Retinal Capillary Density and Foveal Avascular Zone Area Are Age-Dependent: Quantitative Analysis Using Optical Coherence Tomography Angiography

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Purpose. The purpose of this study was to quantify retinal capillary density and the foveal avascular zone (FAZ) area in normal subjects according to age, using optical coherence tomography angiography (OCTA).

Methods. All eyes in this cross-sectional study underwent OCTA using RTVue XR Avanti with AngioVue. OCTA scans were analyzed and processed, and vessel density and FAZ dimensions were calculated.

Results. A total of 113 normal eyes from 70 subjects were included (30 males, 40 females; mean 48 ± 20 years of age). The mean vessel density and FAZ dimensions were significantly smaller in the superficial retinal capillary plexus (SCP) than in the deep retinal capillary plexus (DCP), using quantitative OCTA analysis (all $P < 0.0001$). With 3 × 3-mm scans, the mean vessel density was 13.431 ± 1.758 mm^{-1} in the SCP, 18.812 ± 1.796 mm^{-1} in the DCP, and 5.913 ± 1.308 mm^{-1} and 10.447 ± 1.262 mm^{-1} with 6 × 6-mm scans in the SCP and DCP, respectively. Mean FAZ areas were 0.289 ± 0.108 mm^2 at the SCP and 0.614 ± 0.200 mm^2 at the DCP. Age was a predictor of SCP and DCP vessel density and FAZ area in the SCP. Vessel density decreased 0.0393 mm^{-1} (0.26%) per year in the SCP and 0.0574 mm^{-1} (0.27%) per year in the DCP. FAZ areas increased 0.0014 mm^2 (0.63%) and 0.0011 mm^2 (0.20%) per year in the SCP and DCP, respectively.

Conclusions. SCP and DCP vessel density decreased with increasing age, while FAZ area increased with age. Normal age-matched measurements provide important standardized values that may facilitate management of retinal vascular disorders.

Keywords: foveal avascular zone, OCT angiography, OCTA, optical coherence tomography angiography, retinal capillary plexus

The macula is one of the most metabolically active tissues of the body and derives its oxygen supply from multiple retinal capillary plexuses.[1,2] The superficial retinal capillary plexus (SCP) is found mainly in the nerve fiber layer adjacent to the optic nerve, where it is referred to as the radial peripapillary plexus and progressively migrates into the ganglion cell layer toward the central macula.[3] The intermediate capillary plexus and deep retinal capillary plexus (DCP) are located at the inner and outer borders of the inner nuclear layer, respectively, and comprise the other major vascular layers of the macula.[4–8]

Recent retinal imaging advancements using optical coherence tomography angiography (OCTA) have opened a window with which to directly evaluate the microvasculature of the retina. Although fluorescein angiography can identify the SCP, this imaging modality poorly visualizes the DCP and choroid. OCTA, on the other hand, uses amplitude or phase decorrelation technology with high-frequency and dense volumetric scanning to detect blood flow and to visualize blood vessels at various depth-resolved levels of the retina and choroid, including the DCP.[9]

Although several studies have used OCTA to evaluate various pathological abnormalities involving the DCP in vascular disorders such as diabetic retinopathy and in degenerative diseases such as age-related macular degeneration (AMD), very few robust studies of healthy eyes exist to validate the OCTA findings in abnormal eyes. We used OCTA analysis to calculate the vascular density of the SCP and DCP and to measure the dimensions of the foveal avascular zone (FAZ) at the level of the SCP and DCP in normal eyes. Previous studies have shown that the FAZ area may be independently affected by increased age, but these findings have been inconsistent.[10–13] Furthermore, vessel density of the SCP and DCP has previously been found to decrease with increasing age, although sample size and age distributions were limited and not validated.[14–16] In the present study, OCTA vessel density and FAZ analysis was performed on both the SCP and the DCP in normal eyes across nearly all decades of life, and findings were compared to those in previously published results. In a select group of eyes, the measurements were repeated to assess the accuracy of reproducibility.

