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Association Between Retinal Artery Angle and Visual Function in Eyes With Idiopathic Epiretinal Membrane

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Purpose: This study investigated the relationship between retinal artery angle and visual function in eyes with idiopathic epiretinal membrane (ERM).

Methods: Ultra-wide field fundus imaging was conducted to analyze ERM and normal contralateral eyes. In addition to the logMAR visual acuity (VA) measurement, the average of the vertical and horizontal metamorphopsia scores (Mave) was measured using m-Charts for each eye. We calculated the retinal artery angle (Yugami correlated angle [YCA]) in all the examined eyes using ImageJ software. The YCAs were then compared between the ERM and normal contralateral eyes. Additionally, the relationship between YCA and visual function was investigated in the ERM eyes.

Results: Data from 40 patients with ERM were analyzed. The mean age of the participants was 67.1 ± 8.1 years. The YCA was significantly smaller in the ERM eyes, compared with the contralateral eyes ($P < 0.001$, respectively; Wilcoxon signed rank test). Among age, axial length, YCAs, central retinal thickness (CRT), and central choroidal thickness (CCT), the optimal model for logMAR VA included age, YCA, and CRT. On the other hand, the optimal model for Mave included YCA and CCT.

Conclusions: The retinal artery angle may be useful for predicting visual function in eyes with ERM.

Translational Relevance: Our established quantitative measurements in fundus photography have potential clinical use in predicting visual function in ERM.

Introduction

Epiretinal membrane (ERM) is one of the most common vitreomacular disorders with an estimated prevalence of 2.2% to 28.9% worldwide.[1–5] Although symptoms range widely from asymptomatic to severe visual impairment, the most common symptoms in patients with ERM include decreased visual acuity (VA) and metamorphopsia. In clinical settings, the Amsler grid and m-Charts are used to evaluate metamorphopsia in eyes with ERM. Compared with the Amsler grid, m-Charts can assess the degree of metamorphopsia quantitatively.[6] Several studies have indicated a relationship between visual function and optical coherence tomography (OCT) parameters in eyes with ERM. Okamoto et al. suggested that the thickness of the inner nuclear layer (INL) was associated with the degree of metamorphopsia,[7] and Hirano et al. also reported a close correlation between the metamorphopsia score and the maximum depth of the retinal fold in eyes with ERMs.[8]

On the other hand, retinal vessel displacement has been reported in eyes with ERM using fundus photography.[9,10] Arimura et al. calculated the change in the location of retinal vessels in idiopathic ERM eyes and found a significant correlation between retinal contraction and metamorphopsia score.[11] Therefore, we hypothesized that visual function could be predicted from fundus images in eyes with ERM.

Recent advances in ultra-wide field (UWF) fundus imaging have allowed us to diagnose several retinal diseases, such as diabetic retinopathy and retinal detachment.[12–14] UWF imaging is thought to be a useful tool for screening vitreoretinal diseases in clinical practice. Moreover, our recent report suggested that UWF imaging was also useful for detecting age-related macular degeneration.[15] In the present study, we quantified the contraction of retinal vessels in eyes with idiopathic ERM using UWF fundus images to investigate its association with visual function.

