

Alterations of the Foveal Avascular Zone Measured by Optical Coherence Tomography Angiography in Glaucoma Patients With Central Visual Field Defects

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Submitted: November 8, 2016

Accepted: February 19, 2017

Citation: Kwon J, Choi J, Shin JW, Lee J, Kook MS. Alterations of the foveal avascular zone measured by optical coherence tomography angiography in glaucoma patients with central visual field defects. *Invest Ophthalmol Vis Sci.* 2017;58:1637-1645. DOI: 10.1167/iops.16-21079

PURPOSE. To investigate whether the area and shape of the foveal avascular zone (FAZ) as assessed by optical coherence tomography angiography (OCTA) are altered in glaucomatous eyes with central visual field defects (CVFDs).

METHODS. A total of 78 patients with open-angle glaucoma with central or peripheral visual field defects (PVFDs) confined to a single hemifield were studied retrospectively. Foveal avascular zone area and circularity were measured using OCTA images from the superficial retinal layer. Central retinal visual field (VF) sensitivity using Swedish Interactive Threshold Algorithm 24-2 VF and macular ganglion cell-inner plexiform layer (mGCIPL) thickness were measured. The FAZ area between VF-affected hemimacular segments and VF-unaffected hemimacular segments in eyes with CVFDs and matched hemimacular segments of eyes with PVFDs were compared. Factors associated with the presence and severity of CVFD at initial presentation were determined.

RESULTS. Eyes with CVFDs showed a significantly larger FAZ area, lower FAZ circularity, and lower mGCIPL thickness than the PVFD group. The mean hemi-FAZ area of VF-affected hemimaculars in eyes with CVFDs was significantly larger than that of the PVFD group ($0.256 \pm 0.07 \text{ mm}^2$ vs. $0.184 \pm 0.07 \text{ mm}^2$) and the VF-unaffected hemimaculars of the CVFD group ($0.179 \pm 0.06 \text{ mm}^2$; $P < 0.05$). Age, mean deviation, mGCIPL thickness, FAZ area, and circularity were associated with CVFDs ($P < 0.05$).

CONCLUSIONS. Microcirculatory alterations in the perifovea are spatially correlated with central VF loss. Loss of FAZ circularity was significantly associated with presence of CVFD, whereas FAZ area was significantly associated with severity of CVFD.

Keywords: foveal avascular zone, central visual field defects, optical coherence tomography angiography

Glaucoma is a leading cause of irreversible blindness and is characterized by progressive retinal ganglion cell (RGC) death and axonal loss.^{1,2} Ocular blood flow (OBF) impairment and/or abnormal microcirculation along with elevated IOP may play an important role in glaucoma, particularly in normal-tension glaucoma (NTG)³⁻⁷; however, the exact pathogenesis of glaucoma is still unknown. To assess the vascular integrity of OBF, different types of imaging modalities have been introduced, including fluorescein angiography (FA), Heidelberg retina flowmeter, and color Doppler. Although FA remains the gold standard for detecting vascular pathology in the retina, it is invasive and requires exposure to an exogenous contrast agent. Moreover, the axial and lateral resolution of FA allows for limited visualization of capillaries, especially in macula in which there are overlapping capillary networks.⁸ Recently, noninvasive retinal microvascular imaging has become available using optical coherence tomography angiography (OCTA).^{9,10} Optical coherence tomography angiography is a technique that uses differences between B-scans to generate contrasts associated with motion; in particular, the motion of blood cells through the vasculature. It identifies temporal changes in a specific location and recognizes them as erythrocyte motion. OCTA

obtains detailed images of the macular microvascular networks with a high resolution and in a reproducible manner.¹¹

The foveal avascular zone (FAZ) is the round capillary-free zone within the macula. Manual measurement of FAZ area based on OCTA images at the superficial vascular network is a noninvasive, simple, and useful method for quantifying FAZ dimensions and architecture.¹²⁻¹⁷ Clinical elements affecting FAZ area may include age, diabetic retinopathy (DR), and retinal vascular occlusive diseases.^{12,18-22} Foveal avascular zone circularity (roundness of the FAZ border) can also help characterize FAZ architecture, which can be reduced by vascular diseases in the macula, such as DR or retinal vein occlusion (RVO).^{12,13,15,17-19} Patients with microcirculatory deficiency involving the macula have been shown to have selective alteration in the FAZ area and circularity in the perifoveal region.²³ Measurements of FAZ area and circularity using OCTA have high repeatability in subjects with macular disease and in healthy individuals.^{10,14} Therefore, OCTA-based FAZ metrics (area and circularity) may be candidate biomarkers to study perifoveal capillary networks in ocular diseases associated with vascular comorbidities such as glaucoma.



The central visual field (CVF), including perifoveal vision, is paramount in performing activities of daily living, such as reading and writing. In recent studies, glaucoma patients have been shown to suffer CVF loss even at early stages of the disease^{24–26}; therefore, preservation of the CVF is crucial in glaucoma management. In the macula, RGCs are mainly located in the central 4.5-mm diameter region.²⁷ Loss of RGCs and macular nerve fiber layer thickness have been observed in glaucoma patients.^{28,29} Additionally, a significant correlation between macular inner retinal layer thickness and CVF defect (CVFD) has been reported in several studies.^{26,28–31} Recently, Rao et al.³² reported that macular vascular density (VD), evaluated by OCTA, was reduced in a glaucoma group compared with a healthy group, but diagnostic ability (area under the receiver operating characteristic curve of 0.63) was lower than that of peripapillary VD. To the best of our knowledge, little is known about the relationship between the status of FAZ microcirculation and CVFD in glaucoma patients, but a number of studies have shown reduced peripapillary or optic nerve head (ONH) VD measured with OCTA.^{2,33–37} We hypothesized that the perifoveal vascular architecture corresponding to the CVF may be disrupted in glaucoma patients with CVFDs. In the present study, we investigated the microcirculation of the perifoveal region by measuring the size and shape of the FAZ using OCTA in glaucomatous eyes with CVFDs and compared them to glaucomatous eyes with peripheral visual field defects (PVFDs) matched by age and severity of visual field (VF) damage.

