Glucomatous optic neuropathy (GON) is characterized by progressive retinal ganglion cell (RGC) death and axonal loss. Blood flow insufficiency and/or abnormal microcirculation in the optic nerve head (ONH) and retina is thought to play an important role in some patients with glaucoma. To assess the microcirculation in the eye, different types of imaging modalities have been studied, including fluorescein angiography (FA), Heidelberg retina flowmeter, and color Doppler. Although FA has been widely used to detect vascular pathology in the retina, it does not provide a direct observation of the microvasculature within various layers of the retina and ONH. Moreover, FA does not provide a quantitative assessment of the microcirculation in various regions of the retina. Recent studies have described the use of non-invasive retinal microvasculature imaging, known as optical coherence tomography angiography (OCTA). This approach uses differences between B-scans to generate contrast associated with the motion of red blood cells (RBCs) through the microvasculature at various locations in the eye. OCTA therefore enables detailed and reproducible images of the retinal microvasculature networks to be obtained with a high level of resolution.

The foveal avascular zone (FAZ) is the round, capillary-free zone within the macula. Measurements of FAZ size (area and perimeter) using OCTA have been shown to be highly reproducible in patients with microcirculatory deficiency involving the macula, such as diabetic retinopathy, as well as in healthy individuals. Using OCTA images of the superficial vascular network, our group has previously reported an enlarged FAZ area in the perifoveal region, which was spatially correlated with central visual field (CVF) loss in glaucoma patients. Furthermore, our subsequent study demonstrated that the FAZ area and perimeter showed significant diagnostic value in discriminating glaucomatous eyes with CVF defects from normal eyes. Indeed, FAZ perimeter was seen to have a similar glaucomatous diagnostic value to conventional structural parameters, such as the circumpapillary retinal nerve fiber layer (cpRNFL) or macular ganglion cell-inner plexiform layer (mGCIPL) thickness. These findings suggest the potential role of OCTA-derived FAZ area or perimeter as a novel parameter for the detection of glaucoma patients in a clinical setting.

The macula is the only structure in the eye where the RGC layer is more than a single layer of cells thick, containing up to seven layers of RGC bodies. In terms of spatial location, RGCs are mainly located in the central 4.5 mm diameter region of the macula. Glaucoma patients often present with the loss of macular RGCs and nerve fiber layer thickness in the presence of macular RGCs and nerve fiber layer thickness in the presence of OCT angiography study of the relationship between foveal avascular zone size and retinal vessel density.

Junki Kwon,1 Jaewan Choi,2 Joong Won Shin,1 Jiyun Lee,1 and Michael S. Kook1
1Department of Ophthalmology, University of Ulsan, College of Medicine, Asan Medical Center, Seoul, Korea
2Central Seoul Eye Center, Seoul, Korea

Correspondence: Michael S. Kook, Department of Ophthalmology, University of Ulsan, College of Medicine, Asan Medical Center, 388-1 Pungnap-2-dong, Songpa-gu, Seoul 138-736, Korea; mskook@amc.seoul.kr.
Submitted: February 22, 2018
Accepted: July 11, 2018

PURPOSE. To assess the relationship between the size of the foveal avascular zone (FAZ; area and perimeter) and vessel density (VD) at various retinal regions using optical coherence tomography angiography (OCTA) in patients with open-angle glaucoma (OAG).

METHODS. In this retrospective cross-sectional study, OAG eyes were grouped according to the presence/absence of central visual field (CVF) defects. A control group of normal eyes was also included. OCTA images were obtained from the optic nerve (4.5 × 4.5 mm²) and macular (3 × 3 mm²) area, in which VDs were measured in the circumpapilla, parafovea, and fovea regions. Partial correlation analyses between FAZ parameters representing size and VDs at different retinal regions were performed. The correlation between FAZ parameters and macular ganglion cell-inner plexiform layer thickness (mGCIPL) and CVF mean sensitivity (MS) was also assessed. For spatial correspondence, correlations between FAZ parameters and corresponding VD, mGCIPL, and CVF-MS measurements were assessed at each hemiretina.

RESULTS. A total of 126 OAG eyes and 40 controls were reviewed. Overall, FAZ parameters showed statistically significant correlations with VDs measured at the fovea, parafovea, and circumpapilla (FAZ area: \( r = -0.603, -0.385, -0.256; P < 0.001, < 0.001, \) and 0.003, respectively). These correlations were observed regardless of the presence of CVF defects (all \( P < 0.05 \)). FAZ size showed significant spatial correlations with VD, mGCIPL, and CVF-MS measurements at each hemiretina.

CONCLUSIONS. OCTA-derived FAZ area and perimeter showed statistically significant correlations with VDs measured at various retinal locations with spatial correspondence in OAG.

Keywords: foveal avascular zone, vessel density, OCT angiography
of CVF loss, even at early stages of the disease. Using OCTA, Rao et al. have demonstrated that macular vessel density (VD) in the parafoveal region (central 1-3 mm diameter zone) was reduced in patients with glaucoma compared with healthy eyes. Moreover, glaucomatous change in VD has been detected by serial OCTA measurements in the macular region in patients with primary open-angle glaucoma (POAG), suggesting the potential role of macular VD measurement to detect and monitor microvascular changes in glaucoma.