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Methods

This prospective study was approved by the University of California Los Angeles Institutional Review Board and adhered to the tenets of the Declaration of Helsinki and Health Insurance Portability and Accountability Act. Informed consent was obtained from each subject before OCTA imaging. A total of 74 subjects were recruited for this study, and a total of 128 eyes were evaluated. Inclusion criteria were volunteers with no evidence of retinal disease or ocular media opacity as evaluated by dilated fundus examination. Exclusion criteria included poor quality images with significant artifact, inaccurate or incorrect segmentation at the level of the SCP and DCP, or subject's inability to abstain from blinking or movement during image acquisition.

OCTA imaging was performed using the RTVue XR Avanti spectral-domain OCT device with AngioVue software (version 2015.1.1.98; Optovue, Inc., Freemont, CA, USA) with a light source at 840 nm, a bandwidth of 45 nm, and an A-scan rate of 70,000 scans per second. A 3 × 3-mm and a 6 × 6-mm cube scan were acquired containing 304 × 304 scans each. Each B-scan was repeated at each cross-section in the fast scan axis to separate static tissue from blood flow signals. Two OCTA volume scans with orthogonal fast-scan directions (horizontal and vertical) were acquired for each eye and then merged to minimize motion artifact.[17,18] The signal-to-noise ratio was improved with split-spectrum amplitude decorrelation technology (SSADA).[19]

Each scan was automatically segmented by the AngioVue software in order to visualize the superficial and deep retinal capillary plexuses of the retina. The SCP en face OCTA image was segmented with an inner boundary 3 μm below the internal limiting membrane and an outer boundary set at 15 μm below the inner plexiform layer. The DCP en face OCTA image was segmented with an inner boundary 15 μm below the inner plexiform layer and an outer boundary at 70 μm below the inner plexiform layer. All scans were reviewed to ensure correct segmentation and sufficient image quality and were repeated if deemed inadequate for analysis. Eyes with persistently low-quality scans were excluded from the analysis.

Quantitative analyses of the vessel density and the FAZ at the levels of the SCP and DCP were performed using the en face OCTA projection images by one trained reader. OCTA images were opened in image analysis ImageJ version 1.49 software[20] (provided in the public domain by the U.S. NIH) in order to "binarize" and skeletonize the images, showing each blood vessel as a 1-pixel-wide line. ImageJ software was also used to manually measure the greatest linear dimensions of the FAZ in both the horizontal and the vertical axis (Fig. 1). The vessel density and FAZ area were determined using the image processing program GIMP version 2.8.14 (provided in the public domain by http://gimp.org). Vessel density was calculated from the skeletonized images of all scans as [(pixels of vessels) × (scan width in mm/304)/(area in mm^2)] in mm^{-1}.[21,22] The FAZ was manually outlined in original 3 × 3-mm scans, and its area was calculated as [(pixels of FAZ) × $(3/304)^2$] in mm^2.

Statistical analysis was performed using Excel software (Microsoft, Redmond, WA, USA) for Macintosh (2011 version 14.6.0; Apple, Inc., Cupertino, CA, USA) with SAS Add-In 6.1 for Microsoft Office (SAS, Cary, NC, USA). Because vessel density may be correlated between the 2 eyes of a single patient, one primary eye was selected for analysis at random for each patient to ensure that each data point could be assumed to be independent from each other. Differences between males and females, right and left eyes, and predefined age groups for the primary eye were calculated using independent T tests assuming unequal variances. The paired T test was used to compare vessel densities and FAZ size between the primary and its fellow eye. A two-tailed statistic was used for all calculations. Missing variables were not imputed. Statistical significance was set at 0.05. Scatterplots of the slope of the best-fit trend line in the vessel density and FAZ area versus age were used to calculate the respective annual change.