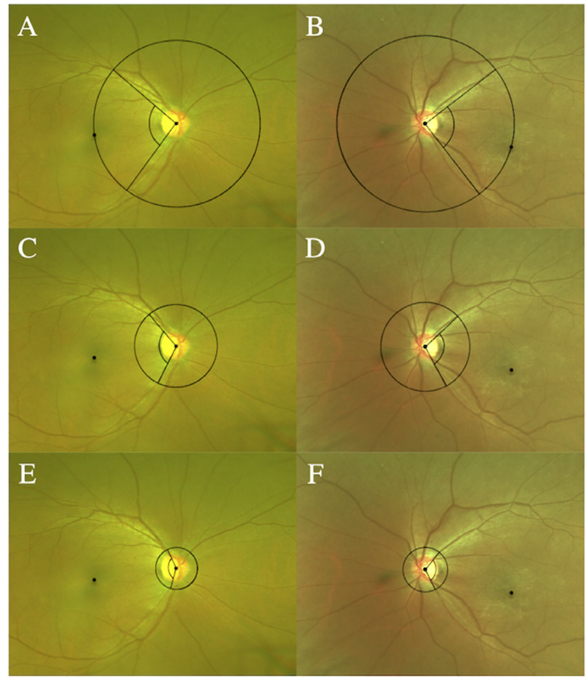

Figure 1. Measurement of retinal artery angles (YCA, YCA$_{1/2}$, and YCA$_{1/4}$). Using ImageJ software, the distance between the optic nerve head (ONH) and the fovea was measured and a circle was drawn, with the radius of the distance centered on the ONH. The intersection points between the drawn circle and the arteries of the upper and lower arcade arteries were determined, and the angle between these intersections and the ONH was calculated as the YCA in the ERM and normal contralateral eyes; normal contralateral eye in panel (**A**), and the ERM eye in panel (**B**). The intersection points of a half circle were also determined, and the angle between these intersections and the ONH was calculated as YCA$_{1/2}$; normal contralateral eye in panel (**C**), and the ERM eye panel (**D**). Finally, the intersection points of a quarter circle were determined, and the angle between these intersections and the ONH was calculated as YCA$_{1/4}$; normal contralateral eye in panel (**E**), and the ERM eye in panel (**F**). YCA, Yugami correlated angle; ERM, epiretinal membrane.

Methods

Study Subjects

This study was a retrospective cross-sectional survey conducted at Yokohama City University Medical Center. All the procedures adhered to the tenets of the Declaration of Helsinki. The study was conducted with the approval of the Ethics Committee of Yokohama City University, Kanagawa, Japan. Written informed consent was obtained from each participant.

All the patients underwent comprehensive ophthalmologic examinations, including measurement of the best-corrected visual acuity (BCVA) and slit-lamp biomicroscopy. Spectral domain OCT images were obtained using the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). Central retinal thickness (CRT) and central choroidal thickness (CCT) were measured using enhanced depth imaging (EDI) mode. In addition, m-Charts (Inami, Tokyo, Japan) was used to measure the degree of metamorphopsia, and the axial length (AL) measurement was performed using A-scan ultrasonography (UD-6000, Tomey Corporation, Nagoya, Japan). The m-Charts examination was performed for both vertical and horizontal lines at a distance of 30 cm with refractive correction. Based on the vertical and horizontal metamorphopsia scores (MV and MH), average of vertical and horizontal metamorphopsia scores (Mave) was calculated. The exclusion criteria were as follows: (i) eyes with other retinal diseases, such as age-related macular degeneration; (ii) eyes with bilateral ERM (iii); and eyes with AL over 26 mm.

To measure the angle between the supratemporal and the infratemporal major retinal artery, we used ImageJ software (ImageJ, version .2.0.0-rc-69/1.52i; National Institutes of Health [NIH], Bethesda, MD, USA) and established novel parameters (Fig. 1). First, we measured the distance between the center of the optic nerve head (ONH) and the fovea and drew a circle with a radius equivalent to the distance between the ONH and the fovea. The intersection points between the drawn circle and the arteries of the upper and lower arcade arteries were determined, and the angle between these intersections and the ONH was calculated in the ERM and the contralateral eye. This angle was defined as the Yugami correlated angle, or YCA (see Figs. 1A, 1B). Second, the intersection points between the 1/2 circle and the arteries of the upper and lower arcade arteries and between the 1/4 circle and the arteries of the upper and lower arcade arteries were also determined, and the angle between these intersections and the ONH was calculated as the $YCA_{1/2}$ and the $YCA_{1/4}$, respectively (see Figs. 1C–1F).