METHODS

Subjects

This study was approved by the institutional review board of Asan Medical Center at the University of Ulsan, College of Medicine, Seoul, Korea. All procedures conformed to the Declaration of Helsinki. Medical records of open-angle glaucoma (OAG) patients were reviewed from March to August 2016 at the glaucoma clinic of Asan Medical Center and Central Seoul Eye Center, Seoul, Korea. All patients underwent a comprehensive ophthalmic examination, including medical history, best-corrected visual acuity (BCVA), Humphrey field analyzer Swedish Interactive Threshold Algorithm (SITA) 24-2 VF testing (Carl Zeiss Meditec, Dublin, CA, USA), stereoscopic optic disc photography, measurement of macular ganglion cell-inner plexiform layer (mGCIPL) thickness by Cirrus HD spectral-domain optical coherence tomography (SD-OCT; Carl Zeiss Meditec), and imaging with a commercial OCTA system (Cirrus HD-OCT Angioplex; Carl Zeiss Meditec). Reliable SITA VF assessment was defined as a VF test with a false-positive error <15%, a false-negative error <15%, and a fixation loss <20%. The second VF test was performed within 2 to 4 weeks after the first test to control for learning effects.

For inclusion in the study, patients had to meet the following criteria: (1) BCVA of 20/30 or better; (2) refractive error within +5 to –10 diopters (D) sphere and ± 3 D cylinder; (3) typical glaucomatous ONH appearance regardless of IOP level, that is, focal or generalized narrowing or disappearance of the neuroretinal rim, disc hemorrhage, or cup-to-disc asymmetry >0.2 not explained by optic disc size; (4) open anterior chamber angles on slit-lamp biomicroscopy and gonioscopy in both eyes; and (5) glaucoma hemifield defects corresponding to ONH appearance. All VF findings were confirmed in two consecutive examinations and the second VF data were used in the final analysis. The definition of glaucoma hemifield defects²⁹ required all of the following: (1) three or more adjacent points with $P < 0.05$ on a pattern deviation (PD)

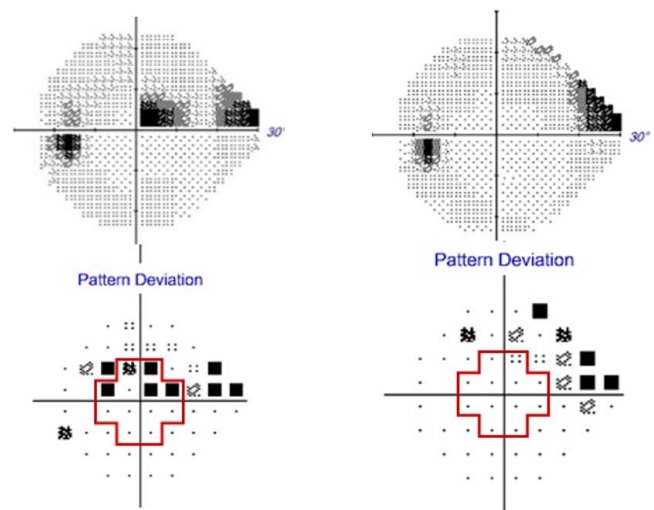


FIGURE 1. Classification of CVFD and PVFD groups. (Left) A cluster of three or more points with a probability of less than 5% or two or more points with a probability of less than 0.02% on a PD probability map was classified as a CVFD. (Right) A cluster only in the 10° to 24° region was classified as a PVFD.

probability map, or two or more test points with $P < 0.02$ or smaller on a PD probability map in a superior or inferior hemifield; (2) no three-point clusters with $P < 0.05$ and no two-point clusters with $P < 0.02$ on both the total deviation and PD probability maps of the opposite hemifield; and (3) a glaucoma hemifield test result outside normal limits. Patients were excluded if they had one or more of the following: severe myopic disc and fundus changes impairing adequate ONH/VF evaluation for glaucoma; myopic eyes with spherical equivalent (SE) of less than –10 D to prevent excessive ocular magnification effect; advanced VF loss (mean deviation [MD] ≤ -10 dB) for the purposes of evaluating eyes with early glaucomatous VF damage; intracranial lesion such as pituitary adenoma or craniopharyngioma that can affect VF testing; a history of massive hemorrhage or hemodynamic crisis; a history of other ophthalmic disease that could result in ONH/VF defects; and/or a history of diabetes mellitus or retinal vaso-occlusive diseases, such as RVO or prior eye surgery/laser treatment. One eye per patient was included and if both eyes were eligible, one eye was selected randomly.

Classification Into CVFD and PVFD Groups

The method of classification has been described in a previous study.³⁸ In brief, the OAG patients were classified into two groups based on PD probability maps of SITA 24-2 VF testing. The CVFD group included patients with clusters of three significant points, with a probability of less than 5%, or two or more test points with a probability of less than 1% or smaller, on a PD probability map within the superior or inferior hemifield of the central 10° regardless of the presence of VF defects outside the central 10° (Fig. 1). The PVFD group consisted of eyes with clusters only in the 10° to 24° region in one hemifield (Fig. 1). In the current study, eyes with PVFDs from the same database were chosen and matched to those with CVFDs for age (≤ 5 years) and severity of VF loss (≤ 1 dB) based on SITA 24-2 VF testing to avoid confounding effects of these variables on measurements of FAZ parameters other than VF defect location. Although it has been reported that SE had no relationship with FAZ parameters or parafoveal vascular density (PVD) measurement,²² SE was matched (≤ 1.5 D) between two groups to minimize the differences between the

