Foveal Shape and Structure in a Normal Population

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PURPOSE. The shape of the human fovea presents important but still poorly characterized variations. In this study, the variability of the shape and structure of normal foveae were examined.

METHODS. In a group of 110 eyes of 57 healthy adults, the shape and structure of the fovea were analyzed by automated segmentation of retinal layers on high-resolution optical coherence tomography scans. In an additional group of 10 normal eyes of 10 patients undergoing fluorescein angiography, the size of the foveal avascular zone (FAZ) was correlated to foveal shape.

RESULTS. From the thickest to the thinnest fovea, there was a structural continuum ranging from a shallow pit with continuity of the inner nuclear layer (INL) over the center (seven eyes; 6.7%), to a complete separation of inner layers overlying a flat and thinner central outer nuclear layer (ONL; eight eyes; 7.5%). Central foveal thickness correlated inversely to the degree of inner layer separation and to the surface of the FAZ.

CONCLUSIONS. Foveal structure strongly correlates with its neurovascular organization. The findings support a developmental model in which the size of the FAZ determines the extent of centrifugal migration of inner retinal layers, which counteracts in some way the centripetal packing of cone photoreceptors. (Invest Ophthalmol Vis Sci. 2011;52:5105-5110) DOI:10.1167/iovs.10-7005

The fovea is a specialized retinal area that supports the highest visual acuity. Histologic features of a normal fovea comprise a central area exclusively containing cones with elongated outer segments (OS) underlying a capillary-free zone and surrounded by separation of inner retinal layers.1 The advent of optical coherence tomography (OCT), which allows noninvasive, cross-sectional imaging of the retina, made possible the study of foveal morphology in humans in vivo. Indeed, OCT allows repeated, oriented “optical biopsy,” which overcomes some of the limitations of histology—namely, the paucity of human samples, but also the uncertainty of the location of the fixation point. Several population-based studies have shown that there are significant interindividual variations in foveal thickness in the normal population.2–16 Sex- and ethnicity-based differences in foveal thickness have also been reported. In particular, it has been shown that subjects of African descent have thinner foveae than do European subjects and that females have thinner foveae than do males.7,11 Interestingly, cases of patients with no foveal depression have been reported in several publications17–23—in some but not all cases, within a well-characterized pathologic context, such as albinism21 or retinopathy of prematurity (ROP).18,22,23 It is likely that variations in the shape of the fovea are related to structural differences—that is, variation in the disposition of the retinal layers. Yet, little is known about the correspondence between the thickness of the fovea and its neurovascular organization. Documenting structural variability also offers the unique possibility of validating in vivo the current concepts of foveal development. It is indeed likely that interindividual variability of the structure of the fovea results from the corresponding variations in its development.24 Current concepts of foveal development postulate an antiparallel, sequential shifting of the inner and outer retinal layers.25–27 In particular, the model developed by Springer and Hendrickson,25 which relied on histologic data and on computerized simulations, suggests the participation of mechanical factors such as anteroposterior compression by intraocular pressure and lateral stretching by ocular growth. Therefore, to investigate these questions, we qualitatively and quantitatively analyzed the variability of the normal foveal structure by high-resolution OCT imaging. We also investigated the relationship between the size of the foveal avascular zone (FAZ) and foveal structure.

SUBJECTS AND METHODS

This study was performed according to the principles outlined in the Declaration of Helsinki. Ethics committee approval was obtained. Data from a full medical history, best corrected visual acuity testing, funduscopy, and axial length measurement (IOLMaster; Carl Zeiss Meditec, Jena, Germany) were compiled for each subject. The sample fell into one of two groups: normal subjects 18 to 45 years old, with a normal vision, central fixation, and no history of ocular disease or prematurity, or patients undergoing a routine ophthalmic workup, including fluorescein angiography, because of unilateral retinal disease. Informed, written consent was obtained from all subjects.