Statistical Analysis

The baseline parameters (YCA, $YCA_{1/2}$, $YCA_{1/4}$, CRT, and CCT) were compared between ERM and contralateral eyes using the exact Wilcoxon signed rank test. A comparison of logMAR VA between ERM and contralateral eyes was also performed. To investigate the relationship between baseline parameters (age, AL, YCAs, CRT, and CCT) and visual function (logMAR VA and Mave), univariate and multivariate linear regression analyses were conducted in eyes with idiopathic ERM. Moreover, the correlations between each YCA and age, AL, CRT, and CCT were investigated. The model selection used to identify the optimal model for visual function (logMAR VA and the degree of metamorphopsia) was performed using the second-order bias-corrected Akaike information criterion (AICc) index from 2^7 patterns using the 7 candidate variables (age, AL, YCA, $YCA_{1/2}$, $YCA_{1/4}$, CRT, and CCT). The AICc is a well-known statistical measure in model selection, and this corrected version provides an accurate estimation even when the sample size is small.[16,17] All statistical analyses were performed using R statistical software version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1 shows the demographic data in the current study. Forty patients (25 women and 15 men) with idiopathic ERM were enrolled, and both the ERM and contralateral eyes were examined. The mean (± standard deviation) age of the participants was 67.1 ± 8.1 years. Significant differences in YCA, $YCA_{1/2}$, and $YCA_{1/4}$ were seen between the ERM eyes and normal contralateral eyes ($P < 0.0001$, $P < 0.0001$, and $P = 0.00089$, respectively; Wilcoxon signed rank test, Fig. 2). In other words, the YCA, $YCA_{1/2}$, and $YCA_{1/4}$ values for the ERM eyes were significantly smaller than those in the contralateral eyes. There were also significant differences in AL, logMAR VA, and CRT between the two groups ($P = 0.0089$, $P < 0.0001$, and $P < 0.0001$, respectively); however, no significant difference was observed in CCT ($P = 0.14$).

Among the baseline parameters, a univariate analysis suggested that age, AL, all three YCAs and CRT were significantly correlated with logMAR VA in eyes with ERM (linear regression analysis, Fig. 3, Table 2). As a result of AICc model selection, the optimal model for logMAR VA included age, YCA, and CRT (see Table 2). The optimal model for logMAR VA was as

Table 1. Demographic Characteristics

	ERM Eyes	Contralateral Eyes	*P* Value
Number of eyes	40	40	–
Age (years)	67.1 ± 8.1	–	–
LogMAR VA	0.16 ± 0.22	−0.045 ± 0.098	<0.0001
AL (mm)	23.8 ± 1.3	23.9 ± 1.2	0.0089
CRT (µm)	412.7 ± 152.2	200.2 ± 35.4	<0.0001
CCT (µm)	221.9 ± 66.4	233.3 ± 69.7	0.14
MV score	0.73 ± 0.44	–	–
MH score	0.64 ± 0.49	–	–
Mave score	0.68 ± 0.41	–	–
YCA	82.6 ± 13.8	92.2 ± 16.3	<0.0001
$YCA_{1/2}$	106.0 ± 19.0	120.4 ± 19.3	<0.0001
$YCA_{1/4}$	130.1 ± 21.3	143.3 ± 22.2	0.00089

Data are presented as the means ± SD.

ERM, epiretinal membrane; logMAR, logarithm of the minimum angle of resolution; VA, visual acuity; AL, axial length; CRT, central retinal thickness; CCT, central choroidal thickness; MV, vertical metamorphopsia; MH, horizontal metamorphopsia; Mave, the average of vertical and horizontal metamorphopsia scores; YCA, Yugami correlated angle.

