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# Functional Visual Acuity in Age-Related Macular Degeneration

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## ABSTRACT

**Purpose.** We evaluated whether a functional visual acuity (FVA) system can detect subtle changes in central visual acuity that reflect pathological findings associated with age-related macular degeneration (AMD).

**Methods.** Twenty-eight patients with unilateral AMD and logMAR monocular best corrected VA better than 0 in both eyes, as measured by conventional chart examination, were analyzed between November 2012 and April 2013. After measuring conventional VA, FVA, and contrast VA with best correction, routine eye examinations including spectral domain–optical coherence tomography were performed. Standard Schirmer test was performed, and corneal and lens densities were measured.

**Results.** The FVA score ( $p < 0.001$ ) and visual maintenance ratio ( $p < 0.001$ ) measured by the FVA system, contrast VA ( $p < 0.01$ ), and conventional VA ( $p < 0.01$ ) were significantly worse in the AMD-affected eyes than in the fellow eyes. No significant differences were observed in the anterior segment conditions. Forward stepwise regression analysis demonstrated that the length of interdigitation zone disruption, as visualized by optical coherence tomography imaging, correlated with the FVA score ( $p < 0.01$ ) but not with any other parameters investigated.

**Conclusions.** The FVA system detects subtle changes in best corrected VA in AMD-affected eyes and reflects interdigitation zone disruption, an anatomical change in the retina recorded by optical coherence tomography. Further studies are required to understand the value of the FVA system in detecting subtle changes in AMD.

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Key Words: functional visual acuity, interdigitation zone, optical coherence tomography, age-related macular degeneration, retina

Recent progress in medical technology and science has facilitated the development of effective treatments for retinal diseases, such as molecular targeted drugs, and anti-vascular endothelial growth factor (anti-VEGF) drugs for age-related macular degeneration (AMD), as well as pars plana vitrectomy. With the improvement in prognosis, treatment is extended to patients who have better visual function at baseline. Thus, a sensitive method for detecting subtle changes in central visual acuity (VA) that reflects pathological findings of AMD and other retinal diseases is warranted. One method proposed for this purpose is the functional VA (FVA) system. The FVA system can detect subtle visual

dysfunction caused by epiretinal membrane in eyes with good VA as measured by conventional Landolt C charts.<sup>1</sup> However, whether this method is able to detect the subtle impairment of visual function caused by AMD and reflect the retinal clinical findings remains obscure.

The FVA system uses a series of charts shown continuously and requires patient responses within 2 s of each chart display, which is in contrast to the conventional Landolt C chart examination, in which patients can stare at the chart before responding. Contrast VA testing involves the use of a lower-contrast Landolt C chart than conventional VA measurement, but this examination is also performed by staring at the chart. Functional VA, on the other hand, therefore uses a different method for measuring central visual function than the conventional chart and contrast VA.

High-resolution optical coherence tomography (OCT) is routinely used for evaluating AMD lesions. The earliest detectable changes associated with AMD occur in the retinal pigment epithelium and choroid. Thus, OCT analysis focuses on photoreceptor-related changes to explain visual function impairment in AMD.

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In addition, OCT imaging of the retina typically shows three lines above the retinal pigment epithelium line: the external limiting membrane (ELM), the ellipsoid zone (also called the inner segment/outer segment junction),<sup>2</sup> and the interdigitation zone (also called the cone outer segment tips).<sup>2</sup> However, the association of changes in these lines with reduced visual function in AMD is not completely understood.<sup>3,4</sup>

In this study, we analyzed patients with advanced unilateral AMD, with a decimal monocular best corrected VA (BCVA) of 1.0 (20/20 in Snellen VA, 0 in logMAR) or better in both eyes. These patients complained of visual disturbances, such as distorted vision and reading disability in the affected eyes, but regarded to have good BCVA in both eyes. The patients' central visual function was evaluated using the FVA system and contrast VA scoring, and retinal images were examined by OCT. Data were collected to compare BCVA and retinal condition of the affected and fellow eyes and to investigate the association between visual function score and OCT retinal findings.

## MATERIALS AND METHODS

This study followed the tenets of the Declaration of Helsinki and was approved by the ethics committee of Keio University School of Medicine.