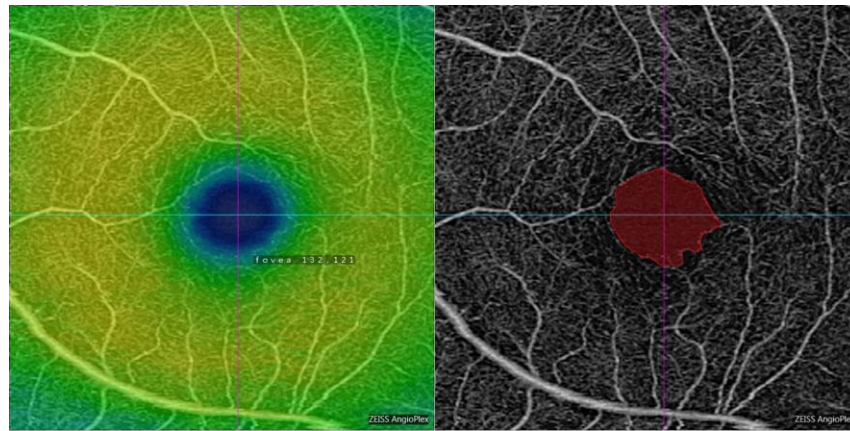


FIGURE 2. Determination of the center of the fovea and measurement of the FAZ using OCTA images. (*Left*) In the retinal thickness map, the center of the circle was considered as the center of the fovea. The retinal thickness map was overlapped onto the OCTA image and the center of the fovea was marked. (*Right*) The margin of the FAZ is marked manually using image analysis software (ImageJ).

groups resulting from the potential ocular magnification effect on FAZ measurement. Central retinal VF sensitivity ($1/\text{Lambert} = 10^{\text{dB value}/10}$; L) was calculated by anti-log absolute sensitivity values of 12 central points, which were then averaged to denote the amount of remaining central retinal VF sensitivity.³⁰

Measurements of FAZ Area and Circularity With OCTA

The Cirrus AngioPlex OCTA device was used for imaging. The device uses an intensity-based frequency filtering technique to generate images with detailed vasculature. The scanning rate is 68,000 A-scans per second. Improved tracking is possible with FastTrac retinal-tracking technology software (Carl Zeiss Meditec, Inc., Jena, Germany).¹¹ Macular $3 \times 3\text{-mm}^2$ images consisting of 245×245 A-scans were obtained from each patient. Optical coherence tomography angiography images of the superficial and deep capillary networks were generated using the automated segmentation algorithm. Because the border of the FAZ can be defined more accurately and reliably at the superficial capillary network than at the deep capillary network,¹³ OCTA images from the superficial retinal layer were analyzed in our study. The inner surface of the superficial retinal layer slab is the internal limiting membrane, and the outer surface is an approximation of the inner plexiform layer, which is estimated by the following equation:

$$Z_{\text{IPL}} = Z_{\text{ILM}} + 70\% \times T_{\text{ILM-OPL}}, \quad (1)$$

where Z is the boundary location, T is the thickness, and OPL is the outer plexiform layer.

Eyes with poor image qualities were excluded based on the following criteria¹¹: (1) poor fixation resulting in a double-vessel pattern and motion artifacts, (2) media opacity obscuring the vessel signal in the field of view or a signal strength index < 8 , and (3) segmentation error resulting in poor outlining of vascular networks.

Measurements of FAZ area and circularity are described in detail elsewhere.^{13,39,40} Two raters (JK and JWS) performed FAZ measurements independently and were blinded to each other's results. The center of fovea was localized by the slice navigator of Cirrus HD-OCT review software. By overlaying a macular GCIPL thickness map, the thinnest point of the fovea is located manually on the OCTA images (Fig. 2). Optical coherence tomography angiography images were loaded into an image analysis program (ImageJ 1.51; <http://imagej.nih.gov/ij/>; provided in the public domain by the National Institutes of

Health, Bethesda, MD, USA). Image size was 1024×1024 pixels and the scale parameter of the software was set to define a 1024-pixel width of the images as 3 mm. The area of FAZ was marked manually by two raters (Fig. 2).¹³ The total and hemispherical areas (superior versus inferior) were used to measure FAZ area. FAZ circularity was measured by the following equation^{41,42}:

$$\text{Circularity} = 4\pi A/P^2, \quad (2)$$

where A is the area and P is the perimeter.

A circularity closer to 0 indicates an irregular shape, and a circularity closer to 1 indicates a circular shape.^{41,42} The average values from the measurements of FAZ area and circularity by two independent raters (JK and JWS) were used in the final analysis to minimize the effect of interrater variation.

Statistical Analysis

To assess the reliability of the measurements of FAZ area and circularity, intraclass correlation coefficients (ICCs) with 95% confidence intervals (CIs) were calculated for test-retest and interrater (JK and JWS) measurements for glaucoma subjects ($n = 30$) who were randomly selected and scanned on two separate occasions. For test-retest measurement, two OCTA sessions with a 10-minute interval for each patient were performed by one rater (JK) on the same day. Intraclass correlation coefficient for test-retest reliability was calculated from two measurements by one rater (JK). Intraclass correlation coefficient for interrater reliability was calculated from ICC(2,1) formula, in which each image was measured by two raters (JK and JWS). Reliability was calculated from a single measurement of each rater.⁴³ Continuous variables are presented as means \pm SD. Numerical data were compared with an independent t -test (data with a Gaussian distribution) and Mann-Whitney U test (data with a non-Gaussian distribution) between the two groups. A χ^2 test was used to assess differences in proportions between groups.

Measurements of FAZ area in the hemimaculas corresponding to VF defects were compared with those in the opposite hemimaculas without VF defects in eyes with CVFDs using a paired t -test. Measurements of FAZ area in the hemimaculas with and without corresponding VF defects in the eyes with CVFDs were compared with those in the matched hemimaculas of eyes with PVFDs using an independent t -test.