Results

A total of 74 subjects (128 eyes) were imaged during the study period. Normal eyes (113) from 70 subjects were included in the study (Table 1) based on the quality of their OCTA images. The sample included 30 males (48 eyes) and 40 females (65 eyes); mean ± SD age was 48 ± 20 years (range, 9–88 years). Each eye yielded 2 en face OCTA images per 3 × 3-mm and 6 × 6-mm scan, with 1 image segmented at the level of the SCP and the other at the level of the DCP (Fig. 1). The SCP images consisted of predominantly radially oriented large vessels with interconnected ladder-like capillaries centered on the FAZ. The DCP images consisted of a denser and more complex distribution of fine capillaries with multifocal spoke-like orientations surrounding the fovea. As previously described, the borders of the FAZ were found to be more clearly defined at the level of the SCP and were more indefinite and obscured in the DCP images.[23]

The mean vessel density (Table 2) of eyes included in the analysis was 13.431 ± 1.758 mm^{-1} in the SCP and 18.812 ± 1.796 mm^{-1} in the DCP for 3 × 3-mm OCTA images. In the 6 × 6-mm OCTA images, the mean vessel density was 5.913 ± 1.308 mm^{-1} and 10.447 ± 1.262 mm^{-1} in the SCP and DCP, respectively. Analysis of the FAZ (Table 3) in 3 × 3-mm scans yielded a mean FAZ area of 0.289 ± 0.108 mm^2 at the level of the SCP and 0.614 ± 0.200 mm^2 at the level of the DCP. In the SCP, the mean greatest linear dimension (GLD) horizontally was 0.644 ± 0.134 mm and vertically was 0.606 ± 0.132 mm. The DCP had a mean GLD of 0.959 ± 0.169 mm horizontally and 0.828 ± 0.136 mm vertically. Across all age groups, the mean vessel density and FAZ dimensions were significantly smaller in the SCP than in the DCP in OCTA scans (all, $P < 0.0001$).

The results from 3 × 3-mm OCTA images were compared between two consecutive decades across all age groups. A statistically significant difference in SCP vessel density was found between subjects aged 60–69 and subjects aged 70–79 ($P = 0.029$); for DCP vessel density, significant differences were found between subjects aged 40–49 and 50–59 years of age ($P = 0.033$) as well as between subjects aged 60–69 and 70–79 years of age ($P = 0.003$). Results were also compared between near-tertile age groups of subjects aged 35 years or less ($n = 25$), 36–64 years ($n = 27$), and 65 years or older ($n = 18$). Statistically significant decreases in SCP and DCP vessel density existed between the lowest and middle tertiles ($P = 0.007$ in SCP, $P = 0.002$ in DCP) and between the middle and highest tertiles ($P = 0.035$ in SCP, $P = 0.001$ in DCP).

The values for vessel density and FAZ dimensions were similar in left and right eyes and between males and females. A negative correlation was found between age and vessel density and a positive correlation between age and FAZ area (Fig. 2). The average annual reduction in vessel density with 3 × 3-mm OCTA scans was 0.0393 mm^{-1} (0.26%) in the SCP and 0.0574 mm^{-1} (0.27%) in the DCP and was 0.0156 mm^{-1} (0.24%) in the SCP and 0.0382 mm^{-1} (0.31%) in the DCP with 6 × 6-mm OCTA scans. The average annual increase in FAZ area was 0.0014 mm^2 (0.63%) and 0.0011 mm^2 (0.20%) at the levels of the SCP and DCP, respectively.

An additional analysis of a subset of 17 subjects who received follow-up scans within the study period was performed. The mean age ± SD of this group was 53 ± 20