OCT imaging was performed with spectral domain OCT combined with a scanning laser ophthalmoscope (Spectralis OCT-SLO; Heidelberg Engineering, Heidelberg, Germany). The high reproducibility of this system has been demonstrated previously.28 All imaging procedures were performed through undilated pupils (except for patients undergoing fluorescein angiography) with infrared illumination. Subjects carrying contact lenses were asked to remove them. During the
examination, the foveal center was identified as the deepest point of the foveal pit, containing a central light reflex. Once the foveal center was identified, 10 horizontal and vertical B-scans in high-resolution mode were averaged by the built-in software, which uses an eye-tracking system to compensate for eye-motion artifacts. Each averaged scan was visually checked for the presence of the above-mentioned features of the fovea.

Averaged OCT scans were then analyzed with custom software. The original image (gray levels encoded on 8 bits, 496 × 1536 pixels) was enhanced by applying a nonlinear diffusion filter. Such filter allows denoising of the retinal layers while preserving the edges. Then, the preprocessed image was processed through a multistep segmentation. Briefly, the retinovitreal interface was first localized by an edge-tracking algorithm, based on the maximization of the local mean gradient. Then, the median location of the area of maximum reflectivity (the retinal pigment epithelium/choriologicapillaris) was estimated using two filters applied sequentially: a Gaussian low-pass filter applied vertically to smooth the image and a recursive low-pass filter applied horizontally to ensure the continuity of the searched line. From this, it was possible to initialize an active contour that converged to the boundaries of the maximum-intensity layer. The outer limit of the choriocapillaris/Bruch’s membrane was detected as the outer limit of this zone of maximum reflectivity.

The next step was the segmenting of the photoreceptors. The junction between the inner (IS) and the outer (OS) segments of the photoreceptors appeared as a highly reflective line just above the area of maximum intensity and could be accurately detected with a peak detector. This line was used for the detection of the outer nuclear layer (ONL)/IS interface, which is assumed to be almost parallel. The parallelism feature was modeled via a Kalman filter that allows tracking the ONL/IS interface, column by column, according to the known position of the IS/OS junction. Similarly, a second Kalman filter was applied on the gradient image, to deduce the inner side of the RPE layer from the outer side of the choriocapillaris/Bruch’s membrane, since both curves are also almost parallel. Finally, the segmentation of the inner layers was performed using random Markov field-based classification techniques. We validated the segmentation method by comparing segments provided by the software with those generated manually by five retina experts. We found similar levels of accuracy between automated and manual segmentation.

Several parameters were then extracted from the processed images (Fig. 1): In the center of the fovea, central foveal thickness (CFT), the ONL, the length of central OS, and the pit depth were measured. At the crest of the clivus, the maximal retinal thickness (MRT) and the pit diameter (crest-to-crest distance) were measured. Two areas were measured: the pit cross-sectional area (defined by the area between the crest of the clivus, and the vitreoretinal interface), and the foveal inner retinal area (FIRA). The latter refers to the cross-sectional area of the inner retinal tissue within 500 μm from the center, delimited by the fovea, the vitreous interface, the outer plexiform layer (OPL), and a vertical limit 500 μm from the foveal center.

**FIGURE 1.** Illustration of the measured parameters. The OS was measured from the IS/OS boundary to the outer limit of the RPE-Bruch’s membrane complex.

Thus, the degree of inner retinal layer separation correlates positively to the pit cross-sectional area and inversely to the FIRA.

In the group of subjects who underwent fluorescein angiography for unilateral disease, the FAZ of the normal fellow eye was imaged by OCT simultaneously with angiography. The surface of the FAZ was measured after manual delineation with ImageJ software (developed by Wayne Rasband, National Institutes of Health, Bethesda, MD; available at http://rsb.info.nih.gov/ij/index.html). Descriptive statistics, Pearson’s correlation coefficients, intraclass coefficients, and statistical significance were calculated (SAS, Cary, NC). The accuracy of foveal localization was estimated by analyzing the agreement between measurements of CFT on horizontal and vertical scans of the same eye. The mean (± SD) difference was −0.27 (± 4.24) μm for the right eye and −0.15 (± 5.09) μm for the left eye. Bland-Altman plots and intraclass correlation coefficients (ICCs) confirmed the high concordance between CFT measures on horizontal and vertical scans (ICC, 0.976), which can be assumed to indicate a high precision of the localization of the fixation point.