At present, although it is known that both FAZ size and retinal VD measurements are altered in glaucoma patients, the relationship between microvascular changes in the FAZ and VD measurements at various retinal locations is unknown. We hypothesized that clarification of this relationship would provide an additional insight into the clinical utility of FAZ size (area or perimeter) in the detection and possible monitoring of glaucoma. In the present study, we have, therefore, investigated the relationships between the FAZ size and VD measurements obtained with OCTA at different retinal locations, including the circumpapillary, parafoveal, and foveal regions in a series of healthy and glaucomatous eyes. The relationship was further evaluated according to the involvement of CVF defects in glaucoma patients, as the FAZ is formed by the superficial vascular complex (SVC) in the central region of the macula, and the location of visual field (VF) defects (i.e., central versus peripheral) may influence the correlation between FAZ parameters and VDs derived from various retinal locations.

**Methods**

**Participants**

This cross-sectional, retrospective study was approved by the Institutional Review Board of the Asan Medical Center and adhered to the tenets of the Declaration of Helsinki. The medical records of patients who visited the glaucoma clinic of the Asan Medical Center between November 2016 and November 2017 were reviewed retrospectively. Open-angle glaucoma (OAG) eyes and normal control eyes were analyzed consecutively. Inclusion criteria for all participants were age >18 years, best-corrected visual acuity (BCVA) of 20/40 or better, and refractive error (RE) within 3 to 3 D cylinder. Exclusion criteria included the presence of any media opacities that resulted in poor quality spectral-domain optical coherence tomography (SD-OCT) or OCTA images, myopia greater than 10 D of spherical equivalent (SE) or axial length (AL) >28 mm (to minimize ocular magnification effect and to exclude degenerative or pathologic myopia), any retinal or neurologic disease other than glaucoma, history of intraocular surgery, uveitis, or ocular trauma, history of diabetes mellitus or retinal vaso-occlusive diseases (such as retinal vein occlusion [RVO]), or prior eye surgery/laser treatment. Participants with unreliable VF results (>20% of fixation loss, >15% false positive or false negative) were also excluded. If both eyes were eligible, only one eye was selected for inclusion at random. All patients had undergone comprehensive ophthalmic examination, including past medical history, measurement of BCVA, RE, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement with Goldmann applanation tonometry (GAT), gonioscopy, central corneal thickness (CCT) measurement with ultrasound pachymetry (DGH-550; DGH Technology, Inc., Exton, PA, USA), AL measurement (IOL Master version 5; Carl Zeiss Meditec, Dublin, CA, USA), optic disc stereophotography, retinal nerve fiber layer (RNFL) photography, Humphrey field analyzer Swedish Interactive Threshold Algorithm (SITA) 24-2 VF testing (Carl Zeiss Meditec), measurement of cpRNFL thickness (cpRNFLT) and mGCIPL thickness (mgGCIPLT) using an OCT device (Cirrus HD; Carl Zeiss Meditec), and imaging with a commercial OCTA system (Angiovue; Optovue, Inc., Fremont, CA, USA).

OAG was defined as the presence of open iridocorneal angle, signs of glaucomatous ONH damage (including neuroretinal rim thinning, notching, or a RNFL defect), and a glaucomatous VF defect regardless of IOP level. A glaucomatous VF defect was defined as follows: ≥3 adjacent points with P < 0.05 on a pattern deviation (PD) probability map and one abnormal point with P < 0.01, Glaucoma Hemifield Test outside normal limits, or a pattern standard deviation (PSD) of P < 0.05 confirmed on two consecutive reliable VF tests. OAG eyes were further classified into two subgroups according to the presence or absence of CVF defects. OAG eyes with CVF damage (CVF−) were defined as those with a glaucomatous VF defect in one hemifield within 10° of fixation, with at least one point at P < 0.01 lying at the two innermost parafoveal points on the PD probability map, as described in a previous study, regardless of extension to 10° to 24° VF area. The OAG eyes with preserved CVF (CVF+) consisted of eyes with glaucomatous VF defect clusters confined only to the 10° to 24° region. Normal healthy control subjects had no family history of glaucoma, IOP <21 mm Hg, open angles on gonioscopy, normal anterior chamber and posterior segment on clinical examination by a glaucoma specialist, nonglaucomatous optic discs on masked examination of stereoscopic optic disc photographs, and normal VF results. Normal VF was defined as a PSD within the 95% confidence limits and a Glaucoma Hemifield Test within normal limits.

**OCTA Image Acquisition and Processing**

OCTA images were obtained from both the circumpapillary and macular areas. At first, a 4.5 × 4.5 mm² area, centered on the ONH, was captured with default segmentation of radial peripapillary capillary (RPC) provided by the manufacturer. The RPC layer slab included the area from the internal limiting membrane (ILM) to the nerve fiber layer (NFL). Whole image VD (wiVD) was obtained over the entire 4.5 × 4.5 mm² scan field. The intrinsic viewing software (version 2016.2.0.35) provided circumpapillary vessel density (cpVD) in a region defined as a 750 µm-wide elliptical annulus extending from the optic disc boundary, based on the 360° global area and 6-sectoral area, according to the Garway-Heath map (superotemporal, ST; temporal, T; inferotemporal, IT; inferonasal, IN; nasal, N; superonasal, SN).