TABLE 1. Test-Retest and Interrater Reliability Measurements of FAZ Area and Circularity in 30 Randomly Selected Subjects

Variables	ICC (95% CI)*	ICC (95% CI)†
FAZ area, mm ²	0.96 (0.91-0.98)	0.93 (0.87-0.97)
FAZ circularity	0.93 (0.86-0.97)	0.91 (0.82-0.96)

* ICC for test-retest reliability.

† ICC for interrater reliability (JK and JWS).

The relationships between FAZ area and circularity and macular inner retinal layer thickness, MD, and central retinal VF sensitivity (1/L) were evaluated using linear regression analyses. For the measurement of macular inner retinal layer thickness, a macular GCIPL thickness map according to Cirrus HD SD-OCT was used. A macular GCIPL map occupies the annular area with an inner circle of a 1.2-mm horizontal and a 1.0-mm vertical diameter and an outer circle with a 4.8-mm horizontal and a 4.0-mm vertical diameter.⁴⁴

Univariate and multivariate logistic regression analyses were performed to determine the clinical factors associated with the presence of CVFD at initial presentation. The presence of CVFD was the independent variable and the dependent variables were age, sex, IOP, global MD, macular GCIPL thickness, FAZ area, and FAZ circularity. Following univariate analyses, dependent variables with *P* less than 0.2 were subsequently included in the multivariate model using a backward elimination approach based on the Wald method. The same dependent variables, with the exception of sex, were used in a linear regression analysis for central retinal VF sensitivity as a continuous dependent variable. All statistical analyses were performed with SPSS software version 18.0 (SPSS, Inc., Chicago, IL, USA). *P* values less than 0.05 (two-tailed) were considered statistically significant.

RESULTS

Comparison of Demographics Between CVFD and PVFD Groups

The ICCs for test-retest reliability (JK) of FAZ area and circularity measurements were 0.96 (95% CI = 0.91-0.98) and 0.93 (95% CI = 0.86-0.97), respectively. The ICCs for interrater reliability (JK and JWS) of FAZ area and circularity measurements were 0.93 (95% CI = 0.87-0.97) and 0.91 (95% CI = 0.82-0.96), respectively (Table 1).

Among the 86 matched eyes of the 86 patients with CVFDs and PVFDs who were initially enrolled, 8 eyes (4 eyes in each group) were excluded because of poor-quality OCTA images. Therefore, 39 eyes from 39 patients were assigned to the CVFD group and 39 eyes from 39 patients were assigned to the PVFD group. Table 2 summarizes the demographic characteristics of the two groups. Age, sex, IOP, SE, location of hemifield defect, and MD were similar between the two groups. There were statistically significant differences between the groups in central retinal VF sensitivity (*P* < 0.001), macular GCIPL thickness (*P* = 0.001), FAZ area (*P* = 0.015), and FAZ circularity (*P* = 0.031).

Hemifield Central Retinal VF Sensitivity, Macular GCIPL Thickness, and FAZ Area

Mean central retinal VF sensitivity values (1/L) were significantly lower in the VF-affected hemifield than in the VF-unaffected hemifield of the CVFD group (662 ± 381 vs. 1619 ± 600; *P* < 0.001; Table 3). Furthermore, the mean central retinal sensitivity value was significantly lower in the VF-

TABLE 2. Comparison of Demographics and Ocular Characteristics According to Location of Glaucomatous VFD: Glaucoma With CVFD Versus Glaucoma With PVFD (*n* = 78)

Variables	Glaucoma With CVFD (<i>n</i> = 39)	Glaucoma With PVFD (<i>n</i> = 39)	<i>P</i> *
Age, y	52.7 ± 14.4	48.3 ± 15.4	0.203
Sex, men/women	19/20	20/19	0.821
IOP, mm Hg	15.5 ± 2.8	15.5 ± 3.1	0.953
SE, D	-2.6 ± 3.0	-2.7 ± 3.3	0.878
Location of VFD, superior/inferior	31/8	25/14	0.131
MD, dB	-4.1 ± 3.1	-3.0 ± 2.4	0.085
Central retinal VF sensitivity, 1/L	1140 ± 431	1532 ± 491	<0.001
mGCIPL average thickness, μm	68.3 ± 7.3	75.2 ± 8.7	0.001
FAZ area, mm ²	0.435 ± 0.11	0.365 ± 0.13	0.015
FAZ circularity	0.637 ± 0.10	0.694 ± 0.12	0.031

Data are represented as mean ± SD for continuous variables and number of incidence for categorical variables. Factors with statistical significance are shown in boldface. VFD, visual field defect.

* Unpaired *t*-test for continuous variables and χ^2 test for categorical variables were used.

affected hemifield in the CVFD group in comparison with the matched hemifield in the PVFD group (662 ± 381 vs. 1386 ± 528; *P* < 0.001; Table 3).

Mean macular GCIPL thickness were significantly lower in the VF-affected hemimaculas than in the VF-unaffected hemimaculas of the CVFD group (62.8 ± 6.70 μm versus 73.8 ± 9.25 μm; *P* < 0.001; Table 3). Mean macular GCIPL thickness was significantly lower in VF-affected hemimaculas in the CVFD group compared with matched hemimaculas in the PVFD group (62.8 ± 6.70 μm versus 72.8 ± 9.89 μm; *P* < 0.001; Table 3).

In the CVFD group, mean hemi-FAZ area was significantly larger in VF-affected hemimaculas than in VF-unaffected hemimaculas (0.256 ± 0.07 mm² ± 0.07 vs. 0.179 ± 0.06 mm²; *P* < 0.001; Table 3). Moreover, the mean hemi-FAZ area showed a significantly larger value in VF-affected hemimaculas in the CVFD group compared with matched hemimaculas in the PVFD group (0.256 ± 0.07 mm² ± 0.07 vs. 0.184 ± 0.07 mm²; *P* < 0.001; Table 3).

