The Association Between the Foveal Avascular Zone and Retinal Thickness

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PURPOSE. To investigate the association between the size and shape of the foveal avascular zone and retinal thickness in healthy subjects.

METHODS. In vivo imaging of the foveal microvasculature was performed on 32 subjects by using an adaptive optics scanning laser ophthalmoscope (AOSLO). Motion contrast maps of the AOSLO images were used to generate a montage revealing the foveal capillary network. Foveal avascular zone (FAZ) diameters along the horizontal (FAZ_H) and vertical (FAZ_V) meridians were measured on the montages. An asymmetry index (AI) of the FAZ was then computed as the ratio of the FAZ_H to FAZ_V. Retinal thickness was investigated by using spectral-domain optical coherence tomography (SDOCT). Inner retinal layer (INL_{FAZ}) thickness and outer nuclear layer (ONL_{FAZ}) thickness were measured at the edges of the FAZ on the horizontal and vertical SDOCT scans on the same eye.

RESULTS. The foveal capillary network was readily visualized in all subjects. As expected there was individual variation in the size and shape of the FAZ. Along the horizontal and vertical meridians, the mean $\pm$ SD (μ m) of the FAZ diameter was 607 ± 217 and 574 ± 155 , respectively. The INL_{FAZ} thickness was 68 ± 9 and 66 ± 9 , and the ONL_{FAZ} thickness was 103 ± 13 and 105 ± 11 , respectively. The mean $\pm$ SD of the AI was 1.03 ± 0.27 . The difference between FAZ_H and FAZ_V decreases with increasing FAZ area ($P = 0.004$). Mean ONL_{FAZ} was negatively correlated with FAZ effective diameter ($P < 0.0001$). No significant correlation was found between mean INL_{FAZ} and FAZ effective diameter ($P = 0.16$).

CONCLUSIONS. Despite large individual variations in size and shape of the FAZ, the INL_{FAZ} has a relatively constant thickness at the margins of the FAZ, suggesting the presence of retinal capillaries is needed to sustain an INL_{FAZ} thickness greater than 60 μ m. A smaller FAZ area is associated with a vertically elongated FAZ.

Keywords: foveal avascular zone, retinal capillaries, retinal thickness, spectral-domain optical coherence tomography, adaptive optics scanning laser ophthalmoscope

The human retinal vascular network is composed of multiple layers of vessels and capillaries,^{1,2} supplying oxygen and nutrients as well as disposing metabolic byproducts for the inner retinal layers.³ The fovea vascular network, in contrast, consists of a single layer of interconnected capillaries that perfuse the inner retinal layer.^{1,2,4} This foveal capillary network forms a ring at the margin of the fovea, producing a capillary-free region called the fovea avascular zone (FAZ). Clinically, the assessment of retinal vasculature perfusion typically requires intravenous injection of fluorescein dye.^{5–7} Owing to the invasive nature of fluorescein angiography, these studies are seldom performed on healthy controls. Noninvasive visualization of the foveal capillary network and foveal pit architecture are now provided by advances in retinal imaging, offering the opportunity to examine the foveal vasculature and pit development in healthy and diseased retina.^{8–14} Several research groups that used entopic perception,^{15,16} optical coherence tomography,^{9,17} and adaptive optics ophthalmoscopy^{11,12,14} have shown that the size of FAZ varies considerably in healthy subject. Previous studies^{12,14,18} have reported that larger FAZ is associated with a broader foveal pit in healthy controls. It has also been demonstrated that patients with a history of retinopathy of prematurity have smaller FAZs and narrower foveal pits when compared to full-term controls.^{19,20} Despite the extensive investigations of the correlations between

the FAZ and foveal pit morphology, considerable individual variation of FAZ dimension and foveal pit architecture limits understanding of the relation between the vasculature, the neural and glial components of the retina, and how they interact during foveal development. In addition, previous data from both ex vivo and in vivo studies show that a high density of cones extends out to a greater eccentricity in the horizontal than the vertical meridian.^{21,22} Thus, if the FAZ develops to provide clear vision in the region of relatively high cone density, it might be expected that the FAZ would extend further laterally than vertically. Conversely, there are presumably physiological penalties for extending cone axons and glia too far from the inner retinal blood supply. To examine the interplay of these factors, we measured the shape and size of the FAZ and the retinal thickness measured at the edge of the FAZ in 32 healthy subjects by using an adaptive optics scanning laser ophthalmoscope (AOSLO) and spectral-domain optical coherence tomography (SDOCT).