OCTA images from the macula were captured from a 3 × 3 mm² field of view centered on the fovea in a superficial slab that extended from the ILM to the posterior boundary of the inner plexiform layer (IPL). In this macula OCTA image, four vascular parameters were derived: macular wiVD, parafoveal vessel density (pVD), foveal vessel density (fVD), and FAZ size consisting of area and perimeter. VDs were provided by intrinsic viewing software. Macular wiVD was measured in the entire 3 × 3 mm² field. pVD was measured in an annular region with an inner diameter of 1 mm and outer diameter of 3 mm centered on the fovea. Global and hemiretinal (superior and inferior) pVD was calculated. The fVD was measured in the most central circular region with a diameter of 1 mm centered on the fovea. Measurements of the FAZ area and perimeter have been described in detail elsewhere. Briefly, two independent raters performed FAZ measurements twice while masked to each other's results, as well as to the clinical information for each participant, including the presence of glaucoma and location of VF defect. Macular OCTA images were loaded into an image analysis program.
TABLE 1. Intra-Rater Repeatability Estimates of FAZ Measurements (All Eyes, n = 166)

<table>
<thead>
<tr>
<th>Repeatability Coefficient</th>
<th>Measurement Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAZ area, mm²</td>
<td>0.050 (0.029–0.051)</td>
</tr>
<tr>
<td>FAZ perimeter, mm</td>
<td>0.120 (0.115–0.125)</td>
</tr>
</tbody>
</table>

Values in parentheses represent 95% CI.

(ImageJ 1.51, http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). Since the macular OCTA image size was 304 × 304 pixels, the scale parameter for the software was set to define a 304-pixel width of the images as 3 mm. After confirmation of proper image centration at the fovea, ImageJ software automatically showed the area and perimeter of FAZ when the raters manually dragged the border of FAZ. The average values from the measurements of FAZ by two independent raters were used in the final analysis to minimize the effect of inter-rater variation. The OCTA system (Optovue, Inc.) has a default AL of 23.95 mm. During the measurement of FAZ area and perimeter, Littmann’s method was used to correct the ocular magnification by each AL. Details of the formula are provided elsewhere. In brief, the relationship between the measured OCTA image diameter, \( D_{m} \), and the true diameter, \( D_t \), can be formulated as \( D_{t} = p \cdot q \cdot D_{m} \), where \( p \) and \( q \) are the image magnification factor of the imaging system and the eye, respectively. The \( p \) of the OCTA system (Optovue, Inc.) is 3.460, which can be calculated from \( 1/(0.01306(23.95 - 1.82)) \), and \( q \) can be determined from Bennett’s formula, as \( q = 0.01306(AL - 1.82) \), where 1.82 is a constant related to the distance between the corneal apex and the second principal plane. Thus, AL-related magnification factor can be corrected by \( D_{t} = 3.460'0.01306'(AL - 1.82)'D_{m} \).

Poor quality OCTA images were excluded from the analysis, including signal strength index (SSI) < 48 (minimum = 1, maximum = 100), poor-clarity images due to severe media opacities; motion artifacts or localized weak signal by vitreous floaters; residual motion artifacts visible as irregular vessel patterns or disc boundary on the en face angiogram; images not centered on the fovea for macular OCTA (fixation error); and segmentation failure.

**SD-OCT and Visual Field Mean Sensitivity Scoring**

Imaging of cpRNFL and mGCIPL was performed using the SD-OCT optic disc cube scans and macular cube scans (Carl Zeiss Meditec), respectively. The optic disc cube scan generated a cpRNFLT map in a 6 × 6 mm² (200 × 200 scans) area centered at the optic disc. The cpRNFLT was measured in a circle of 3.46 mm diameter. Macular cube scan provided a mGCIPLT map of the annulus region centered on the fovea. The annulus region had an outer diameter of 4.8 mm and inner diameter of 1.2 mm horizontally, and an outer diameter of 4.0 mm and inner diameter of 1.0 mm vertically. Only images with a signal strength ≥7 were included. Images with motion artifacts, poor centering, or segmentation error were checked and discarded by the operator, with re-scanning performed during the same visit.

VF test results were converted to mean sensitivity (MS, 1/Lambert; L) unit by the anti-log of the threshold value (dB). The MS of the innermost four points of 24-2 VF testing was used in the current study to represent CVF MS as only these four points represent the central ±8° area, which contains over 50% of RGCs. In the current study, these innermost four points were used to determine the presence of CVF defects.

**Statistical Analysis**

To examine the bias/agreement between the two raters, a Bland-Altman plot analysis was performed for FAZ area and perimeter. In addition, intra-rater repeatability analysis was performed using repeatability coefficient and measurement error, as in previous studies. Repeatability coefficient was calculated as 2.77^average within-subject standard deviation (σ_w), and measurement error was calculated as 1.96*σ_w. The 95% confidence intervals of repeatability coefficient were calculated as 1.96*σ_w/√2n(m − 1).