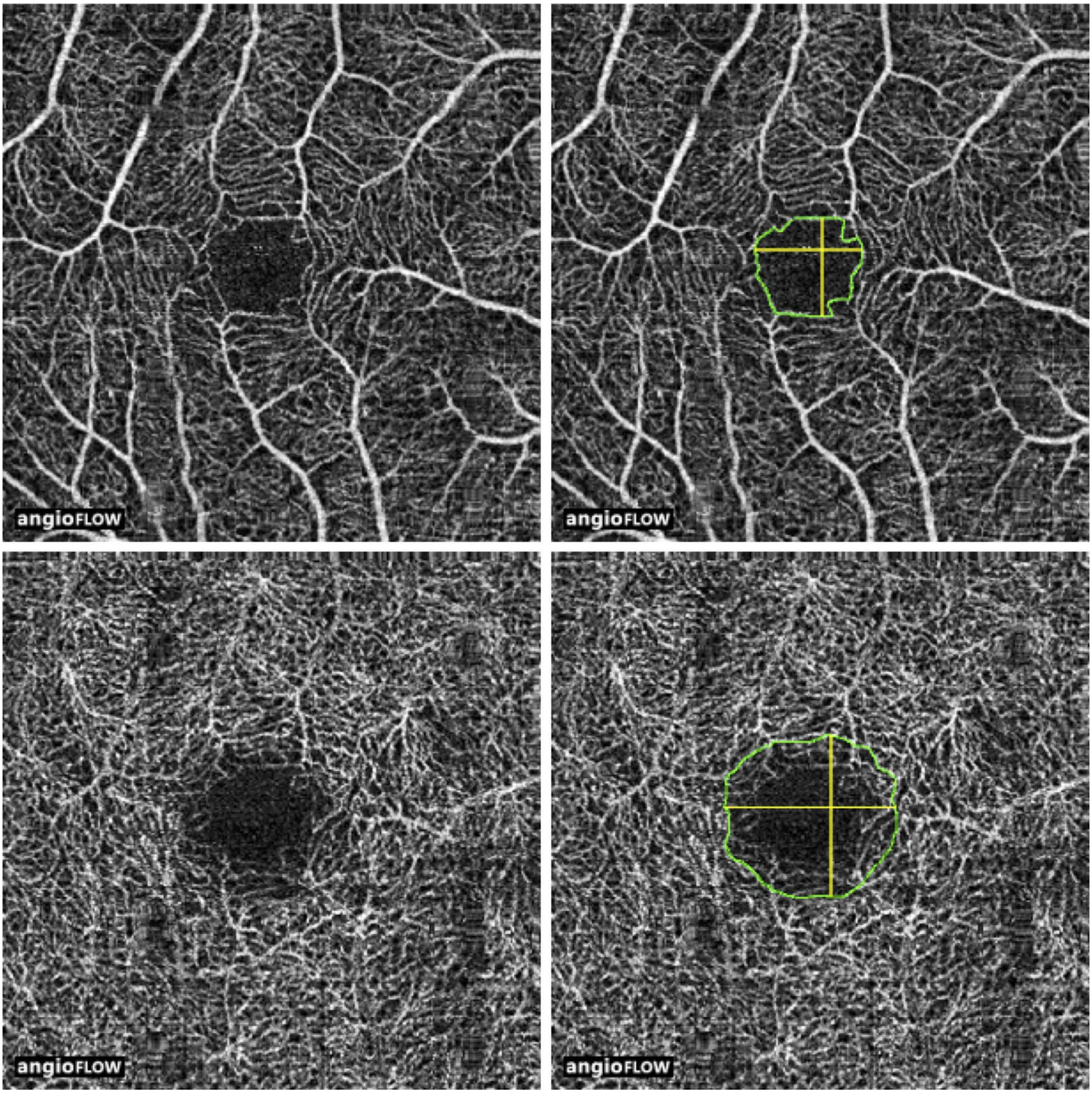

FIGURE 1. Optical coherence tomography angiography 3 × 3-mm scans segmented at the SCP (*top, left*) and the DCP (*bottom, left*). Manual outlining (*green*) of the borders of the FAZ and identification of the greatest linear dimension in the horizontal and vertical axis in the SCP (*top, right*) and DCP (*bottom, right*) are demonstrated. Projection artifact from the vessels surrounding the superficial FAZ can be seen within the borders of the deep FAZ (*bottom, right*).

TABLE 1. Subject Characteristics

Variable	Value
Mean age, y	48 ± 20
Sex	
Males (%)	30 (42.86)
Females (%)	40 (57.14)
Eye	
Right	64 (56.64)
Left	49 (43.36)

Data are mean ± SD or n (%).

years of age and mean ± SD follow-up time was 6.8 ± 2.0 months. The mean vessel density was not significantly different at either the level of the SCP ($P = 0.90$) or the level of the DCP ($P = 0.84$) with 3 × 3-mm scans or the level of the SCP ($P = 0.27$) with 6 × 6-mm scans between initial and follow-up visits. The mean vessel density of the DCP in 6 × 6-mm scans was significantly different ($P = 0.01$) at follow-up. The FAZ area was not statistically different at the follow-up visit in the SCP ($P = 0.61$) and DCP ($P = 0.43$), nor were the GLDs horizontally ($P = 0.37$ in SCP; $P = 0.94$ in DCP) and vertically ($P = 0.89$ in SCP; $P = 0.83$ in DCP) at the level of both plexuses.