### Subjects

Twenty-eight patients (22 men and 6 women; average age, 67.6 ± 9.0 years; range, 51 to 86 years) who had advanced unilateral AMD (9 typical AMD and 19 polypoidal choroidal vasculopathy patients) diagnosed at the Medical Retina Division Clinic of the Department of Ophthalmology, Keio University Hospital, between November 2012 and April 2013 were included in the study. All subjects had a monocular logMAR BCVA of 0 or better in both eyes, as measured by conventional Landolt C chart examination. The AMD diagnosis was based on fundus examination, spectral domain-OCT (SD-OCT), and fluorescein and indocyanine angiographies.<sup>5,6</sup> Patients with other ocular or systemic diseases were excluded from the study. This was a cross-sectional study.

### Eye Examinations

All subjects underwent initial monocular BCVA measurement, including monocular conventional Landolt BCVA, FVA (AS-28 FVA measurement system; Kowa, Tokyo, Japan), and contrast VA (CSV-1000 LanC charts; VectorVision, Inc., Greenville, OH), and data were presented as logMAR scores. Next, patients underwent slitlamp examination, binocular indirect ophthalmoscopy after pupil dilation with 0.5% tropicamide and 0.5% phenylephrine, and further examinations including SD-OCT as described below. Conventional Landolt BCVA was measured at a testing distance of 5 m with a background illumination of 200 cd/m<sup>2</sup>.

Using the FVA system, Landolt optotypes were presented on a monitor, with appropriate size changes depending on the response accuracy.<sup>1,7</sup> The optotypes were displayed automatically, starting with conventional Landolt rings sized to reflect the patient's BCVA as determined by conventional methods. Correct responses were followed by the presentation of one step-smaller optotypes, whereas incorrect responses resulted in the presentation of one

step-larger optotypes. When there was no response within 2 s, the optotype was automatically enlarged. Functional VA was measured during a 60-s period with best correction.

The outcome values of the FVA measurement system were FVA score and visual maintenance ratio (VMR). Functional VA was defined as the average of VAs measured during the 60-s period. To compare changes in VA across time, VMR was determined. Visual maintenance ratio is an objective index calculated as the logMAR values of FVA scores obtained during the testing interval divided by the logMAR baseline VA score: VMR = (lowest logMAR VA score - FVA at 60 s)/(lowest logMAR VA score - baseline VA).

Contrast VA was determined with best correction using Landolt optotypes with 10% contrast compared with conventional Landolt optotypes, and values were recorded in log scale. This test was performed in monocular eyes with undilated pupils at a testing distance of 2.5 m. Background illumination of the translucent chart was provided by a fluorescent source in the instrument and was automatically calibrated to 250 cd/m<sup>2</sup>. For reproducibility of this method,<sup>7</sup> we measured the same eye twice and selected the best value.

The standard Schirmer test was performed without topical anesthesia. Standardized strips of filter paper (Showa Yakuhin Kako, Tokyo, Japan) were placed in the lateral canthus away from the cornea and left in place for 5 min with the eyes closed. Results were recorded as millimeters of wet strip after 5 min.

Corneal and lens densities were measured using an Oculus Pentacam (Oculus, Inc., Wetzlar, Germany). The corneal and lens densities were recorded as the peak value on images, and measurements were automatically changed to numeric values between 0 and 100 using a standardized gray scale. Spectral domain-optical coherence tomography images were recorded using a Heidelberg Spectralis OCT (Heidelberg Engineering GmbH, Dossenheim, Germany). Disruption lengths in the interdigitation zone, ellipsoid zone, and ELM line within a 1.5-mm-diameter area around the