Comparisons between OAG eyes and normal controls were made using independent t-tests or \( \chi^2 \) tests as appropriate. Since the FAZ area and macular VD are significantly correlated with age (positive and negative, respectively), age was adjusted for all correlation analyses between FAZ parameters and VDs at various retinal locations. Therefore, to evaluate the relationship between FAZ size (area, perimeter) and VD measurements at various retinal locations (wVD, cpVD, pVd, and pVD), quantitative correlations were assessed in all eyes as well as each subgroup (CVF+, and CVF−), using partial correlation analysis while using AL-corrected FAZ size according to the Littmann’s formula and adjusting for age effect. Normal eyes were included in all correlation analyses. Partial correlation analyses between FAZ parameters and other structural/functional parameters (cpRNFL, mGCIPLT, and MS) were also assessed in the overall and subgroups of OAG eyes after controlling for age. For the correlation between FAZ size and visual function, retinal sensitivity was expressed in both linear (1/L) and dB scales. In this study, the absolute value of correlation coefficient below 0.19 was regarded as very weak, 0.2 to 0.39 as weak, 0.4 to 0.59 as moderate, 0.6 to 0.79 as strong, and 0.8 to 1.0 as very strong correlation.

For the evaluation of spatial correspondence between the FAZ size and vascular/structural/functional parameters, the correlation between FAZ area and perimeter and various variables (cpVD, pVd, cpRNFLT, mGCIPLT, and CVF MS) was assessed at each hemiretina (i.e., superior and inferior hemiretina) separately. For example, the superior FAZ area and perimeter in the superior hemiretina were matched to cpVD at the ST sector, pVd at the superior hemiretina, cpRNFLT at the superior quadrant, mGCIPLT at the superior hemiretina, MS of 26 test points in the inferior hemi-VF, and MS of two central points in the inferior hemi-VF (Fig. 1). All reported \( P \) values were two-sided and values of \( P < 0.05 \) were considered to indicate statistical significance. All statistical analyses were performed using statistical software (SPSS software version 18.0 for Windows; SPSS, Inc., Chicago, IL, USA) and R program version 3.1.2 (R Foundation, Vienna, Austria).

**RESULTS**

A total of 182 eyes (137 OAG, 45 normal) met the initial inclusion criteria and the quality of the OCT/OCTA images was subsequently checked. Of these, 16 eyes (11 OAG, 5 normal) were excluded because of insufficient image quality; 166 eyes were, therefore, included in the final analysis (126 OAG, 40 normal). Of the 126 OAG eyes, 67 (from 67 subjects) were CVF+ and 59 (from 59 subjects) were CVF−. All participants were Korean.

Figure 2 shows the Bland-Altman plots for FAZ area and perimeter between the two raters. Intra-rater repeatability analyses results are summarized in Table 1. Repeatability coefficient and measurement error of FAZ perimeter was greater than those of FAZ area.
Table 2 summarizes the demographics, ocular characteristics, and measurement data from the VF test, SD-OCT, and OCTA of the entire OAG, CVF+, CVF−, and normal groups. Both the CVF+ and CVF− groups had significantly higher baseline IOP than the normal group (P < 0.001 and 0.014, respectively). Sex proportion, CCT, SE, and AL showed no significant differences between the glaucoma subgroups and the normal group, with the exception that the age of the participants was higher in the CVF+ group than the normal group. As expected, both CVF+ and CVF− groups showed significant differences compared with the normal group in terms of VF parameters (including MD, PSD, and MS), SD-OCT measurements (cpRNFL and mGCIP LT), and OCTA-derived variables, including wiVDs of the disc and macula and cpVD. In addition, the CVF+ group showed significantly lower pfVD and iVD, larger FAZ area, and greater FAZ perimeter than the normal group (all P < 0.05). The differences of FAZ parameters between groups (CVF+ versus normal) were larger than repeatability coefficients, which suggested that these differences were not simply due to the variability of the measurements. Although the CVF− group also showed lower pfVD and iVD, larger FAZ area, and greater FAZ perimeter than the normal group, the differences were not statistically significant (all P > 0.05).

Table 3 shows the correlation between FAZ parameters and VDs at different retinal locations (disc whole image, circum-papilla, macula whole image, parafovea, and fovea). For the overall 166 eyes, FAZ area and perimeter showed a significant correlation between FAZ parameters and VD measurements was highest between FAZ parameters and iVD, followed by that between FAZ parameters and cpVD. A similar trend in association between FAZ parameters and VD measurements at various retinal locations was also noted in the CVF+ group, with the correlation being strongest with the fovea. Of interest, this trend was also observed in the CVF− group.

Table 4 illustrates the relationship between FAZ parameters and various structural and functional indices representing glaucoma severity. FAZ area and perimeter showed a significant negative correlation with SD-OCT parameters (cpRNFL and mGCIP LT), as well as with the VF-MS of all 52 points and the central four points in the overall group (166 eyes) regardless of retinal sensitivity scale, after adjusting for age. A similar trend was also observed in the CVF+ group. However, in the CVF− group, only FAZ area showed a significant negative correlation with cpRNFL and mGCIP LT. In terms of the relationship between FAZ parameters and functional indices, there was no significant correlation between FAZ parameters and any central VF-MS values in the CVF− group, while there were significant correlations between FAZ parameters and VF-MS values (global and central) in the CVF+ group.