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Table 2. Quantitative Analysis of Vessel Density (mm^{-1}) According to Age and Sex

	3 × 3-mm OCTA Scans		6 × 6-mm OCTA Scans	
Variable	**SCP**	**DCP**	**SCP**	**DCP**
Overall	13.431 ± 1.758	18.812 ± 1.796	5.913 ± 1.308	10.447 ± 1.262
Age, y				
<20	14.854 ± 1.023	19.594 ± 1.115	7.154 ± 0.207	11.361 ±0.313
20–29	13.979 ± 1.891	19.716 ± 1.521	6.077 ± 1.637	11.332 ± 0.968
30–39	14.048 ± 1.640	20.201 ± 1.521	5.724 ± 1.637	10.834 ± 0.968
40–49	13.933 ± 1.317	19.646 ± 1.380	6.275 ± 1.188	11.079 ± 1.088
50–59	12.932 ± 1.613	18.276 ± 1.812	6.097 ± 1.299	10.145 ±1.297
60–69	13.342 ± 1.329	18.260 ± 0.950	5.231 ± 1.210	8.523 ± 0.622
70–79	11.957 ± 1.663	16.822 ± 1.101	5.440 ± 1.577	9.875 ± 0.913
≥80	12.145 ± 2.615	16.438 ± 2.043	5.591	8.699
Sex				
Male	13.384 ± 1.704	19.105 ± 1.755	5.453 ± 2.892	10.435 ± 5.170
Female	13.465 ± 1.818	18.592 ± 1.817	6.263 ± 3.198	10.457 ± 5.255

Data are mean ± SD.

Discussion

Although the clinical benefit of OCTA has yet to be fully elucidated, recent advancements in OCTA technology have enabled more precise descriptions and analyses of the retinal microvasculature. Conventionally, fluorescein angiography has been the gold standard imaging modality for identifying and evaluating the retinal capillary system. However, this evaluation has been predominantly limited to the SCP as the deep capillary system is poorly visualized with conventional dye-based angiography systems.[5,24] By contrast, OCTA provides depth-resolved imaging and segmentation of the microvascular layers of the macula, allowing separate evaluation and quantification of the SCP versus the DCP. This has been a critical breakthrough as it has become evident that there can be preferential ischemia at the level of the DCP in various retinal vascular diseases such as diabetic retinopathy, retinal vascular occlusion, and sickle cell retinopathy.[3,4,25–31] These studies underscore the importance of reporting data from the SCP and DCP in normal eyes in order to validate the abnormal OCTA findings in retinal vascular diseases.

This is the first study of its size to report the retinal microvascular density and the FAZ dimensions at the level of the SCP and DCP by decade of life in a heterogeneous normal population. Previous studies have shown a decrease in total retinal blood flow associated with an increase in FAZ area with increasing age.[14,32,33] In a study of Chinese patients with healthy eyes, using OCTA, Yu et al.[14] found decreases in the SCP parafoveal flow index and vessel area density with increasing age at a rate of 0.6% and 0.4% per year, respectively. Shahlaee et al.[15] reported mean parafoveal vascular densities of 46% and 52% in the superficial and deep vascular networks, respectively, and also noted negative correlations with age. In a separate study, Shahlaee et al.[23] measured a mean superficial FAZ area of 0.27 mm^2 and deep FAZ area of 0.34 mm^2. That study also noted a larger mean horizontal FAZ length than vertical length in the SCP, as well as a 17% and 13% increase in the horizontal and vertical length, respectively, when measured in the DCP. Comparing histological and speckle variance OCT images, Mammo et al.[34] demonstrated that capillaries in the DCP terminated farther from the fovea than capillaries in the SCP, leading to an apparently larger FAZ in the deep layer.