METHODS

Subjects

Thirty-two subjects participated in this study (24 males and 8 females; age range, 22–61 years). All subjects received a

complete eye examination, including a subjective refraction, examination of the anterior segment and adnexa, and dilated fundus examination. Exclusion criteria for this study included any evidence of retinal pathology or systemic diseases. For the five subjects older than 50 years, the SDOCT scans were reviewed for the presence of vitreous detachment that could distort the FAZ and drusen. The vitreous was either fully attached, fully detached, or partially detached with the transition from attachment to detachment limited to several hundred microns outside the FAZ. All subjects had best corrected visual acuity of 20/20 or better. Pupil dilation with one drop of 1% tropicamide was performed on all subjects. Informed consent was obtained after a full explanation of the procedures and consequences of the study. This study protocol was approved by the Indiana University Review Board and complied with the tenets of the Declaration of Helsinki.

Axial Length Measurement

Axial length measurement was made by using an IOL master (Carl Zeiss Meditec, Dublin, CA, USA). A mean of five axial length measurements was obtained for each tested eye. The retinal magnification differences induced by different axial lengths were factored into a calculation of linear retinal units in each eye for the AOSLO images²³ and SDOCT b-scans²⁴ as described previously.

AOSLO Instrumentation

The Indiana AOSLO used in this experiment has been described in detail previously.²⁵ In this study the AOSLO used a supercontinuum source (Fianium, Inc., Southampton, UK) to provide both the wavefront-sensing beacon and the imaging sources. Wavefront sensing and infrared imaging were performed at 740 and 820 nm with wavelengths obtained by using interference filters with bandwidths of 13 and 12 nm, respectively (Semrock, Inc., Lake Forest, IL, USA). Light returning from the retina passed through a confocal aperture that was 10× the Airy disk diameter and optically conjugate to the retinal plane. This 10× Airy disk diameter confocal aperture was measured as approximately 500 μm in the detector plane. In this experiment, the vertical scan was programmed to provide full-frame images of $2^\circ \times 1.8^\circ$ at a frame rate of 28 Hz. The subjects' head movements were stabilized by using a chin and head rest. The incident corneal power level of the infrared light source was set at 50 and 100 μW for the wavefront-sensing beacon and the imaging beam, respectively. All light levels were safe according to the American National Standards Institute ANSI Z136.²⁶

AOSLO Imaging of Foveal Capillary Network

Retinal imaging of the foveal capillary network was performed on all subjects by using the Indiana AOSLO modified with the multiply scattered light detection scheme.^{13,27,28} Both eyes were imaged on seven subjects to investigate within-subject variability, and only one eye was imaged on the remaining 25 subjects. During imaging, subjects were instructed to fixate sequentially around the perimeter of the imaging raster (a total of nine fixation points: top right, top middle, top left, left middle, bottom left, bottom middle, bottom right, right middle, and the center of the raster). The center of the fovea was located by comparing the center of fixation on the images when the patient fixated at four different corners and the center of the raster. Typically, a single acquisition of 100 frames (<4 seconds) at each retinal region of interest was sufficient to

collect a data set suitable for further image processing. Following acquisition, all video frames were corrected for scan distortion, then the image sequence was automatically filtered to reject blinks and large eye movements. A video frame without eye motion was then selected by the program, and all images were aligned to this frame automatically to remove the effect of eye movements both within and between video frames. Foveal capillary perfusion maps were generated by using the motion contrast image-processing technique as described previously.¹² In brief, calculations of the pixel standard error across a stack of ~50 to 80 aligned image sequence of each image region were performed to produce high-resolution maps delineating the capillary network distribution of the fovea.