**RESULTS**

In the first group, a total of 110 eyes of 57 healthy subjects were included. Four eyes from four subjects were excluded because of the suboptimal quality of the OCT scans. In the second group, 10 fellow eyes of patients with unilateral retinal disease (comprising six cases of branch retinal vein occlusion, three cases of central serous chorioretinopathy, and one case of ischemic optic neuropathy) were separately included and analyzed.

In the first group, there were 34 women and 23 men, with a mean (±SD) age of 31.7 ± 6.8 years (range, 18–45). Among them, 48 were of European and 9 were of Afro-Caribbean descent. The mean axial length was 24.29 ± 1.39 mm (range, 20.7–26.9). The distribution of all parameters was in accordance with a Gaussian distribution (not shown).

Within eyes, superior, nasal, and inferior MRT were on average not significantly different (332 ± 16, 329 ± 17, and 325 ± 15 μm, respectively) and correlated strongly (ICC, 0.875–0.915), whereas MRT was significantly lower temporally (306 ± 16 μm; P < 0.001). The FIRA values in the temporal, superior, and inferior areas correlated highly (ICC > 0.860); the nasal FIRA showed smaller ICCs than other areas (0.775–0.806). The pit diameter was higher horizontally than vertically (2205 vs. 2450 μm; P < 0.001). Between fellow eyes, there was a high degree of symmetry, as demonstrated by the high ICCs of all morphometric parameters (CFT, 0.850; pit surface, 0.932; pit depth, 0.952; pit diameter, 0.810; nasal MRT, 0.805; temporal MRT, 0.725; and FIRA between 0.865 and 0.873).

Examination of OCT scans showed a clear trend toward an increasing pit depth and increased inner layer separation with decreasing CFT (Video 1 and Fig. 2). In seven eyes (6.3% of the whole population) of four subjects, a shallow, triangle-shaped foveal depression with continuity of the inner nuclear layer...
Figure 3 illustrates the variations in the morphometric parameters between different subgroups of patients. The Afro-Caribbeans had significantly thinner central thicknesses and a higher degree of separation of inner retinal layers than did the Europeans. CFT was indeed on average 9% thinner and the pit surface 21% wider in Afro-Caribbeans than in Europeans ($P < 0.001$ for both). The women also showed a trend toward a thinner CFT (average 10.5 μm; $P = 0.059$).

In the group of participants who underwent fluorescein angiography, we observed that the perifoveal capillary ring projected on the inner edge of the ganglion cell layer (Fig. 4, top). Overall, the surface of the FAZ correlated with the degree of inner layer separation (Fig. 4, bottom).

**DISCUSSION**

In the present study, we investigated the structural variability of the fovea in normal eyes. The variability of parameters related to foveal shape, such as CFT, foveal pit depth and diameter, and interocular symmetry, was similar to that reported in other studies. Yet, to the best of our knowledge the overall correlation between these parameters has received little attention. A recent paper 12 showed that the overall foveal morphology varied with fundus pigmentation, as a more pronounced choroidal pigmentation was associated with a steeper foveal slope and a thinner central thickness, but similar perifoveal thickness. As we found a smaller value for FIRA and a thinner CFT in darkly pigmented subjects without difference in MRT, our findings are in accordance with theirs. In addition, we found that there was a strong relationship between foveal thickness, foveal shape, and neurovascular organization. Taken together, our results show that from the thickest to the thinnest foveae, the foveal structure varies from a shallow pit with continuity of the INL over the center and a small FAZ to a deep pit several hundred micrometers wide overlying a thin ONL with a large FAZ.