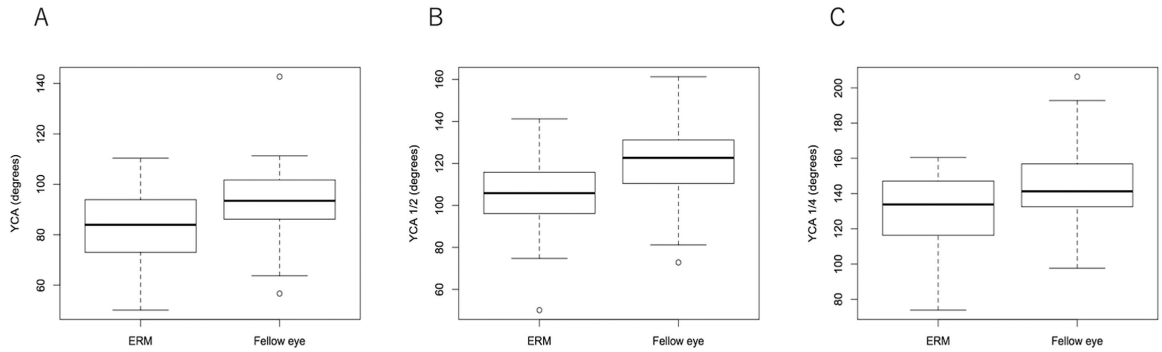

Figure 2. **Comparison of YCAs between eyes with idiopathic ERM and normal contralateral eyes.** Significant differences in YCA (**A**), $YCA_{1/2}$ (**B**), and $YCA_{1/4}$ (**C**) were seen between the ERM and normal contralateral eyes ($P < 0.0001$, $P < 0.0001$, and $P = 0.00089$, respectively, Wilcoxon signed rank test). YCA, Yugami correlated angle; ERM, epiretinal membrane.

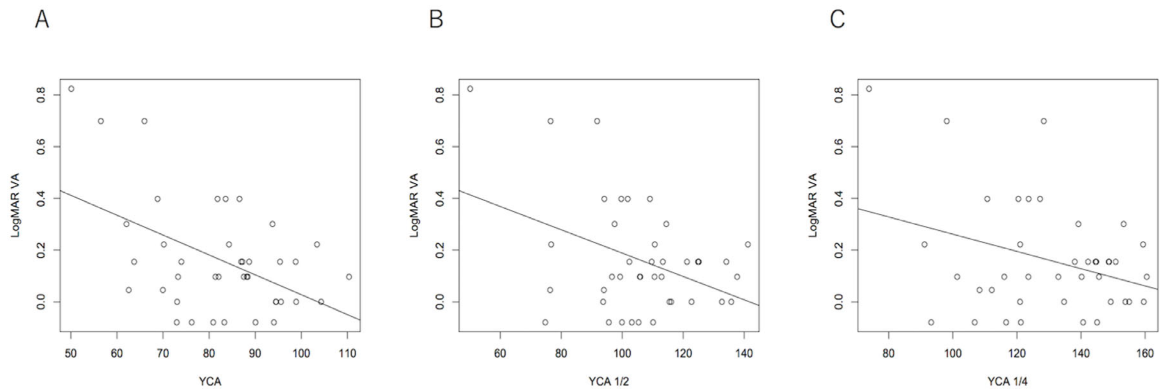

Figure 3. **Relationship between YCAs and logMAR VA.** YCA, $YCA_{1/2}$, and $YCA_{1/4}$ were significantly related to logMAR VA ($P = 0.0015$, $P = 0.012$, and $P = 0.040$, respectively; linear regression analysis). YCA, Yugami correlated angle; logMAR, logarithm of the minimum angle of resolution; VA, visual acuity.

Table 2. Correlation Between logMAR VA and Age, AL, YCAs, CRT, and CCT in Eyes With ERM

	Univariate Analysis			Optimal Model		
Variable	Coefficient	SE	*P* Value	Coefficient	SE	*P* Value
Age	0.0085	0.0041	0.047	0.011	0.0032	0.0017
AL	−0.054	0.026	0.045		N.S.	
YCA	−0.0077	0.0022	0.0015	−0.0045	0.0023	0.054
$YCA_{1/2}$	−0.0045	0.0017	0.012		N.S.	
$YCA_{1/4}$	−0.0033	0.0016	0.040		N.S.	
CRT	0.00078	0.00019	0.00026	0.00061	0.00021	0.0048
CCT	0.000076	0.00053	0.89		N.S.	