FAZ Measurements

The FAZ was delineated manually on a layer mask of the foveal capillary montage by using Adobe Photoshop CS5 (Adobe Systems, San Jose, CA, USA). The FAZ mask was then processed by using custom MATLAB software (The Mathworks, Inc., Natick, MA, USA) for further computation of the FAZ measurements of vertical diameter, the horizontal diameter, and the total FAZ area. The FAZ effective diameter was computed as the diameter of the circle that had the same area as measured FAZ. The FAZ area and diameter along the horizontal (FAZ_H) and vertical (FAZ_V) meridians were measured (Fig. 1A). An asymmetry index (AI) of the FAZ was computed as the ratio of the FAZ_H to FAZ_V.

SDOCT Imaging of the Retinal Thickness

Foveal retinal thickness was measured by using SDOCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany). The SDOCT uses a superluminescent diode with a wavelength of 870 nm as a light source. The axial and lateral resolution of the SDOCT are approximately 7 and 14 μm , respectively. Horizontal and vertical SDOCT b-scans centered at the fovea were obtained for each tested eye. Subjects were instructed to look at the center of the fixation target closely while obtaining the SDOCT b-scans using the manufacturer's eye-tracking feature. Each b-scan was created by averaging 16 frames. All b-scan images were exported as tiff files for further image processing, as previously described.¹² To segment the cross-sectional images obtained from SDOCT, the anterior boundary of the RPE layer was identified manually and read into MATLAB (Fig. 1B). The MATLAB program then applied a polynomial algorithm to flatten the RPE layer, based on individual SDOCT images by moving each pixel column vertically.

Next, the inner limiting membrane (ILM), the external limiting membrane (ELM), and the border between the outer nuclear layer and the outer plexiform layer (ONL/OPL) were traced manually on the flattened image.²⁹ A spline algorithm was used to interpolate between sample points marked on the ILM, the ELM, and the ONL/OPL separately. After manual segmentation, the outer nuclear layer thickness at the FAZ margin (ONL_{FAZ}) was defined as the distance between the ELM and ONL/OPL (Fig. 1B). The inner retinal layer thickness measured at the FAZ margin (INL_{FAZ}) was defined as the distance between the ILM and ONL/OPL. Two measurements of ONL_{FAZ} and INL_{FAZ} were obtained on each horizontal (nasal and temporal measurements) and vertical (superior and inferior measurements) SDOCT scan. The means of ONL_{FAZ} and INL_{FAZ} were then computed by averaging the measurements obtained from both horizontal and vertical SDOCT scan for each subject.

FIGURE 1. Parameters measured from (A) montage of the foveal capillary network. FAZ_{Hori} indicates the FAZ diameter measured along the horizontal meridian. (B) Horizontal foveal SDOCT scan. The same parameters were also measured along the vertical foveal SDOCT scan (not shown). ILM, border of the inner limiting membrane (red); ONL/OPL, border of the outer nuclear layer and outer plexiform layer (yellow); RPE, anterior boundary of the retinal pigment epithelium (black dashed), CFT, central foveal thickness (red arrow); INL_{FAZ} , inner retinal layer thickness measured at the FAZ margin; ONL_{FAZ} , outer nuclear layer thickness measured at the FAZ margin.

Central foveal thickness (CFT) was defined as the minimum distance between the ILM and the anterior boundary of the RPE. The center of the fovea on the horizontal and vertical foveal SDOCT scans was defined as the location of the CFT. Foveal photoreceptor thickness (FPT) was then measured at the same location with the maximum distance between the ONL/OPL and the anterior boundary of the RPE.