**TABLE 1.**

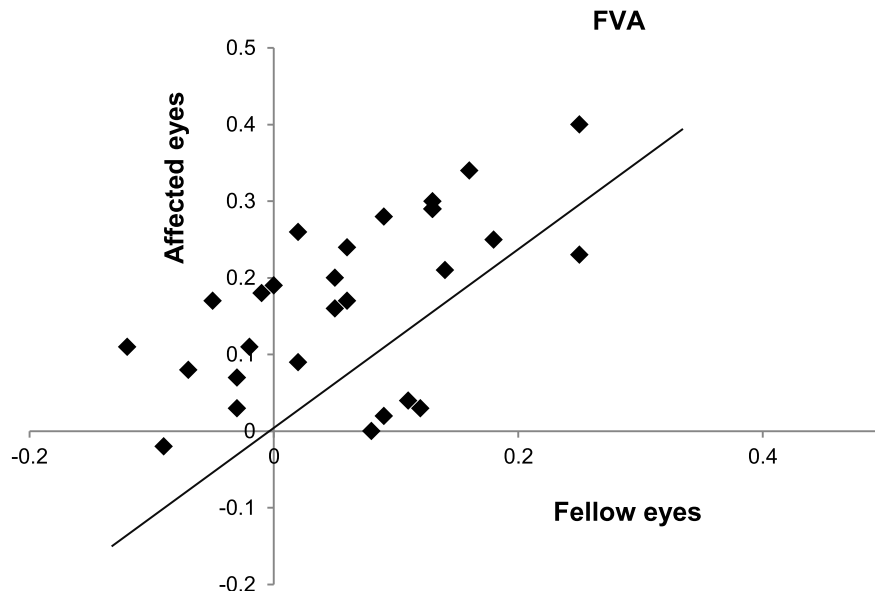
Average examination values for eyes affected with AMD and healthy fellow eyes

|                                 | Affected eyes<br>(N = 28) | Fellow eyes<br>(N = 28) | p       |
|---------------------------------|---------------------------|-------------------------|---------|
| Best corrected VA               | -0.05 ± 0.04              | -0.07 ± 0.02            | <0.01*  |
| FVA score                       | 0.17 ± 0.11               | 0.06 ± 0.10             | <0.001* |
| VMR                             | 0.92 ± 0.04               | 0.95 ± 0.03             | <0.001* |
| Contrast VA                     | 0.43 ± 0.21               | 0.28 ± 0.13             | <0.01*  |
| Schirmer test, mm               | 8.5 ± 6.2                 | 8.1 ± 4.7               | 0.81    |
| Density of cornea               | 19.4 ± 1.9                | 18.7 ± 2.5              | 0.21    |
| Density of lens                 | 13.1 ± 2.9                | 12.7 ± 3.4              | 0.44    |
| OCT findings, μm                |                           |                         |         |
| Interdigitation zone disruption | 1265 ± 199                | 283 ± 403               | <0.001* |
| Ellipsoid zone disruption       | 581 ± 502                 | 0                       | —       |
| ELM line disruption             | 199 ± 302                 | 0                       | —       |

Data are shown as the mean ± SD.

\*p < 0.001.

AMD, age-related macular degeneration; ELM, external limiting membrane; FVA score, functional visual acuity score; OCT, optical coherence tomography; VA, visual acuity; VMR, visual maintenance ratio.



**FIGURE 1.**

Comparison of functional visual acuity (FVA) scores in the affected and fellow eye of each patient. The FVA score for the affected eye versus the fellow eye was plotted for each patient. The FVA score in the affected eye was inferior to the fellow eye in most patients.

fovea were measured in horizontal and vertical scans passing through the fovea using software embedded in the SD-OCT system by two retina experts (T.Y. and N.N.) and averaged.