Relationship Between FAZ and Macular GCIPL, MD, and Central Retinal VF Sensitivity

For completeness, associations between OCTA-derived FAZ metrics and structural and functional parameters were evaluated. Figure 3 shows the correlations between FAZ area and macular GCIPL thickness, MD, and central retinal VF sensitivity values in 78 eyes. There were significant correlations observed between FAZ area and macular GCIPL thickness, MD, and central retinal VF sensitivity values after adjusting for age (all *P* < 0.05). However, FAZ circularity did not correlate significantly with macular GCIPL thickness, MD, or central retinal VF sensitivity (*r* = 0.128, -0.201, -0.083, respectively; all *P* > 0.05).

Logistic Regression Analyses

In the univariate logistic regression analysis, macular GCIPL thickness, FAZ circularity, and FAZ area were significantly associated with the presence of CVFD. In the multivariate analysis, MD (*P* = 0.035), macular GCIPL thickness (*P* = 0.028),

TABLE 3. Comparison of Hemifield Central Retinal VF Sensitivity, mGCIPL Thickness, and FAZ Area Between Affected Hemifield and Unaffected Hemifield in Terms of the Location of VFD (for Glaucoma Subjects, $n = 78$; Affected Hemifield Is Inferior for Subjects With Superior VFD, and Vice Versa)

Variables	Glaucoma With CVFD ($n = 39$)			Glaucoma With PVFD ($n = 39$)			P_{\dagger} 1 vs. 3	P_{\dagger} 2 vs. 4
	Affected Hemifield 1	Unaffected Hemifield 2	P^* 1 vs. 2	Affected Hemifield 3	Unaffected Hemifield 4	P^* 3 vs. 4		
Central retinal VF sensitivity, 1/L	662 ± 381	1619 ± 600	<0.001	1386 ± 528	1678 ± 562	0.001	<0.001	0.666
mGCIPL average thickness (μm)	62.8 ± 6.70	73.8 ± 9.25	<0.001	72.8 ± 9.89	77.5 ± 7.62	0.004	<0.001	0.093
FAZ area (mm ²)	0.256 ± 0.07	0.179 ± 0.06	<0.001	0.184 ± 0.07	0.184 ± 0.07	0.970	<0.001	0.778

Data are represented as mean ± SD. Factors with statistical significance are shown in boldface.

* Paired *t*-test was used for intraindividual comparison.

† Unpaired *t*-test was used for interindividual comparison.

and FAZ circularity ($P = 0.014$) remained significantly associated with the presence of CVFD (Table 4).

Linear Regressions Analyses

Univariate linear regression analysis showed age, MD, macular GCIPL thickness, and FAZ area were significantly associated with central retinal VF sensitivity. Multivariate analysis found age ($P = 0.001$), MD ($P < 0.001$), and FAZ area ($P = 0.002$) remained significantly associated with central retinal VF sensitivity (Table 5).

Representative Cases

Figures 4 and 5 show two representative cases. In Figure 4, a 52-year-old female glaucoma patient presented with CVFD in the superior hemifield of the left eye. She had a lower superior central retinal VF sensitivity, lower macular GCIPL thickness, and a greater FAZ area in the inferior hemimacula compared with the opposite VF-unaffected hemifield and hemimacula. Figure 5 shows a 36-year-old male glaucoma patient who presented with PVFD (nasal step) in the superior hemifield in the right eye. He had similar macular GCIPL thickness and FAZ areas in both hemimacula.

DISCUSSION

In this study, the OCTA-derived FAZ area was significantly greater in glaucomatous eyes with CVFDs compared with eyes with PVFDs, whereas FAZ circularity was significantly less in eyes with CVFDs compared with those with PVFDs despite no differences in age, SE, or glaucoma severity between the two

groups. Enlargement in hemimacular FAZ area also showed a topographic relationship with the location of the hemifield defects on SITA 24-2 VF testing in the CVFD group. Moreover, there were significant correlations between FAZ area and macular GCIPL thickness, MD, and central retinal VF sensitivity after adjusting for age. The presence of CVFD in OAG eyes with different VF defect locations (central versus peripheral) was significantly associated with the loss of FAZ circularity, whereas the severity of central VF sensitivity loss was significantly related to the size of the FAZ area. These results provide important information regarding the relationship between disruption of perifoveal microcirculation and CVFDs in glaucoma patients.

The FAZ area is enlarged in DR and RVO disease due to destruction of the vascular arcades.^{12,18,20} Furthermore, a correlation between FAZ area and visual acuity in DR and RVO has been reported.⁴⁵ Foveal avascular zone circularity measures the roundness of a two-dimensional shape quantitatively. It is also a measurement of roughness. As shape becomes less round or less smooth, the circularity approaches zero.⁴⁶ As described by the formula, circularity is proportional to the area and inversely proportional to the square of the perimeter.^{41,46} In DR, the FAZ has a higher amount of irregular outlines, thus increasing the perimeter for a given surface value compared with a healthy control.¹⁸ Thus, diminished FAZ circularity is a good indicator of vascular dropout and is associated with disease progression in vascular maculopathy.^{18,39,40} Although FAZ area and circularity are relatively unknown parameters in the field of glaucoma, our investigation using OCTA may provide evidence that these parameters can be used as biomarkers for studying the relationship between perifoveal microcirculation and CVFDs in glaucoma. Of interest, Arend et al.⁴⁷ reported that FAZ area measured by conventional FA was