Regarding spatial correspondence, Table 5 summarizes the results of correlation analyses for each hemiretina. For the overall group of 166 eyes, FAZ area and perimeter showed a significant correlation between FAZ parameters and VD measurements was highest between FAZ parameters and iVD, followed by that between FAZ parameters and cpVD. A similar trend in association between FAZ parameters and VD measurements at various retinal locations was also noted in the CVF+ group, with the correlation being strongest with the fovea. Of interest, this trend was also observed in the CVF− group.
perimeter showed a significant correlation with all OCTA, SD-OCT, and VF-derived parameters, including cpVD, pVD, cpRNFL, and mGCIPL at the inferior hemiretina, and MS of the central two points and MS of the global 26 points at the superior hemi-VF (all \( P < 0.05 \)).

**Representative Case**

Figure 3 shows a representative case from the glaucoma cohort; 24-2 VF testing showed that glaucomatous VF defects involving the CVF area and MS were lower in the superior hemi-VF than in the inferior hemi-VF, especially in the central...

**Figure 2.** Bland-Altman plots of FAZ (A) area and (B) perimeter measurements between two raters. Solid lines represent the mean difference between the two measurements, black dashed lines represent the 95% confidence interval (CI, ±1.96 standard deviation) on the bias, and red dashed lines represent the 95% CI on the limits of agreement.
**TABLE 2.** Demographics, Ocular Characteristics, and Other Variables From VF Testing, SD-OCT, and OCTA (All Eyes, n = 166)

<table>
<thead>
<tr>
<th>Variables</th>
<th>OAG (Including CVF+ and CVF−)</th>
<th>Normal</th>
<th>Subgroups of OAG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 126)</td>
<td>(n = 40)</td>
<td>CVF+ (n = 67)</td>
</tr>
<tr>
<td>Demographics</td>
<td>Age, y</td>
<td>54 ± 14</td>
<td>50 ± 14</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>62/64</td>
<td>15/25</td>
<td>35/32</td>
</tr>
<tr>
<td>CCT, μm</td>
<td>537 ± 41</td>
<td>541 ± 40</td>
<td>532 ± 39</td>
</tr>
<tr>
<td>Baseline IOP, mm Hg</td>
<td>17.7 ± 4.9</td>
<td>15.0 ± 3.1</td>
<td>18.0 ± 4.8</td>
</tr>
<tr>
<td>SE, d</td>
<td>−2.5 ± 3.6</td>
<td>−2.4 ± 3.2</td>
<td>−1.9 ± 3.2</td>
</tr>
<tr>
<td>AL, mm</td>
<td>24.8 ± 1.7</td>
<td>24.8 ± 1.6</td>
<td>24.5 ± 1.6</td>
</tr>
<tr>
<td>Visual field</td>
<td>MD, dB</td>
<td>−7.4 ± 7.2</td>
<td>0.0 ± 1.5</td>
</tr>
<tr>
<td>PSD, db</td>
<td>7.3 ± 4.3</td>
<td>1.6 ± 0.3</td>
<td>9.3 ± 4.0</td>
</tr>
<tr>
<td>Whole VF MS (1/L)</td>
<td>668 ± 413</td>
<td>1373 ± 468</td>
<td>534 ± 592</td>
</tr>
<tr>
<td>Whole VF MS (dB)</td>
<td>26.8 ± 4.6</td>
<td>31.1 ± 1.7</td>
<td>25.2 ± 5.5</td>
</tr>
<tr>
<td>Central 4 points MS (1/L)</td>
<td>1235 ± 764</td>
<td>2388 ± 819</td>
<td>825 ± 568</td>
</tr>
<tr>
<td>Central 4 points MS (dB)</td>
<td>29.2 ± 5.8</td>
<td>35.5 ± 1.7</td>
<td>26.8 ± 7.0</td>
</tr>
<tr>
<td>SD-OCT</td>
<td>cpRNFLT, μm</td>
<td>73 ± 13</td>
<td>91 ± 10</td>
</tr>
<tr>
<td></td>
<td>mGCIPLT, μm</td>
<td>69 ± 8</td>
<td>79 ± 7</td>
</tr>
<tr>
<td>OCTA</td>
<td>SSI (disc)</td>
<td>58.7 ± 6.6</td>
<td>57.9 ± 5.1</td>
</tr>
<tr>
<td></td>
<td>SSI (macula)</td>
<td>60.1 ± 5.5</td>
<td>61.2 ± 4.8</td>
</tr>
<tr>
<td></td>
<td>wVd disc, %</td>
<td>48.0 ± 6.3</td>
<td>54.1 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>cpVD, %</td>
<td>57.0 ± 7.2</td>
<td>63.6 ± 3.5</td>
</tr>
<tr>
<td></td>
<td>wiVD macula, %</td>
<td>47.2 ± 5.0</td>
<td>51.0 ± 4.4</td>
</tr>
<tr>
<td></td>
<td>pfVD, %</td>
<td>51.2 ± 4.8</td>
<td>53.8 ± 5.2</td>
</tr>
<tr>
<td></td>
<td>FVD, %</td>
<td>28.4 ± 5.6</td>
<td>30.1 ± 5.0</td>
</tr>
<tr>
<td></td>
<td>FAZ area, mm²</td>
<td>0.431 ± 0.12</td>
<td>0.385 ± 0.11</td>
</tr>
<tr>
<td></td>
<td>FAZ perimeter, mm</td>
<td>3.042 ± 0.63</td>
<td>2.702 ± 0.47</td>
</tr>
</tbody>
</table>