LogMAR, logarithm of the minimum angle of resolution; VA, visual acuity; AL, axial length; YCA, Yugami correlated angle; CRT, central retinal thickness; CCT, central choroidal thickness; ERM, epiretinal membrane; SE, standard error; N.S., not selected.

follows:

$$\text{LogMAR VA} = -0.45 + 0.011\ (\pm 0.0032) \times \text{Age} - 0.0045\ (\pm 0.0022) \times \text{YCA} + 0.00061\ (\pm 0.00021) \times \text{CRT}\ (\text{AICc} = -25.6).$$

Table 3 shows the relationships between Mave and age, AL, YCAs, CRT, and CCT. A univariate analysis suggested that YCA was significantly associated with Mave ($P = 0.030$, linear regression

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Table 3. Correlation Between Mave and Each of Age, AL, YCAs, CRT, and CCT in Eyes With ERM

	Univariate analysis			Optimal model		
Variable	Coefficient	SE	*P* Value	Coefficient	SE	*P* Value
Age	0.0096	0.0081	0.24		N.S.	
AL	−0.019	0.051	0.71		N.S.	
YCA	−0.010	0.0045	0.030	−0.0082	0.0044	0.070
$YCA_{1/2}$	−0.0041	0.0034	0.23		N.S.	
$YCA_{1/4}$	−0.0016	0.0031	0.61		N.S.	
CRT	0.00074	0.00042	0.087		N.S.	
CCT	0.0023	0.00092	0.153	0.0020	0.00091	0.035

Mave, the average of vertical and horizontal metamorphopsia scores; AL, axial length; YCA, Yugami correlated angle; CRT, central retinal thickness; CCT, central choroidal thickness; ERM, epiretinal membrane; SE, standard error; N.S., not selected.

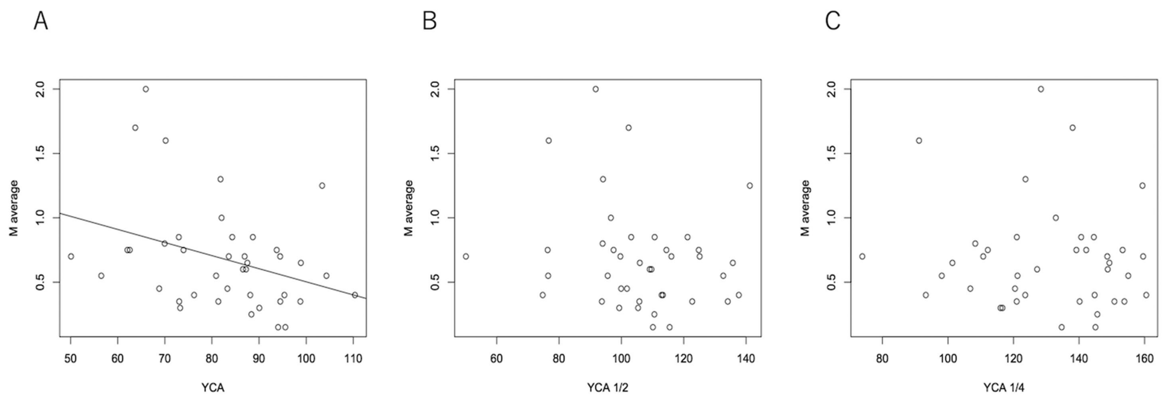

Figure 4. Association between YCAs and degree of metamorphopsia. YCA was significantly correlated with Mave (**A**), ($P = 0.030$), but $YCA_{1/2}$ and $YCA_{1/4}$ were not (**B**), ($P = 0.23$); (**C**), ($P = 0.61$); linear regression analysis. YCA, Yugami correlated angle; Mave, average of vertical and horizontal metamorphopsia scores.