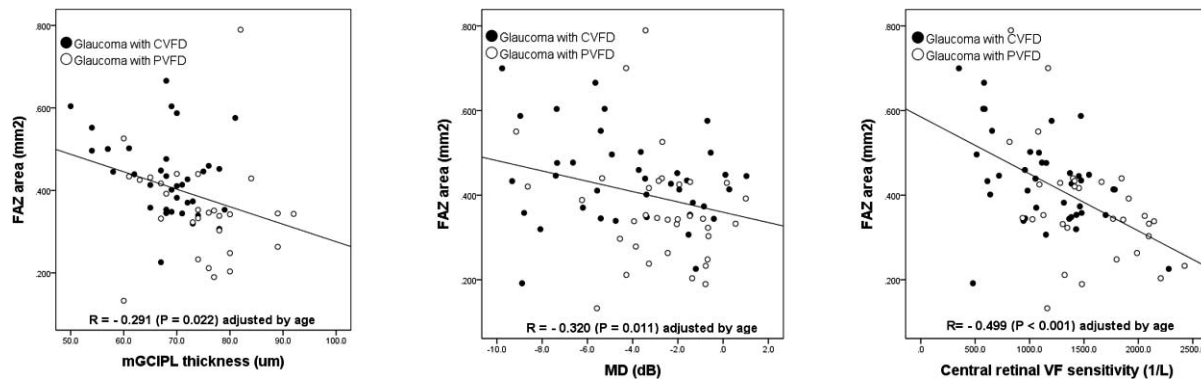


FIGURE 3. Scatter plots showing significant correlations between the area of the FAZ measured by OCTA and structural/functional parameters ($n = 78$). (Left) Foveal avascular zone area versus mGCIPL average thickness. (Middle) Foveal avascular zone area versus MD. (Right) Foveal avascular zone area versus central retinal VF sensitivity.

TABLE 4. Logistic Regression Analysis for the Presence of CVFD as an Independent Variable ($n = 78$)

Variables	Univariate		Multivariate*	
	OR (95% CI)	P	OR (95% CI)	P
Age, y	1.020 (0.989–1.052)	0.201		
Sex, men as control	1.108 (0.456–2.693)	0.821		
IOP, mm Hg	0.995 (0.853–1.162)	0.953		
MD, dB	0.865 (0.733–1.022)	0.088	0.732 (0.547–0.978)	0.035
mGCIPL average thickness, μm	0.892 (0.828–0.962)	0.003	0.910 (0.837–0.990)	0.028
FAZ area, mm^2 , for 0.1 increase	1.660 (1.077–2.557)	0.022		
FAZ circularity, for 0.1 increase	0.624 (0.402–0.969)	0.036	0.470 (0.257–0.858)	0.014

Factors with statistical significance are shown in boldface. OR, odds ratio.

* Multivariate model using a backward elimination approach based on Wald method; variables with $P < 0.20$ in univariate model were entered in the multivariate model; variables were entered in the model if $P < 0.05$ and removed if $P > 0.10$ in the saturated multivariate model.

similar between NTG eyes and healthy controls in 2002. Unlike our study, glaucoma subjects in that report were not studied according to the location of VF defects (central versus peripheral).⁴⁷

To establish the accuracy of measuring OCTA-based FAZ metrics, it is crucial to test measurement reproducibility. Hence, we calculated ICCs for FAZ area and circularity in randomly selected glaucoma patients ($n = 30$) in the present study. Our study showed excellent correlation coefficients in both OCTA-derived FAZ parameters of the same glaucoma subjects when measured across different imaging sessions as well as when measured by different raters. Our findings agree with those of Shahladee and associates,¹⁰ who found high test-retest reliability of VD in the macula using healthy subjects. Yu and associates²² also demonstrated good reliability of VD and flow index measurements in the macula between two OCTA measurements in healthy eyes. Likewise, high interrater reliability for FAZ area and circularity measurements have been reported based on healthy eyes and those with geographic atrophy.^{13,42} Therefore, our results demonstrate the potential for the application of OCTA-derived FAZ parameters in glaucoma patients and healthy subjects in a clinical setting.

Several reports have been published regarding the utility of OCTA in glaucoma research and treatment.^{2,9,33–37,48,49} These reports have primarily focused on measuring VD of ONH or the peripapillary retina using OCTA, which uses estimates of the proportion of the measured area occupied by flowing blood vessel in glaucoma patients. Akagi et al.⁹ reported that reduced VD in the peripapillary retina and optic disc was associated with VF defect in a region-specific manner. Another study demonstrated a significant reduction in radial peripapillary capillary VD, which was correlated with sites of retinal nerve fiber layer (RNFL) thinning and VF loss in glaucoma.³³ Conversely, Rao et al.³² recently reported that the diagnostic

ability of the macular VD for glaucoma using OCTA was significantly lower than peripapillary VD; however, this study did not specifically target glaucomatous eyes with CVFDs.

In the present study, we demonstrated that the FAZ area in OAG eyes with a similar severity of glaucoma was significantly larger when CVFDs were present than when PVFDs were present in 24-2 SITA VF testing. Furthermore, FAZ circularity was significantly lower when in CVFDs than PVFDs. Our findings support the results of previous studies suggesting that glaucomatous VF defects and impaired ocular hemodynamics may be etiologically related and that vascular mechanisms may play an important role in glaucomatous optic nerve damage.^{4,5} To our knowledge, this is the first study to report the relationship between OCTA-derived FAZ parameters and CVFD in OAG patients.

This study also confirms previous results that microvascular reduction is associated with topographically matched VF defects in glaucoma patients.⁹ Glaucoma often starts with a localized VF defect in one hemifield.^{29,27} The peripapillary VDs in retinal regions corresponding to perimetrically glaucomatous hemifields in myopic glaucomatous eyes with localized VF defects confined to one hemifield have been reported to be lower than those in the corresponding retinal regions in healthy eyes.⁹ Our current study using OCTA-derived FAZ parameters supports the findings that the mean FAZ area in the hemimacular segments corresponding to VF defects is significantly larger than that in the hemimacular segments without VF defect in glaucomatous eyes with CVFDs. Furthermore, the mean FAZ area in the hemimacular segments corresponding to VF defects in glaucomatous eyes with CVFDs was significantly larger than the corresponding values in the matched hemimacular segments of eyes with PVFDs. Therefore, our findings suggest that functional deficits in the CVF and perifoveal microvascular damage are spatially correlated.

