = 24)</th>
<th>P Value vs. Control</th>
<th>P Value vs. RP F-PFS ≥ 50 dB</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>38.6 ± 8.1 (23–50)</td>
<td>0.6100</td>
<td>40.2 ± 7.8 (21–50)</td>
<td>0.2419</td>
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<tr>
<td>Males:females</td>
<td>15:13</td>
<td>0.9541</td>
<td>9:15</td>
<td>0.4928</td>
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<tr>
<td>A1, mm</td>
<td>24.1 ± 1.2</td>
<td>0.0036</td>
<td>24.1 ± 1.2</td>
<td>0.0051</td>
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<tr>
<td>IOP, mm Hg</td>
<td>13.2 ± 2.3</td>
<td>0.9994</td>
<td>12.9 ± 2.3</td>
<td>0.8816</td>
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<tr>
<td>SBP, mm Hg</td>
<td>120.8 ± 16.0</td>
<td>0.9784</td>
<td>114.9 ± 12.0</td>
<td>0.2937</td>
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<tr>
<td>DBP, mm Hg</td>
<td>72.9 ± 13.3</td>
<td>0.9683</td>
<td>71.8 ± 10.8</td>
<td>0.8494</td>
</tr>
<tr>
<td>OPP, mm Hg</td>
<td>44.8 ± 9.3</td>
<td>0.9727</td>
<td>45.2 ± 7.3</td>
<td>0.6918</td>
</tr>
<tr>
<td>MBR, arbitrary units</td>
<td>8.0 ± 2.3</td>
<td>0.0006</td>
<td>6.5 ± 1.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Choroidal area, µm²</td>
<td>0.60 ± 0.21</td>
<td>0.0006</td>
<td>0.64 ± 0.21</td>
<td>0.0075</td>
</tr>
<tr>
<td>Hyporeflective area, µm²</td>
<td>0.41 ± 0.16</td>
<td>0.0015</td>
<td>0.44 ± 0.16</td>
<td>0.0097</td>
</tr>
<tr>
<td>Hyperreflective area, µm²</td>
<td>0.18 ± 0.06</td>
<td>0.0006</td>
<td>0.20 ± 0.06</td>
<td>0.0172</td>
</tr>
<tr>
<td>% Hyporeflective area</td>
<td>68.3 ± 4.9</td>
<td>0.6635</td>
<td>67.3 ± 7.2</td>
<td>0.3305</td>
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<tr>
<td>Visual acuity, logMAR</td>
<td>−0.08 ± 0.07</td>
<td>0.25 ± 0.25</td>
<td>0.0001</td>
<td>0.0001</td>
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<tr>
<td>MD value, dB</td>
<td>−7.9 ± 5.4</td>
<td>−25.1 ± 7.0</td>
<td>0.0001</td>
<td>0.0001</td>
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<tr>
<td>FS, dB</td>
<td>34.1 ± 1.6</td>
<td>23.0 ± 6.8</td>
<td>0.0003</td>
<td>0.0001</td>
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<td>F-PFS, dB</td>
<td>32.8 ± 1.7</td>
<td>15.9 ± 7.7</td>
<td>0.0001</td>
<td>0.0001</td>
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<tr>
<td>CFT</td>
<td>245.6 ± 26.0</td>
<td>200.3 ± 39.1</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
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<tr>
<td>SCT, µm</td>
<td>240.7 ± 84.1</td>
<td>173.7 ± 55.0</td>
<td>0.0121</td>
<td>0.4903</td>
</tr>
<tr>
<td>EZ width, mm</td>
<td>3.5 ± 1.5</td>
<td>&lt;0.0001</td>
<td>0.9 ± 0.9</td>
<td>&lt;0.0001</td>
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Data are the mean ± SD. The bolded values indicate statistical significance, P < 0.05.

### Correlations Among the Foveal Blood Flow, Retinal-Choroidal Structure, and Central Visual Function

We analyzed the relationships among the MBR, OCT retinal-choroidal parameters, and central visual function in the 52 RP patients. The Spearman’s rank testing demonstrated that decreased MBR was significantly correlated with reductions in VA, MD, FS, F-PFS, CFT, and EZ width (Fig. 3; Table 3). In contrast, there was no correlation between the choroidal structural parameters (i.e., choroidal area, hyporeflective area, hyperreflective area, and SCT) and central visual function (Figs. 4A–E; Table 4). The choroidal area, hyperreflective area, and SCT were inversely associated with CFT (Figs. 4F, 4I, 4J), and the hyperreflective area was inversely related to EZ width (Fig. 4M; Table 4).