Values with statistical significance are shown in bold. L. Lambert.
* Comparison between OAG (including CVF+ and CVF−) versus normal.
† Comparison between glaucoma with CVF+ versus normal.
‡ Comparison between glaucoma with CVF− versus normal.

two points. Based on macular OCTA imaging, the FAZ area and perimeter were greater in the inferior hemiretina than in the superior hemiretina. VDs at the parafovea and circumpapilla provided by intrinsic automatic software were lower in the inferior hemiretina than in the superior hemiretina. The difference between the superior hemiretina and inferior hemiretina was greater in the pfVD (4.00%) than in the cpVD (2.45%). SD-OCT also showed lower mGCIPLT and cpRNFLT in the inferior hemiretina than in the superior hemiretina. The

**FIGURE 3.** A representative case from the glaucoma cohort with glaucomatous CVF defects. Based on the macular OCTA image, the FAZ area and perimeter were greater in the inferior hemiretina than in the superior hemiretina. Vessel densities at the parafovea and circumpapilla were lower in the inferior hemiretina than in the superior hemiretina. Spectral-domain optical coherence tomography also showed lower mGCIPLT and cpRNFLT in the inferior hemiretina than in the superior hemiretina. Mean sensitivity was lower in the superior hemi-VF than in the inferior hemi-VF, particularly in the central two points.
difference between the superior hemiretina and inferior hemiretina was 22 μm for mGCIPLT and 2 μm for cpRNFLT.

**DISCUSSION**

In this study, the area and perimeter of the FAZ were significantly greater in OAG eyes, including those with CVF defects (CVF+), than in normal control eyes. FAZ area and perimeter were also larger in the OAG eyes without CVF defects than in normal control eyes, although this was not statistically significant. Of interest, disc and macular wVd measurements were significantly lower in OAG eyes without CVF defects than in normal control eyes, suggesting that the CVF− group may also experience widespread reductions in the microvasculature (including the optic disc and macula), despite the absence of CVF defects. Correlation analysis showed a significant negative correlation between FAZ size and VD measurements at all retinal locations (p < 0.01), with an increasing degree of correlation seen when going from the optic disc to the fovea. Additionally, there was also significant correlation between FAZ parameters and structural parameters (cpRNFLT and mGCIPLT) in OAG eyes, which was also noted in the CVF+ group. The CVF+ group showed significant correlations between FAZ size and global and central VF MS, while there were no significant correlations between FAZ parameters and central VF MS in the CVF− group. These findings suggest that FAZ size is closely related to central visual function status. Regarding spatial correspondence, each hemiretinal FAZ parameter (superior or inferior hemiretina) showed significant topographic correlation with vascular/structural/functional measurements at the corresponding locations. To our knowledge, this is the first study to assess the relationship between OCTA-derived FAZ size and VF measurements at various retinal locations in OAG patients. Therefore, our findings provide important information regarding the relationship between FAZ size enlargement and reduction of superficial VF measurements at various retinal locations in patients with glaucoma.

In normal eyes, the FAZ diameter range is about 0.4 to 0.5 mm, as determined by previous histologic or fluorescein angiographic studies. Studies assessing FAZ measurement using OCTA technology have recently been published. These studies reported the FAZ area of normal eyes to be 0.250 to 0.474 mm², depending on the characteristics of the study participants, type of OCTA machine, segmentation, and image analysis method. In patients with glaucoma, the FAZ area is reported to be enlarged compared with that in normal controls, which ranged from 0.360 to 0.435 mm² in the current study consisting of Korean patients, the mean FAZ area was 0.583 and 0.431 mm² for normal control and OAG eyes, respectively, which is similar to measurements seen in previous studies.

In this study, FAZ area and perimeter showed the highest correlations with VD measurements at the fovea (degree of correlation: moderate to strong), which is defined as a 1-mm diameter circular area. Histologically, the border of the FAZ is formed by a single-layered capillary arcade that lies within the ganglion cell layer (GCL). The FAZ area is highly sensitive to ischemic events and is enlarged in conditions such as old age, diabetic retinopathy, RVO, and sickle cell disease. The diameter of the FAZ is ~400 μm in normal eyes. A recent study found that the FAZ area was ~0.373 to 0.377 mm² in normal eyes with ICIs >0.9. In the present study, the mean FAZ area was 0.467 mm², 0.393 mm², and 0.383 mm² for the CVF+, CVF−, and normal groups, respectively. The area of the fovea in normal eyes is ~0.785 mm², and the area of the fovea should, therefore, be large enough to contain the FAZ border. Consequently, it is not unexpected that FAZ parameters and VD showed a strong negative correlation.