Statistical Analysis

Statistical analysis was performed on one eye of each of the 32 subjects. Correlation and statistical significance were computed on the FAZ and SDOCT thickness measurements by using StatView for Windows (Version 5.0; SAS Institute, Inc., Cary, NC, USA). Correlation between FAZ area and axial length was also studied. Intrasubject variability of the FAZ area was tested in seven subjects who had both eyes imaged.

RESULTS

The in vivo and noninvasive imaging techniques using AOSLO and SDOCT visualized the foveal capillary network and provided retinal thickness measurements in all 32 subjects (39 eyes). Using these data, we quantified the FAZ size and shape differences across individuals, then compared the retinal thicknesses of selected layers with respect to FAZ size and shape.

FAZ Dimensions

Complete connections between arterioles and venules were clearly visualized in all subjects. A well-demarcated FAZ was seen in all tested eyes. While there was considerable similarity between fellow eyes (Fig. 2A), there was considerable individual variation in FAZ size and shape (Fig. 2B), with the FAZ area ranging from 0.02 to 0.63 mm². The mean $\pm$

FIGURE 2. Foveal avascular zone area masks in 32 subjects with the corresponding axial lengths. A well-demarcated FAZ was seen in all eyes. There was considerable variation in size and shape of the FAZ. (A) Both eyes were examined in 7 of the 32 subjects. No statistical significance was found on FAZ area between two eyes (paired *t*-test, $P = 0.09$). (B) Foveal avascular zones in the remaining 25 subjects. Foveal avascular zone and axial length were uncorrelated.

standard deviation of FAZ area, effective diameter, FAZ_H and FAZ_V diameter, and asymmetry indices are shown in the Table. The variation between individuals for FAZ_H had a ratio of more than 10.1 (largest FAZ_H /smallest FAZ_H), while the FAZ_V varied by only a ratio of 3.6 (largest FAZ_V /smallest FAZ_V), with a coefficient of variation 36% and 27%, respectively (Fig. 3A). The difference between FAZ_H and FAZ_V increased with increasing FAZ_H (correlation coefficient = 0.72; $P < 0.001$) and FAZ area (correlation coefficient = 0.49; $P = 0.004$), indicating that the FAZ shape is more vertically elongated with a small FAZ area but more horizontally elongated with larger FAZ area. Figure 3B shows that the AI (ratio of FAZ_H to FAZ_V) increased with increasing FAZ effective diameter, also suggesting that the FAZ shape is more vertically elongated (when $AI < 1$) with a small FAZ effective diameter and more horizontally elongated (when $AI > 1$) with a large FAZ effective diameter. No significant correlation was found between FAZ area and axial length (correlation coefficient = 0.15, $P = 0.41$).

The FAZ area in both eyes was examined in 7 of the 32 subjects. The mean difference between two eyes was 13%

(range, 0.1%–27%) for FAZ area and 6% (range, 0.05%–14%) for FAZ effective diameter. The shapes appear similar (Fig. 2). No statistically significant difference was found on FAZ area between two eyes (paired *t*-test, $P = 0.09$).

Retinal Thickness Measurements

The mean $\pm$ standard deviation of INL_{FAZ} and ONL_{FAZ} thickness measured at the FAZ margin along the horizontal and vertical meridians, CFT, and FPT are shown in the Table. The mean of the horizontal and vertical ONL_{FAZ} was negatively correlated with FAZ effective diameter with a correlation coefficient = -0.68 ; $P < 0.0001$. No significant correlation was found between the mean of horizontal and vertical INL_{FAZ} and FAZ effective diameter (correlation coefficient = 0.26; $P = 0.16$) (Fig. 4).

Central foveal thickness, FPT, and their difference ($CFT - FPT$) were negatively correlated with the FAZ effective diameter with a correlation coefficient of -0.8 ($P < 0.0001$), -0.6 ($P = 0.0001$), and -0.8 ($P < 0.0001$), respectively (Fig. 5).