The MBR did not correlate with the choroidal area, hyporeflective area, hyperreflective area, or SCT, but the MBR was significantly positively correlated with the percentage hyporeflective area (r = 0.3940, P = 0.0039; Fig. 5; Table 5).

We also analyzed the relationship between MBR and OCT parameters in control subjects. There were no significant correlations between these parameters (Fig. 6; Table 6).

### DISCUSSION

We investigated the changes of foveal blood flow and retinal-choroidal structure in RP patients. Our findings demonstrated that foveal blood flow, as measured by LSFG, was attenuated in a relatively early phase of RP with preserved foveal structure/function, and it showed a trend of further decrease at a more advanced stage of RP with foveal thinning and reduced sensitivity. The choroidal structure was also thinned in the RP patients with preserved fovea; however, the choroidal...
FIGURE 2. Representative findings of the LSFG (A–C), EDI-OCT (D–F), binarized analysis of the choroid (G–I), and HFA10-2 static perimetry tests (J, K) in a control subject (A, D, G), an RP patient with VA 20/13 (B, E, H, J), and an RP patient with VA 20/25 (C, F, I, K). The MBR (arbitrary units) in the 2.4 × 2.4-mm boxed area was calculated (A–C). The CFT, SCT, and EZ width of each subject were measured as indicated by the arrows (D–F). The choroidal area between the RPE line and the lower margin of the choroid in a 2.4-mm-wide region centered on the fovea were converted to a binarized image (G–I). The retinal sensitivities of the central 16 points in the HFA10-2 program, which topographically match the 2.4-mm-wide region analyzed by LSFG, were averaged, and these values (F-PFS) were used for the correlation analyses.
thickness did not decrease along with the foveal thinning and reduced sensitivity, but rather showed an inverse association with the foveal thickness. Consequently, the choroidal structure did not correlate with its flow, and the choroidal flow, rather than the choroidal structural parameters, was better associated with central visual function and foveal structure in RP patients.

The reduction of the foveal MBR in RP patients was consistent with our previous observation in different RP populations. The present study included relatively younger RP patients (≤50 years). The subgroup analysis showed that the foveal MBR was reduced to 71.4% in the RP patients with F-PFS ≥ 30 dB compared with the control subjects, and it was further decreased to 56.2% in the RP patients with F-PFS < 30 dB. In line with our results, Shiga et al. have recently reported that the optic nerve MBR is significantly decreased in preperimetric glaucoma and declines along with glaucoma progression. Isono et al. have reported that the speckle pattern observed in LSFG largely originates from the choroid (over 90% of the total circulation). These findings suggest that the alteration of the choroidal blood flow may be implicated in the progression of retinal and optic nerve degeneration in the early phase of the disease.

Several studies have reported the changes of choroidal structural profiles in patients with RP. Dhoot et al. have observed that the subfoveal choroidal thickness is thinned to 72.7% in 21 RP patients with a mean logMAR VA of 0.5 compared to control subjects, and Ayton et al. have reported that the subfoveal choroidal thickness is reduced to 63.6% in 42 RP patients with a mean logMAR VA of 2.0. Our present findings showed that the choroidal area in the central 2.4-mm-wide region was reduced to 71.8% in 52 RP patients with a mean logMAR VA of 0.07. Our subgroup analysis demonstrated that there were no significant differences in the choroidal area between the RP patients with F-PFS ≥ 30 dB and those with F-PFS < 30 dB. These findings suggest that thinning of the choroidal structure may occur extensively in the early phase of cone degeneration in RP. Moreover, correlation analyses demonstrated an inverse correlation between choroidal area/thickness and foveal thickness in RP patients, suggesting that some remodeling process of the choroid, rather than merely attenuation, could be involved in the later stages of the disease.

However, in contrast to these findings, Kawano et al. have recently reported that the choroidal area in the central 7.5-mm-wide region is only mildly thinned to 87.9% in 24 RP patients with a mean logMAR VA of 0.22 compared to controls. They also show that there is no reduction of choroidal area in the RP patients when the central region inside the hyper-autofluorescence (HAF) ring (mean diameter, 2.5 mm) is analyzed. That study includes RP patients with a clear HAF ring. Because there are several variations of AF patterns in RP patients among genotypes and disease stages, the difference of inclusion criteria between the study of Kawano et al. and our present investigation may have led to the difference of results. This point should be confirmed in independent and larger patient populations.