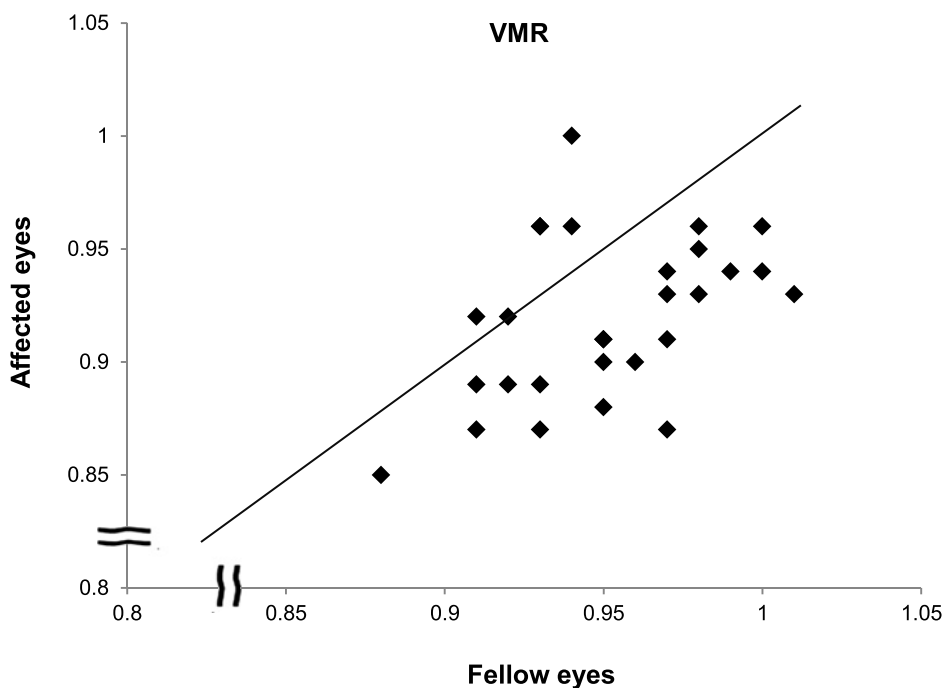
**Statistical Analysis**

Data are expressed as mean ± SD. Affected eye and healthy eye data were compared using the Wilcoxon signed rank test; the OCT finding did not distribute normally. Spearman’s correlation analyses and forward stepwise regression analyses were performed

to determine correlations between FVA score, VMR, or contrast VA and OCT findings. SPSS version 22.0.1 (SPSS Japan, Tokyo, Japan) was used to analyze the sample data. Statistical significance was defined as  $p < 0.05$ .

**RESULTS**

Of the 28 patients with advanced unilateral AMD included in the study, 9 had typical AMD, 19 had polypoidal choroidal vasculopathy, and none had retinal angiomatous proliferation or



**FIGURE 2.**

Comparison of visual maintenance ratios (VMRs) in the affected and fellow eye of each patient. The VMR for the affected eye versus the fellow eye was plotted for each patient. The VMR in the affected eye was inferior to the fellow eye in most patients.

**TABLE 2.**

Relationship between FVA, VMR, contrast VA, conventional VA, and other parameters in the AMD-affected eyes

|                                 | FVA score<br>(N = 28) |         | VMR<br>(N = 28) |         | Contrast VA<br>(N = 28) |        | Conventional VA<br>(N = 28) |        |
|---------------------------------|-----------------------|---------|-----------------|---------|-------------------------|--------|-----------------------------|--------|
|                                 | r                     | p       | r               | p       | r                       | p      | r                           | p      |
| Age                             | 0.47                  | 0.01*   | − 0.39          | 0.04*   | 0.19                    | 0.34   | 0.28                        | 0.15   |
| FVA score                       | —                     | —       | − 0.94          | <0.001* | 0.54                    | 0.03*  | 0.51                        | 0.006* |
| VMR                             | − 0.94                | <0.001* | —               | —       | − 0.58                  | 0.001* | − 0.33                      | 0.09   |
| Contrast VA                     | 0.54                  | 0.003*  | − 0.58          | 0.001*  | —                       | —      | 0.14                        | 0.48   |
| OCT findings, $\mu\text{m}$     |                       |         |                 |         |                         |        |                             |        |
| Interdigitation zone disruption | 0.42                  | 0.03*   | − 0.35          | 0.07    | 0.09                    | 0.65   | 0.39                        | 0.04*  |
| Ellipsoid zone disruption       | 0.46                  | 0.01*   | − 0.36          | 0.06    | 0.09                    | 0.65   | 0.29                        | 0.13   |
| ELM disruption                  | − 0.10                | 0.61    | 0.15            | 0.45    | 0.13                    | 0.51   | − 0.11                      | 0.60   |

\* $p < 0.05$ .

AMD, age-related macular degeneration; ELM, external limiting membrane; FVA score, functional visual acuity score; OCT, optical coherence tomography; VA, visual acuity; VMR, visual maintenance ratio.

geographic atrophy. One patient had received prior photodynamic therapy (PDT), and 11 patients had received prior intravitreal anti-VEGF treatment. Fifteen patients had received no prior treatment. Nine of the previously untreated patients received anti-VEGF drugs after the study. The remaining seven patients who had fibrosis, pigment epithelial detachment only, or massive subretinal hemorrhage caused by AMD just after the study were not treated with either PDT or anti-VEGF drugs after the study according to their clinical records.