TABLE 5. Linear Regression Analysis for Central Retinal VF Sensitivity (1/Lambert) as an Independent Variable ($n = 78$)

Variables	Univariate			Multivariate*		
	Regression Coefficient	95% CI	P	Regression Coefficient	95% CI	P
Age, y	–13.9	–20.9 to –6.8	<0.001	–11.3	–17.6 to –5.0	0.001
IOP, mm Hg	1.9	–38.6 to 42.3	0.927			
MD, dB	99.7	66.6 to 132.9	<0.001	83.2	47.8 to 118.7	<0.001
mGCIPL average thickness, μm	22.3	9.7 to 35.0	0.001			
FAZ area, mm^2 , for 0.1 increase	–193.4	–272.2 to –114.6	<0.001	–127.3	–204.5 to –50.1	0.002
FAZ circularity, for 0.1 increase	–35.7	–140.0 to 69.0	0.496			

Factors with statistical significance are shown in boldface.

* Multivariate model using a stepwise approach; variables with $P < 0.20$ in univariate model were entered in the multivariate model; variables were entered in the model if $P < 0.05$ and removed if $P > 0.10$ in the saturated multivariate model.

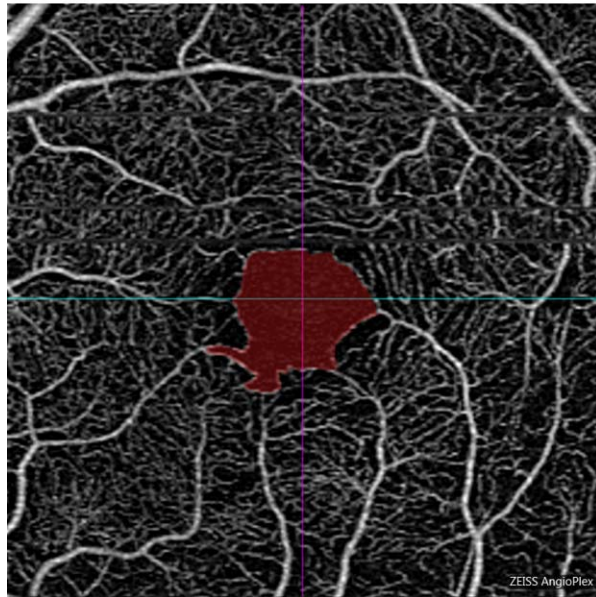
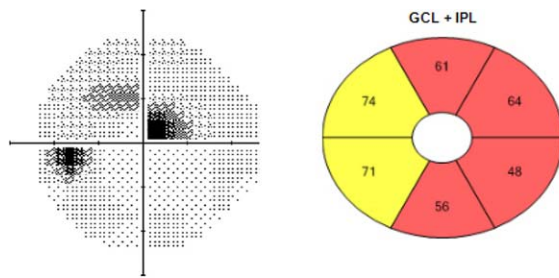


FIGURE 4. A representative case of a 52-year old female patient with glaucoma. (*Top, left*) She had a CVFD in the superior VF. Central retinal sensitivity (1/Lambert) from six points was 415 in the superior hemifield and 1693 in the inferior hemifield. (*Top, right*) The average mGCIPL thickness was thinner in the inferior hemiretina (58.3 μm versus 66.3 μm). (*Bottom*) Optical coherence tomography angiography shows the area of the FAZ was larger in the inferior hemimacula compared with the superior hemimacula (0.218 mm^2 vs. 0.137 mm^2).

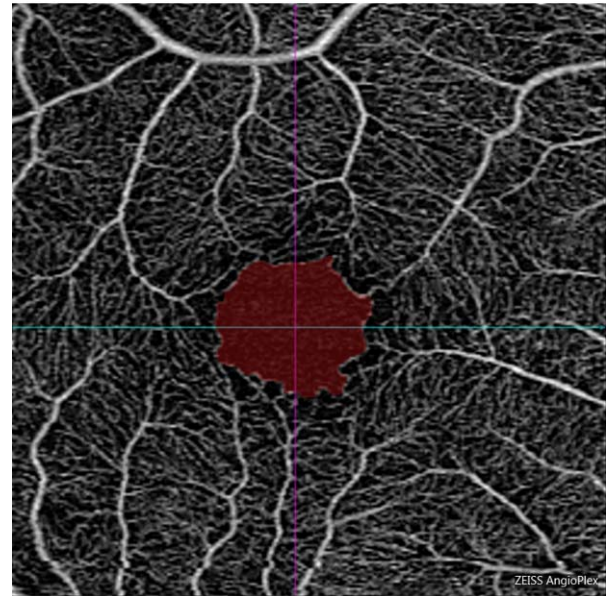
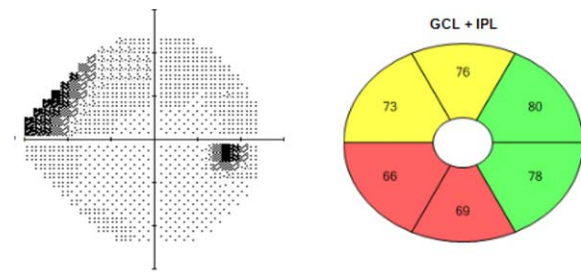


FIGURE 5. A representative case of a 36-year-old male patient with glaucoma. (*Top, left*) He had a PVFD in the superior VF. Central retinal sensitivity (1/Lambert) from six points was 1574 in the superior hemifield and 2117 in the inferior hemifield. (*Top, right*) The average mGCIPL thickness was similar in both hemimacula (76.3 μm versus 71.0 μm). (*Bottom*) Optical coherence tomography angiography shows the area of FAZ was similar between superior and inferior hemimacula (0.235 mm^2 vs. 0.204 mm^2).