TABLE. Parameters (Mean $\pm$ Standard Deviation) Measured From the Foveal Capillary Network Montage and SDOCT Images in 32 Healthy Subjects

FAZ Measurements		Retinal Thickness Measurements	
FAZ area	$0.32 \pm 0.16 \text{ mm}^2$	Horizontal INL_{FAZ}	$68 \pm 9 \mu\text{m}$
Effective diameter	$614 \pm 184 \mu\text{m}$	Vertical INL_{FAZ}	$66 \pm 9 \mu\text{m}$
FAZ_H	$607 \pm 217 \mu\text{m}$	Horizontal ONL_{FAZ}	$103 \pm 13 \mu\text{m}$
FAZ_V	$574 \pm 155 \mu\text{m}$	Vertical ONL_{FAZ}	$105 \pm 11 \mu\text{m}$
Asymmetry index	1.03 ± 0.27	CFT	$214 \pm 26 \mu\text{m}$
		FPT	$194 \pm 16 \mu\text{m}$

FIGURE 3. (A) Relationship between FAZ_H and FAZ_V. *Black line*: Linear regression to the data. *Dashed line*: 1:1 ratio of FAZ_H to FAZ_V. (B) Asymmetry index increases with increasing FAZ effective diameter (correlation coefficient = 0.67; $P < 0.0001$). All data indicate that the FAZ shape is more vertically elongated with small FAZ area but more horizontally elongated with larger FAZ area. Data were corrected by individual axial length.

DISCUSSION

This study used a noninvasive method to visualize the individual capillaries comprising the FAZ, then quantitatively examined the association between the FAZ dimensions and the retinal thickness at the FAZ margin in normal eyes by using AOSLO and SDOCT. Consistent with prior studies,^{12,30,31} our results demonstrated that the use of an AOSLO with multiply scattered light detection scheme allows direct and noninvasive visualization of the foveal capillary network without the use of exogenous agent. Our findings of FAZ area and effective diameter are in close agreement with previous studies.^{5,6,11,12,14,32} Also in agreement with previous studies, we found a large individual variation of the FAZ size and shape in healthy retinas (Fig. 2). Further, although the expected large individual differences were found, there were consistent relations among quantitative parameters.

FAZ Dimensions and Development

It is not clear why there is a link between the size of FAZ and the degree of horizontal/vertical asymmetry. Histologic studies

have indicated that the development of incipient fovea occurs at ~22 to 26 weeks gestational age, occurring while the superior and inferior primary vessels grow toward the horizontal meridian temporal to the fovea. The FAZ is completed and establishes supply to the raphe area by 37 weeks gestational age.^{33,34} At this point, the FAZ is small and it does not reach its adult dimensions until after birth.³⁴ During this period of foveal development the most complete models tie the formation of the foveal pit and the displacement of the inner retinal layers to mechanical stresses³⁵ caused by the interplay of intraocular pressure and eye growth. We found that a smaller FAZ area is associated with a vertically elongated FAZ (Fig. 3). Within this framework the relation between size and shape could occur owing to differences in the mechanical stresses when forming the foveal pit. That is, the retina vascularizes from the superior and inferior aspects toward the midline during development and this could cause a slight anisotropy in the mechanical properties of the retina, such that enlargement occurred preferentially along the horizontal direction. We have limited data suggesting a lower vascular density along the raphe (Chui TY, et al. *IOVS* 2012;53:ARVO E-

FIGURE 4. Relation between FAZ effective diameter and retinal thickness measured at the FAZ margin. The average INL thickness, but not the average ONL thickness, is significantly correlated with the size of the FAZ.

FIGURE 5. Relation between FAZ effective diameter and foveal retinal thickness. *Open circles* indicate the difference between CFT (*black circles*) and FPT (*pluses*). The CFT, FPT, and difference all decreased significantly as FAZ increased in size.