The FAZ area and perimeter showed a significant negative correlation with macular wVd and pVd (degree of corolla-

---

**Table 4. Age-Adjusted Partial Correlations Between the FAZ (Area and Perimeter) and SD-OCT and VF Parameters**

<table>
<thead>
<tr>
<th></th>
<th>cpRNFLT, μm</th>
<th>mGCIPLT, μm</th>
<th>Whole VF MS, 1/L</th>
<th>Whole VF MS, dB</th>
<th>Central 4 Points MS, 1/L</th>
<th>Central 4 Points MS, dB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 166 eyes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAZ area, mm²</td>
<td>-0.263 (0.001)</td>
<td>-0.336 (&lt;0.001)</td>
<td>-0.281 (0.002)</td>
<td>-0.290 (&lt;0.001)</td>
<td>-0.256 (0.002)</td>
<td>-0.333 (&lt;0.001)</td>
</tr>
<tr>
<td>FAZ perimeter, mm</td>
<td>-0.257 (0.004)</td>
<td>-0.294 (&lt;0.001)</td>
<td>-0.297 (&lt;0.001)</td>
<td>-0.291 (&lt;0.001)</td>
<td>-0.287 (&lt;0.001)</td>
<td>-0.340 (&lt;0.001)</td>
</tr>
<tr>
<td>Central visual field defects subgroup, 107 eyes (40 normal + 67 CVF+)</td>
<td>-0.285 (0.007)</td>
<td>-0.372 (&lt;0.001)</td>
<td>-0.327 (0.002)</td>
<td>-0.287 (0.006)</td>
<td>-0.287 (0.007)</td>
<td>-0.347 (0.001)</td>
</tr>
<tr>
<td>FAZ area, mm²</td>
<td>-0.231 (0.010)</td>
<td>-0.338 (0.001)</td>
<td>-0.338 (0.001)</td>
<td>-0.283 (0.007)</td>
<td>-0.313 (0.002)</td>
<td>-0.345 (0.001)</td>
</tr>
<tr>
<td>FAZ perimeter, mm</td>
<td>-0.209 (0.007)</td>
<td>-0.275 (0.061)</td>
<td>-0.265 (0.025)</td>
<td>-0.297 (0.007)</td>
<td>-0.170 (0.121)</td>
<td>-0.174 (0.117)</td>
</tr>
</tbody>
</table>

Values with statistical significance are shown in bold. Data are presented as age-adjusted partial correlation coefficient (r value).
FAZ and Retinal Vessel Density by OCT Angiography

Age-Adjusted Correlations Between the FAZ (Area and Perimeter) Versus cpVD, pfVD, cpRNFL, mGCIPLT, Global 26 Points MS, and the Most Central Two Points MS at Each Hemiretina and n = 166

<table>
<thead>
<tr>
<th>Variables</th>
<th>IT Sector</th>
<th>Superior hemiretina (with inf hemi-VF)</th>
<th>Inf Central 2 Points MS, db</th>
<th>Sup Central 2 Points MS, db</th>
</tr>
</thead>
<tbody>
<tr>
<td>cpVD, %</td>
<td></td>
<td>-0.231 (0.016)</td>
<td>-0.240 (0.007)</td>
<td></td>
</tr>
<tr>
<td>pfVD, %</td>
<td></td>
<td>-0.349 (&lt;0.001)</td>
<td>-0.389 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>cpRNFLT, µm</td>
<td></td>
<td>-0.386 (0.002)</td>
<td>-0.403 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>mGCIPLT, log Q</td>
<td></td>
<td>-0.308 (0.034)</td>
<td>-0.346 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Global 26 Points MS, dB</td>
<td></td>
<td>-0.345 (&lt;0.001)</td>
<td>-0.369 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Central 2 Points MS, dB</td>
<td></td>
<td>-0.387 (&lt;0.001)</td>
<td>-0.405 (&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

Values with statistical significance are shown in bold. Data are presented as age-adjusted partial correlation coefficient (p values). Inf, inferior; L, Lambert; Q, quadrant; sup, superior.

It is noteworthy that FAZ parameters showed a significant correlation with disc wiVD or cpVD in the current study, although the degree of correlation was weak (FAZ area: $r = -0.274$ and $-0.256$, $P = 0.001$ and 0.003, respectively; FAZ perimeter: $r = -0.279$ and $-0.260$, $P = 0.003$ and 0.003, respectively). Measurements of disc wiVD or cpVD correlated significantly with glaucoma severity, as previously reported. In the present study, FAZ parameters also showed a significant correlation with glaucoma severity in that FAZ area and perimeter showed a significant negative correlation with cpRNFL, mGCIPLT, and global/central VF MS (Table 4). Therefore, it is not surprising that there was a significant correlation between FAZ parameters and disc wiVD or cpVD, even though these measurements were derived from different retinal locations. Validation from histological studies is essential.