The AMD-affected eyes showed significantly worse VA score ( $p < 0.01$ ), FVA value (FVA score and VMR;  $p < 0.001$ ), and contrast VA ( $p < 0.01$ ) compared with healthy fellow eyes (Table 1). The FVA value was also worse in the AMD-affected eye than the fellow eye in most patients (Figs. 1 and 2). There were no significant differences in Schirmer test results or in corneal or lens densities between affected and fellow eyes. Optical coherence tomography images showed clear anatomical changes in the AMD-affected eyes, including disruption of the interdigitation zone, ellipsoid zone, and ELM line.

Next, we evaluated whether the conventional VA, FVA values, or contrast VA correlated with any other parameters investigated, including OCT findings in the AMD-affected eyes (Table 2). There was a significant correlation between each FVA value, FVA score, and VMR and respective contrast VA, as well as between FVA score and VMR. Functional VA value, but not contrast VA, correlated with age. Conventional VA correlated with FVA score but not with the other VA parameters or age. Notably, the lengths of the interdigitation zone disruption correlated with FVA score ( $p < 0.05$ ) and conventional VA ( $p < 0.05$ ) but not with VMR or contrast VA.

Interestingly, stepwise regression analysis revealed that FVA score, but not conventional VA, was associated with interdigitation zone disruption (Table 3). Functional VA score was not associated with age or ellipsoid zone disruption.

A representative case of a 52-year-old man with advanced unilateral AMD in his left eye, whose conventional logMAR BCVA in each eye was 0, is shown in Fig. 3. The FVA scores of the affected eye (Fig. 3D) and fellow eye (Fig. 3C) were 0.26 and 0.02, respectively. Visual maintenance ratio was 0.9 in the affected eye and 0.96 in the fellow eye, and contrast VA was 0.9 in the affected eye and 0.2 in the fellow eye. In the affected eye, the average length

of the disrupted interdigitation zone was 1500  $\mu\text{m}$ , and the length of the disrupted ellipsoid zone was 1381  $\mu\text{m}$ , whereas the ELM line was observed continuously within the 1.5 -mm diameter area around the fovea (Fig. 3B). In the fellow eye, there were no detectable disruptions in any of the zones or lines in the OCT image (Fig. 3A).

## DISCUSSION

Here we demonstrate that the FVA system, not only conventional Landolt C chart or contrast VA examination, detected visual dysfunction related to advanced AMD. Moreover, FVA score correlated with the length of interdigitation zone disruption, which reflects the extent of anatomical changes in OCT images, whereas conventional BCVA and contrast VA did not reflect any of the OCT findings.

Importantly, the FVA score correlated with an OCT finding representing photoreceptor change in the AMD-affected eyes, whereas the other methods did not. Thus, the FVA score may be a sensitive indicator of AMD-related retinal findings. There were disruptions of the interdigitation zone, ellipsoid zone, and ELM line in OCT images of AMD-affected eyes with a logMAR BCVA