FIGURE 6. Comparison of the FAZ and horizontal retinal thickness in subjects with different FAZ diameter. (A) Foveal capillary network in a subject with relatively smaller FAZ diameter. (B) The horizontal OCT scan from the same subject in (A) shows an overall thickening of the foveola. (C) Foveal capillary network in a subject with relatively larger FAZ diameter. (D) The horizontal OCT scan from the same subject in (C).

Abstract 5662), but we do not have this extensive data set for most of the subjects in the current study. Thus, our data cannot test this framework but do point to the need for more complete developmental studies.

FAZ and Cone Packing Density

Previously, we found that there is a marked asymmetry between cone packing density in the horizontal and vertical meridians for younger and older subject groups.²⁹ A similar horizontal elongation is found for the thickness of the outer nuclear layer + Henle fiber layer.²⁹ Again, for both age groups and for both the nearer and farther regions of interest, the nasal retina had the thickest layer measurement and the inferior, the thinnest. Notably, however, there was no tendency for the FAZ to be extended horizontally, as would be expected if there was a strong relation between cone density and the shape of the FAZ. While the presence of an FAZ is clearly related to the presence of a fovea, there is no evidence that the extent of the FAZ conforms to underlying cone distribution, and since photoreceptors are primarily supplied from the choroidal circulation this result is not surprising.

Correlations of FAZ Dimensions and Inner Retinal Thickness

While there are known correlations between the FAZ dimensions and foveal pit morphology such as foveal pit depth, width, and volume,^{12,14,18} it is difficult to directly relate these overall geometric relations to potential metabolic demands. We know that the inner retinal neurons and glia require a nearby vascular supply, and this can explain the branching pattern of the vasculature.³⁶ For the inner retina this supply comes from the inner retinal circulation, and thus the existence of the FAZ should be related to the thickness of the inner retinal tissue, based on some critical diffusion distance.

In the healthy eye, it is unlikely there would be a thick inner retina without sufficient vasculature to support it. Our findings are in close accordance with this supposition. We found that the inner retinal thickness measured at the margin of the FAZ remains constant with increasing FAZ effective diameter (Fig. 4, circle symbols). If indeed a given amount of vascular supply is required to support a fixed amount of neural tissue this lack of correlation with distance is exactly what would be predicted, the inner retinal thickness is constant at the edge of the FAZ. Examples of example vascular maps and horizontal SDOCT b-scan in patients with different FAZ diameters are shown in Figures 6A through 6D. Thus, during the development of the fovea the migration of the inner retinal cells matches the metabolic support provided by the inner capillary loop. This capillary loop cannot sustain the metabolic demands of inner retinal tissue with a thickness greater than approximately 60 μm. Assuming that this single-layered capillary bed is located at the middle of the inner retinal tissue, oxygen and nutrients are therefore diffused across a distance of ~30 μm from the capillaries to the surrounding tissue. The edges of the FAZ have a lower density of capillaries than nearby regions (for instance see Fig. 1). This presumably occurs for two reasons. First, as the retina thickens outside the central fovea, more layers of capillaries are needed. Second, the actual metabolic demand is approximately set by the mitochondrial demand of neuronal layers, and the edges of the FAZ have a high proportion of Henle fibers and thus cell bodies represent a smaller proportion of the total retinal thickness than they do slightly more eccentrically. A full understanding of the relation of vascular supply and the combined neural/glial activity requires more detailed measurements and modeling; however, the consistency of the inner retinal thickness in the presence of the large anatomic variation in FAZ size suggests that this metabolic interplay is acting during the migration of the cell bodies during development. Gaining further insight will require examining the relation of the inner retinal thickness

to total retinal vasculature at retinal regions with multiple capillary beds and different metabolic demands, but this is beyond the scope of the current article.

CONCLUSIONS

In summary, our results provided evidence that a smaller FAZ area is associated with a vertically elongated FAZ. The inner retinal layer has a relatively constant thickness at the margins of the FAZ, whether the FAZ is large or small, suggesting the presence of retinal capillaries is needed to sustain an INL_{FAZ} thickness greater than 60 μm .

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