In our study, although we did not observe statistically significant differences ($P = 0.093$), macular GCIPL thickness in the hemimacular segments without VF loss in the eyes with CVFDs was lower than that of the matched hemimacular segments in the eyes with PVFDs, suggesting that macular GCIPL loss may have already occurred in the hemimacular segments corresponding to the normal VF of glaucomatous eyes with CVFDs confined to a single hemifield. Conversely, the enlargement of the FAZ area due to perifoveal capillary dropout was not apparent in the hemimacular segments corresponding to hemifield without VF loss in the eyes with CVFDs. These findings suggest that capillary dropout in the perifoveal region may occur after macular GCIPL loss in glaucoma. In line with our findings, Akagi and associates⁹ reported that the reduction in the peripapillary RNFL thickness was significant not only at the corresponding location of the VF defects, but also at the noncorresponding location, whereas the reduction in the VD was limited only to the corresponding location in the glaucomatous eyes with hemifield VF defects.

Yarmohammadi et al.³⁴ demonstrated that OCTA-derived peripapillary VD was significantly correlated with the severity of VF damage as defined by global MD and pattern standard deviation in glaucoma. Our current findings not only confirm

that such correlations also exist for global retinal sensitivity, but show that there is also a significant correlation for the central 12 points of 24-2 VF testing when using the OCTA-derived FAZ area instead of VD. Of particular interest, our results show the association in the central VF (FAZ area versus central retinal VF sensitivity, $r = -0.499$, $P < 0.001$) was stronger than the global VF (FAZ area versus MD, $r = -0.320$, $P = 0.011$). Our study has shown significant correlations between OCTA-derived FAZ area and macular GCIPL thickness, which confirms our hypothesis. These findings suggest that the OCTA-derived FAZ area may be a useful parameter in monitoring vascular changes in the perifoveal region of glaucoma patients with CVFDs.

Our current study revealed that the loss of FAZ circularity and enlargement of the FAZ area was significantly associated with the presence and severity of CVFDs at initial presentation based on multivariate logistic and linear regression analysis. Central visual function is partly maintained by perifoveal microcirculation, and it is therefore plausible that the loss of FAZ circularity and/or enlargement of the FAZ area resulting from vascular dropout in the perifoveal region may result in the observed CVFDs in glaucoma patients. Although histologic correlations for the architectural disruption of the FAZ with the presence or severity of CVF loss have not been previously

performed in glaucoma patients, it is likely that alterations in the FAZ vascular architecture using in vivo OCTA imaging may correlate with the loss and advancement of CVF in glaucoma patients. Our results show a significant association between reduction of macular GCIPL thickness and the presence of CVFD, which may also support our hypothesis. Although our results may implicate an important relationship between pathologic alterations of OCTA-derived FAZ parameters and CVFDs in glaucoma, it will be important to validate these findings using longitudinal studies.

We acknowledge several limitations of this study, including its retrospective design. Although we found significant alterations of OCTA-derived FAZ parameters in association with CVFDs in our OAG patients, prospective longitudinal studies are needed to determine the temporal relationship between microcirculatory changes in the perifoveal region and the CVFDs noted in glaucomatous eyes. Another limitation is the relatively small sample size in each group. A small number of patients in each group may be due to the matching of the glaucomatous eyes with CVFDs and PVFDs by age and glaucoma severity to avoid their effects on FAZ metrics other than VF defect location. This patient matching also may have limited the generalizability of our findings to the general population with glaucoma. We used 24-2 VF testing to assess the CVFDs. Although 24-2 VF testing is routinely used in glaucoma patients at relatively early to moderate stage as in our study population, VF 10-2 test could have increased the sensitivity to detect CVFDs⁵⁰ and association between central VF defects and OCTA-derived FAZ alterations. Another limitation is that measurements of FAZ area and circularity were based on subjective measurements using the ImageJ software program by our raters. However, this limitation was addressed by excellent test-retest and interrater reliability (ICCs: 0.91–0.93), which also has been demonstrated in other published studies.^{10,14} In addition, the OCTA technology used in our study uses an eye-tracking system to minimize motion artifacts, which may have contributed to the low exclusion rate of its images due to poor quality (9.3%). In the current study, we did not investigate the relationship between OCTA-derived peripapillary VD and glaucomatous VF defects, particularly in the eyes with PVFDs, as we intended to explore novel FAZ-related vascular parameters using OCTA. Future studies regarding the correlation between the OCTA-derived peripapillary VD and VF defects in patients with PVFDs are needed to elucidate the role of vascular mechanism in the glaucoma pathogenesis. With new biomarkers such as OCTA-derived FAZ area and parameters, it is important to test the ability of these parameters to distinguish glaucomatous eyes from healthy eyes, which was not performed in the present study. Last, the relationship between foveal threshold and FAZ area and circularity was not evaluated in the current study despite that foveal sensitivity can sometimes be affected even in early stage of glaucoma.⁵¹ Therefore, further studies regarding the relationship between foveal threshold and OCTA-derived FAZ parameters are needed in glaucoma patients with different locations of VF defects.

In conclusion, OAG eyes with CVFDs confined to a single hemifield showed a larger FAZ area and a less circular FAZ than those of the PVFD group according to OCTA. Furthermore, a greater FAZ area was spatially correlated with the location of CVFDs. Loss of FAZ circularity and increased size of the FAZ area were significantly associated with the presence and severity of CVFD at initial presentation. Future longitudinal studies are needed to determine the temporal relationship between alterations in OCTA-derived FAZ metrics and central VF loss in glaucoma.

Acknowledgments

Disclosure: **J. Kwon**, None; **J. Choi**, None; **J.W. Shin**, None; **J. Lee**, None; **M.S. Kook**, None

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