The present study corroborates and expands upon previously published results of vessel density and FAZ measurements by OCTA analysis in several important ways. First, our data provide vessel density analysis of the entire en face area of both the 3 × 3-mm and the 6 × 6-mm OCTA scans, which is more clinically feasible and applicable than separate foveal and

Table 3. Quantitative Analysis of FAZ Dimensions in 3 × 3-mm OCTA Scans According to Age and Sex

	FAZ Area, mm^2		FAZ Greatest Linear Dimension, mm			
Variable	**SCP**	**DCP**	**SCP Horizontal**	**SCP Vertical**	**DCP Horizontal**	**DCP Vertical**
Overall	0.289 ± 0.108	0.614 ± 0.200	0.644 ± 0.134	0.606 ± 0.132	0.959 ± 0.169	0.828 ± 0.136
Age, y						
<20	0.210 ± 0.129	0.492 ± 0.242	0.550 ± 0.186	0.493 ± 0.128	0.828 ± 0.259	0.725 ± 0.189
20–29	0.294 ± 0.112	0.672 ± 0.256	0.629 ± 0.115	0.615 ± 0.152	0.971 ± 0.177	0.868 ± 0.161
30–39	0.249 ± 0.075	0.550 ± 0.116	0.593 ± 0.109	0.573 ± 0.117	0.909 ± 0.115	0.771 ± 0.082
40–49	0.317 ± 0.039	0.650 ± 0.167	0.707 ± 0.057	0.663 ± 0.090	1.053 ± 0.151	0.907 ± 0.117
50–59	0.313 ± 0.132	0.642 ± 0.241	0.699 ± 0.110	0.640 ± 0.182	0.969 ± 0.155	0.839 ± 0.164
60–69	0.280 ± 0.110	0.649 ± 0.168	0.622 ± 0.145	0.579 ± 0.107	0.957 ± 0.172	0.843 ± 0.090
70–79	0.293 ± 0.122	0.554 ± 0.234	0.641 ± 0.172	0.604 ± 0.131	0.956 ± 0.218	0.808 ± 0.174
≥80	0.429 ± 0.080	0.744 ± 0.210	0.810 ± 0.090	0.720 ± 0.063	1.078 ± 0.125	0.883 ± 0.118
Sex						
Male	0.276 ± 0.091	0.606 ± 0.175	0.637 ± 0.113	0.595 ± 0.134	0.949 ± 0.147	0.827 ± 0.123
Female	0.300 ± 0.119	0.620 ± 0.219	0.650 ± 0.150	0.614 ± 0.131	0.967 ± 0.186	0.829 ± 0.146

Data are mean ± SD.