**TABLE 3.**

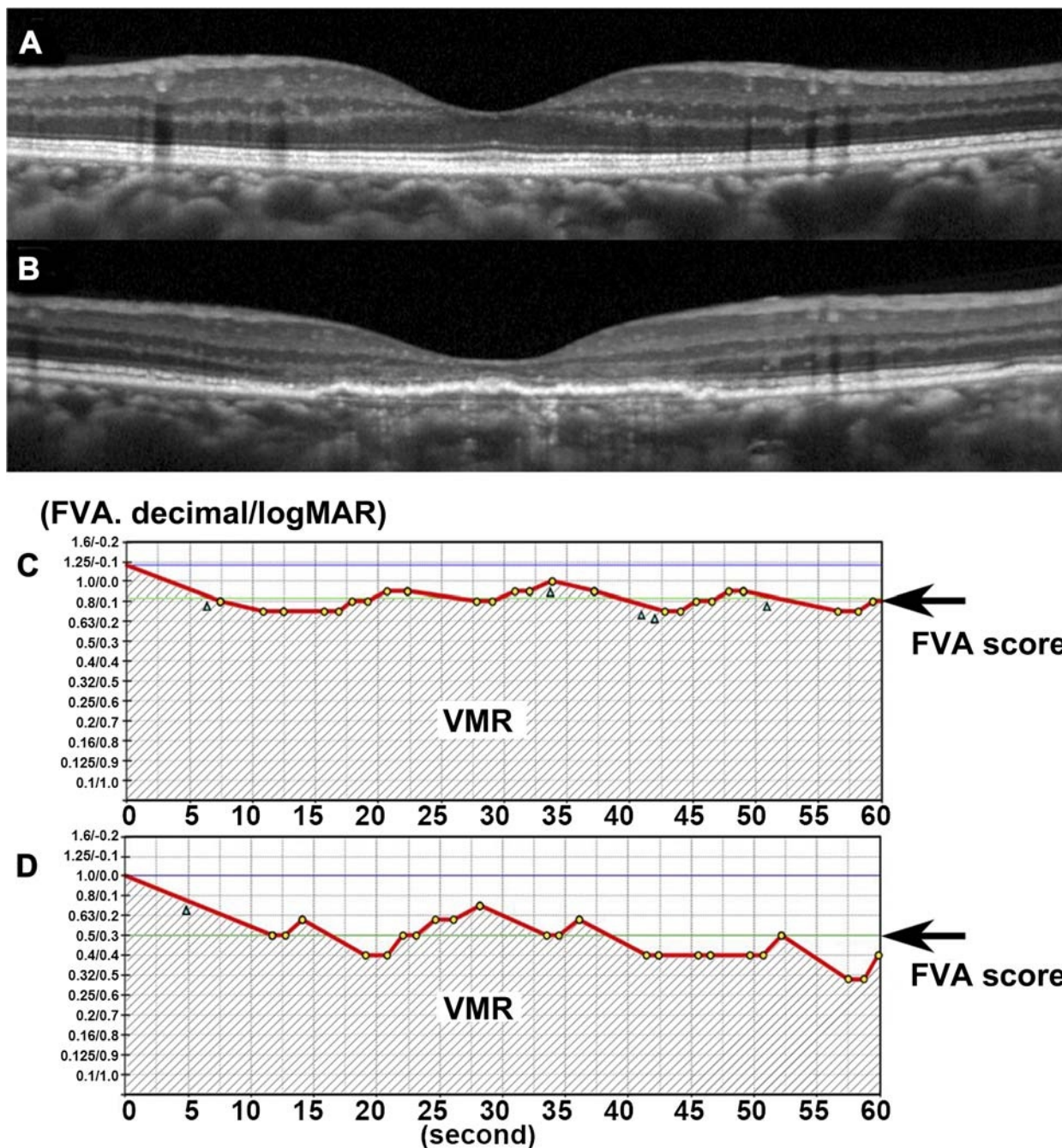
Forward stepwise regression analysis between FVA, conventional VA, and other parameters in the AMD-affected eyes

|                                                   | FVA<br>(N = 28) |        | Conventional<br>VA (N = 28) |      |
|---------------------------------------------------|-----------------|--------|-----------------------------|------|
|                                                   | SPRC            | p      | SPRC                        | p    |
| Age                                               | 0.24            | 0.27   | −0.05                       | 0.90 |
| Interdigitation zone<br>disruption, $\mu\text{m}$ | 0.52            | <0.01* | 0.4                         | 0.24 |
| Ellipsoid zone<br>disruption, $\mu\text{m}$       | 0.19            | 0.39   | 0.01                        | 0.98 |

\* $p < 0.05$ .

AMD, age-related macular degeneration; FVA score, functional visual acuity score; SPRC, standardized partial regression coefficient; VA, visual acuity.





**FIGURE 3.**

Optical coherence tomography (OCT) images and functional visual acuity (FVA) results from a representative case. A and B, The OCT images of a 52-year-old man with advanced unilateral age-related macular degeneration (AMD). The unaffected right eye (A) and AMD-affected left eye (B) are shown. In the AMD-affected eye, the average lengths of interdigitation zone and ellipsoid zone disruption were 1500 and 1381  $\mu\text{m}$ , respectively, whereas the ELM line was continuously observable within the 1.5-mm-diameter area around the fovea (B). In the fellow eye, there was no disruption in any of the three lines in the OCT image (A). C and D, Functional VA results from both eyes. The logMAR FVA scores of the AMD-affected eye and fellow eye were 0.26 (D) and 0.02 (C), and the visual maintenance ratios (VMRs) were 0.9 (D) and 0.96 (C), respectively.

of 0 or better, indicating that morphological retinal changes that can influence photoreceptor cell function were present in AMD-affected eyes. Considering the pathophysiology of AMD, in which choroidal neovascularization causes impaired vision by modulating the microenvironment of photoreceptor cells,<sup>8</sup> it is not surprising that retinal changes were found in AMD-affected eyes that had a good BCVA score by conventional testing. Therefore, it is important to detect subtle changes involved in AMD, as the

changes seen in OCT images can affect visual function, as detected by the FVA system.