Sonoda et al. have developed a method to analyze the hyporeflective luminal and hyperreflective stromal areas of the choroid, using a binarization technique. In those reports, they demonstrate the excellent repeatability and reproducibility of this method. In patients with age-related macular degeneration,
FIGURE 4. Relationships between choroidal structural parameters, central visual function, and foveal structure in RP patients. Scatter plots show the associations of choroidal structure (choroidal area, hyporeflective area, hyperreflective area, percentage hyporeflective area, and SCT) with F-PFS (A-E), CFT (F-J), and EZ width (K-O).

FIGURE 5. Relationships between MBR and choroidal structural parameters in RP patients. Scatter plots show the associations of MBR with choroidal area (A), hyporeflective area (B), hyperreflective area (C), percentage hyporeflective area (D), and SCT (E).
both the hyper- and hyporeflective areas are thinned after photodynamic therapy (PDT), and the hyporeflective area is more prominently reduced.33 In patients with central serous chorioretinopathy, the hyperreflective area is larger in the inner choroid, whereas the hyporeflective area is increased in the outer choroid, which may reflect the inflammation and the dilation of vessels in the respective regions.34

Our present findings demonstrated that both the hyper- and hyporeflective areas in the choroid were proportionally decreased in the central 2.4-mm-wide region in the RP patients. In contrast, Kawano et al.18 have reported that the hyporeflective area but not the hyperreflective area is reduced in the 7.5-mm-wide region, and there is no reduction in either area in the central region inside the HAF ring. Although the difference between our findings and those of the previous studies should be reexamined in independent studies, the choroidal pattern in RP patients at least partly resembles that after PDT.33 Because the ocular expression of vascular endothelial growth factor (which is critical for the survival of choroidal vascular endothelial cells) is substantially decreased in RP patients,35 the choroidal vessels may be regressed owing to an attenuation of endothelial cells and/or thrombotic obstruction.

Our analyses also showed a correlation between the MBR and the percentage hyporeflective area in RP patients. However, the biological meaning of this finding is unclear because there was no difference in the percentage hyporeflective area between the controls and the RP patients.

There were several limitations in our study, including the lack of genetic information. We have started a genetic study in our department, but the analyses are not yet completed. Although RP is initiated with rod dysfunction and cell loss due to genetic mutations, the disease progression, including the cone cell loss, is influenced by several microenvironmental factors (e.g., inflammation, oxidation, nutrient imbalance) that occur concurrent with and subsequent to rod cell death.2,3 The finding that the change of choroidal thickness occurred earlier than the foveal thinning may suggest a possible primary role of the choroidal circulation in the cone degeneration in RP; however, because of the cross-sectional aspect of the study, we

| Choroidal area | 0.1871 | 0.1841 |
| Hyporeflective area | 0.2564 | 0.0916 |
| Hyperreflective area | 0.0070 | 0.9609 |
| % Hyporeflective area | 0.3940 | 0.0039 |
| SCT | 0.1778 | 0.2074 |

The bolded values indicate statistical significance, \( P < 0.05 \).

<table>
<thead>
<tr>
<th>MBR</th>
<th>( r )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choroidal area</td>
<td>0.1760</td>
<td>0.4453</td>
</tr>
<tr>
<td>Hyporeflective area</td>
<td>0.2027</td>
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<td>Hyperreflective area</td>
<td>0.0331</td>
<td>0.8866</td>
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<tr>
<td>% Hyporeflective area</td>
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<td>0.2135</td>
</tr>
<tr>
<td>SCT</td>
<td>0.2549</td>
<td>0.2648</td>
</tr>
<tr>
<td>CFT</td>
<td>0.1778</td>
<td>0.2074</td>
</tr>
</tbody>
</table>

The bolded values indicate statistical significance, \( P < 0.05 \).
were not able to address the cause-effect relationships. Further longitudinal studies investigating whether reduced choroidal blood flow is associated with a faster decline of central visual function are needed to answer this question.

In conclusion, our study showed that the choroidal structure in EDI-OCT did not correlate with the foveal blood flow, as assessed by LSFG, in RP patients. The decreased choroidal blood flow, rather than the alteration of choroidal structure, was more closely associated with central visual function and foveal structure. These results suggest the divergence between the choroidal structure and its blood flow, and they suggest that caution should be used when interpreting OCT choroidal images as a reflection of blood function in RP patients.

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References