In this study, it is important to note that mGCIPLT in the OAG eyes without CVF defects was significantly lower than that in normal control eyes ($P < 0.001$), while it was higher than that in the OAG eyes with CVF defects. This suggests that some reduction of the mGCIPLT may have already occurred even in the eyes with peripheral VF defects without CVF involvement. In line with these findings, macular wiVD in the CVF− eyes was significantly lower than that in normal control eyes ($P = 0.023$), while it was greater than that in the CVF+ OAG eyes, suggesting that some reduction of the macular VD may have also occurred in the eyes without CVF defects.

FAZ area showed a significant negative correlation with mGCIPLT and cpRNFLT regardless of the presence of CVF defects in this study. However, the degree of correlation between FAZ area and mGCIPLT appeared stronger than between FAZ area and cpRNFLT. More than 50% of RGCs reside in the macula. By contrast, the RNFL is absent within the fovea; it is thickest at the border of the optic disc and becomes thinner with distance from the optic disc. Therefore, the difference in the anatomical locations of RGC and RNFL may explain why the FAZ area showed a stronger relationship with RGC (represented as mGCIPLT) than with RNFL (represented as cpRNFLT).

In this study, FAZ parameters showed a significant negative correlation with VF MS at both global and central VF areas (entire 52 points and central four points) in the overall OAG group and CVF+ subgroup. Of interest, the CVF− subgroup showed no correlation between FAZ parameters and central VF MS. Since the FAZ border is formed by the SVC in the central region of the macula, the involvement of CVF defects may influence the correlation between FAZ parameters and VF MS measurements that are derived globally and regionally. In other...
words, OAG eyes without VF defects may have relatively intact FAZ architecture as well as CVF MS measurements, which may lead to a lack of correlation between FAZ parameters and central VF MS measurements. Our findings suggest that the OCTA-derived FAZ area or perimeter may be a useful parameter for monitoring VF changes in glaucoma patients with CVF defects.

Of note, significant topographic correlations were seen between FAZ size and OCTA, SD-OCT, and VF-derived parameters in both the inferior hemiretina (with superior hemi-VF) and superior hemiretina (with inferior hemi-VF). These findings may confirm our previous observations,12 which showed that the mean FAZ area derived from OCTA in the hemiretinal segments corresponding to VF defects is significantly larger than that in the hemiretinal segments without VF defects in glaucomatous eyes with hemifield CVF defects. Moreover, the current study demonstrates that good topographic correlations also exist between changes in FAZ size and OCTA-derived VD measurements at the circumpapilla and parafovea. Therefore, our findings suggest that vascular/structural/functional deficits in glaucomatous eyes and perifoveal microvascular damage are spatially correlated throughout various retinal locations.

We acknowledge that this study has several limitations. The first relates to the method of measuring the FAZ parameters. We assessed FAZ size by marking the border of vessels from OCTA images using ImageJ software, as previously validated.12,13,23,30–32 Although excellent reproducibility was observed in this study and has been reported in previous studies,12,13,23,30 it is possible that measurement error or inter-rater variability may exist and act as a confounding variable. While we corrected the ocular magnification effect from different ALs in the measurement of FAZ size using Littmann’s formula, the use of OCTA-derived VD measurements remains a possible source of error in our correlation analyses. In this study, we set the cutoff value of OCTA image quality at SSI >48, as used in many previous studies.25,26,28,30,31,34,35 Venugopal et al. recently reported that SSI value had a significant effect on the repeatability of VD measurement by OCTA.43 The mean SSI values of our cohort were relatively high, being close to 60, and there was no significant difference among groups in terms of SSI values. Therefore, we do not consider that SSI had a significant impact on our correlation analyses. In this study, we evaluated the central visual function using VF 24-2 testing. As Hood et al.16 proposed, glaucomatous damage to the macula can be missed or underestimated with standard VF tests using a 6° grid, such as VF 24-2 testing. Furthermore, none of the test points used in VF 24-2 testing corresponded to the FAZ topographically due to the smaller size of the FAZ. In this study, we focused on the innermost four points of VF 24-2 testing that correspond to the central ±8° area, where RGCs are concentrated, to investigate whether a correlation between FAZ size and CVF retinal sensitivity exists. However, VF 10-2 testing with foveal threshold value may yield more accurate measurement of central visual function and more accurate topographic correspondence with FAZ size than the VF 24-2 test. Since this study demonstrated a significant correlation between FAZ size and JVD and pJVD, we can deduce the vascular status of the macula through the observation of FAZ size. Finally, our study participants are the same race (Koreans). Previous studies revealed that foveal pit morphology showed differences between races, and FAZ size had significant correlation with foveal fit morphology.38,39 Therefore, the utility of FAZ size may be complicated or limited in a clinic where patients from various races are examined.

In conclusion, when measured with OCTA, FAZ area and perimeter showed a significant correlation with VDs at the fovea, parafovea, and circumpapilla, with the strongest correlation being noted in the fovea, followed by the parafovea and circumpapilla. FAZ size (area and perimeter) showed a significant correlation with cpRNFLt/mGCIPLt and central and global visual function measured by the innermost 4 and 52 points of VF 24-2 testing in the OAG eyes, with spatial correspondence. These findings suggest that FAZ size may be a potential vascular biomarker representing macular RGC status and central visual function in patients with glaucoma.

Acknowledgments

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

References