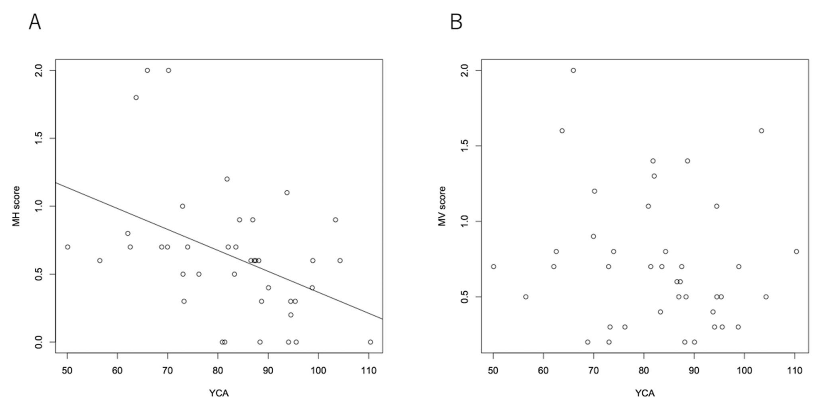

Figure 5. YCA was significantly associated with the MH score but not with the MV score. YCA was significantly related with the MH score ($P = 0.0049$) but not with the MV score ($P = 0.34$, linear regression analysis). YCA, Yugami correlated angle; MH, horizontal metamorphopsia; MV, vertical metamorphopsia.

analysis; Fig. 4). No significant differences between $YCA_{1/2}$ and Mave or between $YCA_{1/4}$ and Mave were seen ($P = 0.23$ and $P = 0.61$, respectively). The optimal model for Mave included YCA and CCT among the baseline parameters (see Table 3). The optimal model for Mave was as follows:

$$\text{Mave} = 0.91 - 0.0082\ (\pm 0.0044) \times \text{YCA} + 0.0020\ (\pm 0.00091) \times \text{CCT}\ (\text{AICc} = 40.2).$$

Moreover, YCA was significantly correlated with the MH score but not with the MV score in eyes with ERM ($P = 0.0049$ and $P = 0.34$, respectively; Fig. 5).

In eyes with ERM, a univariate analysis suggested that YCA was significantly associated with CRT ($P = 0.00030$) but not with age, AL, or CCT ($P > 0.05$, respectively; linear regression analysis). A multivariate analysis also suggested that YCA was associated with only CRT. $YCA_{1/2}$ was also related to only CRT in both univariate and multivariate analyses ($P < 0.0001$). A univariate analysis suggested that $YCA_{1/4}$ was significantly associated with only CRT ($P = 0.00013$), whereas a multivariate analysis suggested that age and CRT were correlated with $YCA_{1/4}$.

$$YCA = 103.7 - 0.050\ (\pm 0.013) \times CRT$$
$$YCA_{1/2} = 137.4 - 0.076\ (\pm 0.016) \times CRT$$
$$YCA_{1/4} = 121.3 + 0.59\ (\pm 0.34) \times age - 0.075\ (\pm 0.018) \times CRT$$

Discussion

In the present study, we newly identified a metamorphopsia-related parameter in eyes with ERM. We named this two-dimensional parameter as the YCA. *Yugami* means distortion in Japanese. The YCA, $YCA_{1/2}$, and $YCA_{1/4}$ were significantly smaller in ERM eyes than in the contralateral eyes, respectively. Moreover, YCA was significantly associated with visual function, suggesting that the measurement of the retinal artery angle was useful for predicting both the logMAR VA and the degree of metamorphopsia in patients with ERM.

Previous researchers have indicated that some OCT parameters were correlated with visual function. For instance, some reports suggested that the INL thickness is correlated with metamorphopsia.[7,18] Another report suggested that the retinal fold depth is associated with metamorphopsia in eyes with ERM.[8] More recently, the foveal avascular zone (FAZ), measured with OCT angiography, was reportedly correlated with metamorphopsia in ERM.[19] In the current study, the two-dimensional parameter, YCA, was associated with visual function. In the present study, the YCA was not compared with OCT parameters, such as INL thickness, retinal fold depth, and FAZ, but a significant merit of the current approach is that visual function can be predicted using the retinal artery angle, which can be easily obtained using only UWF imaging.