Functional VA values may reflect changes other than those caused by AMD because changes in corneal and lens densities<sup>9,10</sup> as well as tear volume (measured by the Schirmer test)<sup>7,11,12</sup> also affected the FVA score and VMR.<sup>7,11</sup> However, these parameters were not significantly different in the affected eyes in our study compared with fellow eyes, indicating that the FVA values directly

reflected AMD-induced changes in the retina. This finding is consistent with our previous study, which demonstrated that the FVA system detects visual function impairment caused by the retinal abnormality in the epiretinal membrane.<sup>1</sup> The association between age and FVA score may be caused by age-related retinal changes, such as age-related photoreceptor loss.<sup>13</sup> Taken together, our results suggest that both FVA and contrast VA are valuable methods for evaluating visual disturbances associated with AMD.<sup>14</sup>

Contrast VA is a more sensitive measurement of central visual function than conventional VA.<sup>15</sup> However, contrast VA did not correlate with OCT findings in the current study. Both contrast VA and conventional VA measurements involve staring at the Landolt chart, in contrast to the FVA system, in which a series of charts is presented on which the optotypes must be identified within 2 s. Thus, contrast VA and FVA may reflect different aspects of visual ability. Further studies examining the different aspects of visual function detected by these methods, and their relationships with interdigitation zone disruption, may contribute to a better understanding of the mechanisms underlying AMD development.

Correlation of interdigitation zone disruption with FVA score suggests that this could be related to the general health of the retina in the macular area and not just the status of the fovea. Alternatively, reduced foveal function may correlate with interdigitation zone disruption in the macular area, around the fovea. Further studies analyzing the relationship between VA and retinal lesions surrounding the fovea would be useful for determining the role of these lesions in visual disorders.

Interdigitation zone disruption was also observed in some of the healthy fellow eyes. This may be partly because discontinuous interdigitation zones are sometimes detected in healthy eyes. In a recent report, intact foveal interdigitation zones were detected in only 95% of normal healthy individuals.<sup>16</sup> In the current study, interdigitation zone disruption was found in 20% of the unaffected eyes. Given that more than 20% of AMD patients have bilateral lesions,<sup>17,18</sup> our finding suggests that the OCT may have detected predisease changes that were not detected by either fundus examination or angiographies in the fellow eyes.

A recent report indicated that ellipsoid zone integrity is closely related to central VA under AMD conditions. Eyes with a continuous or discontinuous ellipsoid zone beneath the fovea had improved BCVA after PDT than eyes without an ellipsoid zone.<sup>19</sup> In a separate study, ELM status was the most strongly associated parameter with BCVA in PDT-treated AMD patients.<sup>3</sup> Thus, the ellipsoid zone or ELM status may also be related to visual function. However, in the current study, there was no correlation between FVA score and the ellipsoid zone or ELM status. These differences in results may be caused in part by the selection of AMD-affected eyes with a better BCVA in our study, in which the ellipsoid zone and ELM line disruptions may have been less obvious than in those in previous reports of AMD. In contrast, the interdigitation zone disruption was obvious and its length correlated with FVA score, suggesting that this may be an early retinal change in AMD involved in visual function impairment.

A limitation of this study was the relatively small number of cases investigated. Further studies with larger subject numbers are required to confirm the current findings and to test whether FVA values are a useful indicator of visual function change after AMD treatment. In addition, the average conventional BCVA was

different between the affected and the fellow eyes, which might underestimate the value of FVA. Future studies with patients who do not have different conventional BCVA in affected and fellow eyes may help elucidate which visual mechanism is reflected by the FVA system in AMD-related visual dysfunction.

In conclusion, we have shown that the FVA system detected subtle changes in BCVA in AMD-affected eyes and reflected the extent of interdigitation zone disruption, an anatomical change in the retina. These results suggest that the FVA system is potentially useful for evaluating changes in central visual function caused by advanced AMD. Although further studies are required, the FVA system may facilitate the evaluation and treatment of AMD.

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