It is conceivable that the structure of the fovea determines its response to vitreoretinal diseases such as macular holes, epiretinal membranes, or macular edema. It has also been shown that the amount of macular pigment varies with retinal thickness. 34–36 A reduced amount of macular pigment has been reported in cases of fovea plana/hypoplasia. 19 Analysis of the foveal structure may hence reveal predisposition for the foveal complications of retinal diseases and hence be of clinical interest. Fine analysis of the foveal profile may also help to identify early-stage and/or minimally damaging diseases such as recently shown in patients with asymptomatic macular telangiectasia. 37

The structural variability of the fovea may correspond to variations of foveal development. 21 During development, differentiation of the fovea from the surrounding retina involves differential migrations of postmitotic neurons. Proviss et al. 23 suggested that the centripetal migration of cones leads to a relative metabolic starvation of the inner retina, which triggers an active mechanism of centrifugal migration of inner retinal neurons. Springer and Hendrickson 25–27 refined this model by insisting on the contribution of biomechanical factors on foveal differentiation. Their model, based on histology findings and computer modeling, suggests that structural and mechanical factors, such as the size of the FAZ, which precede foveal pit formation, 38–41 and intraocular pressure are major determinants of the organization of neuronal layers in the fovea. This model postulates that, once the FAZ is delimited, the foveal pit progressively deepens under the effect of intraocular pressure. Then, axial growth triggers the centrifugal migration of inner layers, the centripetal migration of cones, and the elongation of the central OS. Thus, an antiparallel, sequential

**Figure 2.** Illustration of the relationship between thickness and structure in the fovea in representative cases. The foveal thickness is indicated in the top left corner. In the thickest fovea (top), there was continuity of the INL over the fovea center (arrowheads). In the thinnest fovea (bottom), the pit floor was flat, as indicated by the large light reflex (arrow), and there was a large cleavage of central inner layers. The thickness of the ONL also decreased from top to bottom.

(1m) over the fovea was observed (Fig. 2, top). By contrast, eight eyes (7.3% of the whole population) of six subjects had a flat central foveal reflex with a large separation of the inner layers (Fig. 2, bottom). The difference in CFT between these two types of foveae was significant (161 vs. 232 layers (Fig. 2, bottom). The difference in CFT between these two types of foveae was significant (161 vs. 232 layers (Fig. 2, bottom). The difference in CFT between these two types of foveae was significant (161 vs. 232 layers (Fig. 2, bottom). The difference in CFT between these two types of foveae was significant (161 vs. 232 layers (Fig. 2, bottom). The difference in CFT between these two types of foveae was significant (161 vs. 232 layers (Fig. 2, bottom).

Morphometric variables of the whole population of this group are shown in Table 1. Among the measured parameters, those related to the morphology of the pit (depth, surface, and FIRA) showed the highest variability, whereas MRT showed the lowest.

The correlation matrix of the study parameters is given in Table 2. This showed that parameters related to the pit depth and separation of inner layers correlated inversely with central thicknesses. The only parameter significantly associated with axial length was the pit diameter. Age did not correlate with foveal shape or structure (data not shown).

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<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>CV (%)</th>
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<tr>
<td>Temporal MRT, μm</td>
<td>349 ± 17</td>
<td>4.8</td>
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<tr>
<td>Central IS + OS length, μm</td>
<td>68 ± 4.8</td>
<td>7.3</td>
</tr>
<tr>
<td>Pit diameter, μm</td>
<td>2.474 ± 243</td>
<td>9.8</td>
</tr>
<tr>
<td>CFT, μm</td>
<td>250 ± 21</td>
<td>11.6</td>
</tr>
<tr>
<td>Central ONL thickness, μm</td>
<td>105 ± 14</td>
<td>15.2</td>
</tr>
<tr>
<td>Pit depth, μm</td>
<td>131 ± 22</td>
<td>16.7</td>
</tr>
<tr>
<td>Pit cross-section, μm²</td>
<td>134,839 ± 29,866</td>
<td>22.1</td>
</tr>
<tr>
<td>FIRA, μm²</td>
<td>46,850 ± 17,860</td>
<td>38.1</td>
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**Table 1.** Morphometric Parameters for the Study Population, Ordered by Increasing Coefficient of Variation

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shifting of inner and outer retinal layers occurs. Therefore, according to the latter models, the size of the FAZ, axial length, degree of inner layer separation, and central thickness (CFT, OS, and ONL) should all correlate positively. Yet, to date, there has been no validation of this model with in vivo data from a normal population.