We initially speculated that YCA, $YCA_{1/2}$, and $YCA_{1/4}$ might have similar associations with visual function, because all YCAs were significantly smaller in the ERM eyes than in the normal contralateral eyes. Unexpectedly, although a univariate analysis suggested that all YCAs were related to logMAR VA, the optimal model for logMAR VA only included YCA. In addition, YCA was most closely correlated with metamorphopsia in eyes with idiopathic ERM. The reason why only YCA was strongly associated with visual function remains unclear, however, it might be simply due to the fact that the arteries near the ONH are less mobile than the more peripheral arteries since the arteries are anchored by the ONH. Another possibility is that the contraction of the retina as a result of ERM traction may occur around the fovea in general (presumably up to the location of ERM), and the angle passing the fovea was most closely associated with the deterioration of visual function. In addition, the optic disc is involved in the horizontal retinal contraction but not in the vertical retinal contraction in ERM eyes. A smaller space in the horizontal direction might result in a less-apparent horizontal contraction by ERM. Such vertical retinal contraction may be best described using YCA. Indeed, YCA was significantly correlated with the MH score, but not with the MV score in eyes with ERM (see Fig. 5). Shiihara and colleagues assessed the shape of the FAZ in addition to the area of the FAZ in ERM eyes.[19] Interestingly, they reported that 68.5% of ERM eyes had a horizontally long-shaped FAZ, whereas 31.5% had a vertically long-shaped FAZ, supporting our current results.

Yamashita et al. previously suggested that the peripapillary retinal artery angles (PRAAs) were significantly associated with the AL.[20] A more recent report indicated that correcting the circumpapillary retinal nerve fiber layer thickness profile using the retinal artery position significantly strengthened the structure-function relationship in eyes with glaucoma.[21] Using the color fundus photographs (TOPCON 3D OCT-1000 MARK II), a 3.4-mm diameter peripapillary circle was drawn on the scan, and the center of the circle and the points where the circle and the superotemporal/infratemporal major retinal artery intersected were used for measuring PRAA. Among the YCAs, $YCA_{1/4}$ had the greatest similarity to the PRAA described by Yamashita and colleagues. This previous report suggested the PRAA was closely related to the AL. In contrast, our current result indicated that all YCAs were significantly related to the CRT, but not with AL, in eyes with ERM. This might be due to the fact that the AL measured using an A-scan ultrasound was significantly shorter in eyes with macular disease than that measured using partial coherence interferometry and that the difference in retinal thickness was associated with the AL.[22] Further investigations are needed to clarify the relationship between the YCAs and AL in eyes with ERM.

The current study had some limitations. First, the present study was retrospective and cross-sectional in nature, and the number of examined eyes was relatively small. The current study did not include postoperative data in eyes with ERM. Observations of the retinal artery angle after vitrectomy surgery might be useful for predicting improvements in VA or metamorphopsia in eyes with ERM. The retinal artery angle might be a valid indicator of visual acuity and metamorphopsia if UWF images before and after vitrectomy surgery are compared. It would be interesting to investigate the relationship between the change in YCA and the improvement in visual function after vitrectomy surgery for ERM. Second, in the present study, we performed the AL measurements using A-scan ultrasound. Using A-scan ultrasound, the AL was measured from the cornea to the inner limiting membrane; therefore, the AL measured using A-scan ultrasound was shorter than that measured using partial coherence interferometry.[23] Consequently, our results demonstrated that the ALs in eyes with ERM were significantly shorter than those in the normal contralateral eyes (see Table 1). However, in a multivariate analysis, the association between the YCA and visual function was still significant when other baseline parameters (age, AL, CRT, and CCT) were considered. This suggests the importance of measuring the retinal artery angle in eyes with ERM.

In conclusion, we introduced a novel vision-related parameter that is closely associated with VA and metamorphopsia in eyes with idiopathic ERM. The retinal artery angle may provide useful two-dimensional information for predicting visual function in clinical settings.

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