Takén together, our results are in accordance with the concept that the surface area of the FAZ is associated with the degree of separation of the inner retinal layers. Accordingly, the structural characteristics of the thickest foveae—that is, continuity of the INL over the fovea and a relatively thick central ONL—were very similar to those reported in ROP subjects.22,23 These subjects are known to have a small or absent FAZ.42 However, our finding of an inverse correlation between central ONL thickness and separation of inner layers on the one hand and the absence of clear correlation of the inner layers separation with OS length or axial length on the other hand, do not entirely fit with this model. Instead, the inverse correlation that we found between central ONL thickness and the separation of inner layers suggests that lateral separation of the inner layers counteracts, rather than promotes, centripetal shifting of cones. Accordingly, Marmor et al.20 and MacAllister et al.21 showed that in eyes with a complete absence of a foveal pit, a certain degree of foveal specialization (i.e., central OS packing and elongation) can be present. Hence, to some extent, inner and outer retinal specialization in the fovea may proceed independently. A seemingly normal OS morphology in ROP patients who had incomplete inner retinal separation was also reported by Hammer et al.25 Thus, the concept that thicker foveae are due to a premature arrest of the development of the macula as a whole is misleading. We would rather suggest describing these cases as having solely premature interruption of inner layer separation, which does not presume about the maturation of the outer retina.

Potential limitations to these findings need to be acknowledged. The shape and structure of the fovea were largely independent of axial length, except for pit diameter which correlated negatively with axial length. The interpretation of this latter correlation, however, is uncertain, given that the quantitative relationship between pixel measures and actual size of measured structures remains uncertain. In a separate study in contact lens wearers, we observed that lateral, but not axial, measures were significantly influenced by refraction in such a way that myopic refraction was associated with decreased pit diameter (Paquez M, et al., unpublished data, 2011). This may account for the inverse relationship that we found between AL and pit diameter. On the other hand, such refraction-induced bias may have weakened other correlations referring to lateral measures such as pit cross-sectional surface and FIRA. Such an error may also account for similar relationships between foveal shape and refraction that were reported in other studies.

Hammer et al.25 have suggested the use of foveal thickness at midheight to characterize foveal shape. We preferred not to retain this parameter in our study, because we believe that it overlaps rather than summarizes other parameters related to foveal shape (foveal pit height and width). Moreover, changes in foveal width at midheight have equivocal significance (change in ONL thickness and/or of inner layer thickness).

It has also to be kept in mind that there are some limitations to the histologic correspondence of OCT images. Few studies have been conducted in an attempt to correlate OCT imaging to histology, and there are remaining uncertainties regarding the anatomic correspondence of the outer layer.43,44 For instance, what is termed the ONL contains in fact the photoreceptor nuclei, the axons of photoreceptors (the Henle fibers), and Müller cell bodies; hence, there may not be a strict correspondence between the central ONL thickness as defined by OCT and the actual amount of foveal cones. Also, we cannot ensure that we measured the length of central foveal cone OS, which is a very small zone that may have been missed because of microsaccades during scan acquisition. Other limitations relate to the intrinsic features of eye growth, as growth rate during the formation of the foveal pit may indeed not correlate strictly with the axial length of adult eyes.

To conclude, we found that, in a normal population, foveal structure strongly correlates with its neurovascular organization. Our findings support a developmental model in which the size of the FAZ determines the extent of centrifugal migration of inner retinal layers, which itself counteracts the centripetal shifting of cone photoreceptors. In the near future, a better knowledge of foveal anatomy should be obtained by combin-
ing technologies such as high speed OCT, high resolution OS imaging by adaptive optics,\(^\text{46}\) and noninvasive measure of the FAZ.\(^\text{47}\) It would also be of interest to further document the relationship between fundus pigmentation and foveal structure, and, more important, the functional correspondence of such structural variability. Such approaches may significantly improve our understanding of foveal function and diseases.

References