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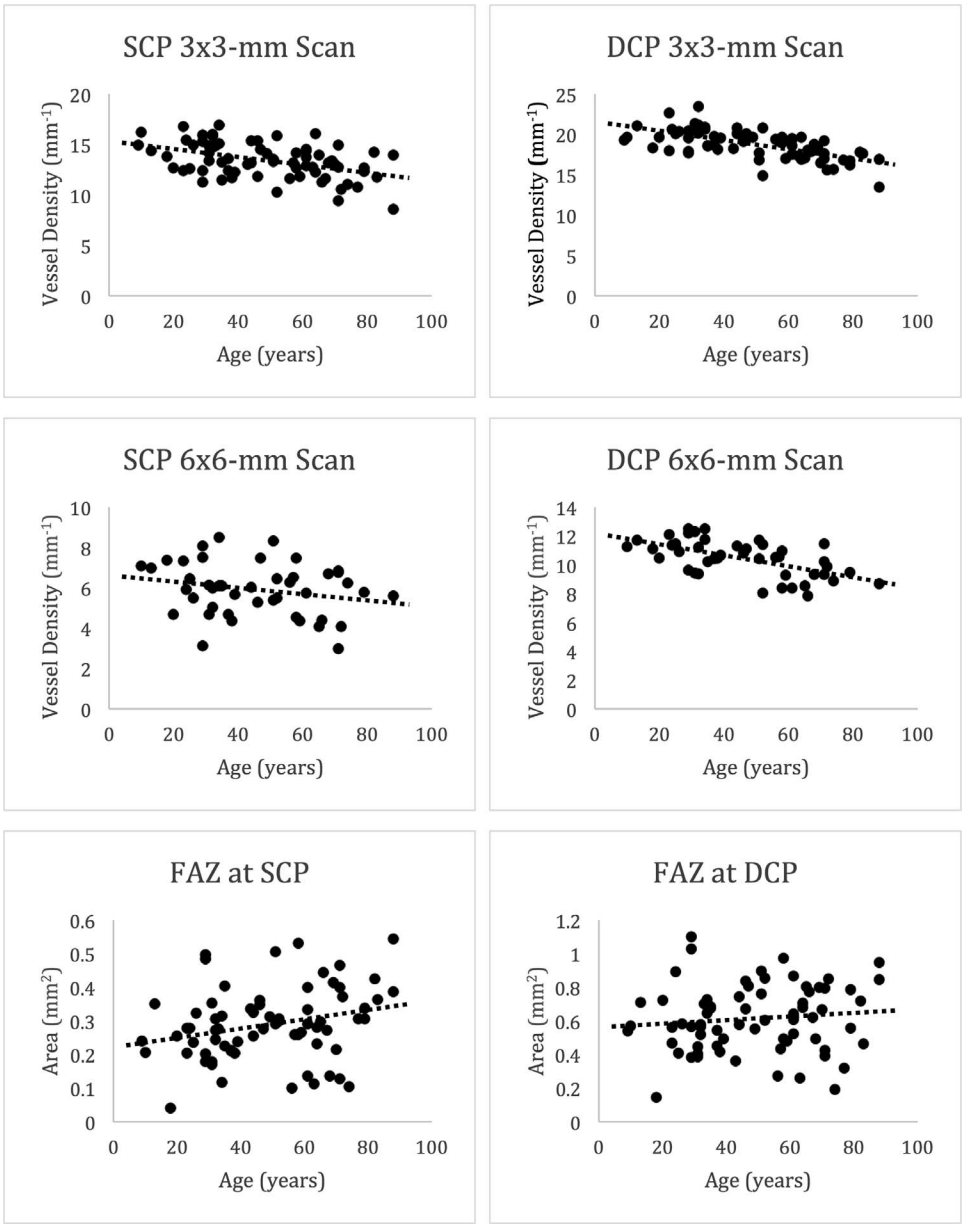

FIGURE 2. Scatterplots of data according to age show the relationship between vessel density (mm^{-1}) and foveal avascular zone area (mm^2) with increasing age (years). The *dotted lines* represent the corresponding linear regression line with respect to age.

parafoveal calculations. Second, we report vessel density in units of mm^{-1}, which more accurately reflects perfusion of both retinal capillary plexuses. Third, our study sought to quantify and validate annual rates of change in vessel density and FAZ measurements. In addition, we performed a reproducibility analysis and validated the accuracy of repeatable measurements, particularly with the 3 × 3-mm scans. Reproducibility of 6 × 6-mm scans of the DCP was not validated by this study.

Our study analyzed 113 healthy eyes from 70 subjects of various ethnic backgrounds whose ages ranged from 9 to 88 years old (mean: 48 ± 20 years). Compared to the study of parafoveal vessel area density by Yu et al.,[14] our results show a smaller rate of change in vessel density with increasing age occurring in the SCP with an annual rate of reduction of 0.04 mm^{-1} (0.26%) per year in 3 × 3-mm scans. The annual change in density at the level of the DCP was similar at 0.06 mm^{-1} (0.27%) per year. It should be emphasized that previous studies calculated vessel area density by comparing the area occupied by retinal vessels to defined areas of interest (i.e., foveal or parafoveal regions), reporting vessel area density as a percent of the total.

We report vessel density in units of mm^{-1} since we believe this value is more important for comparison in pathologic studies. Previous reports on neovascular complexes in AMD[9,35,36] and paracentral acute middle maculopathy lesions in retinal vascular diseases[28] have quantified changes in vessel density based on the presence or absence of finer vessels and capillaries which are more accurately quantified in units of mm^{-1}. Since current OCTA technology produces two-dimensional en face representations of volumetric scan data, quantitative analysis of capillary vessel density is limited to the measurement of vessel length per surface area (i.e., $mm/mm^2 = mm^{-1}$) as opposed to vessel length per volume ($mm/mm^3 = mm^{-2}$). Quantifying the presence of vessels, that is, vessel length, in the macula holds more significance with

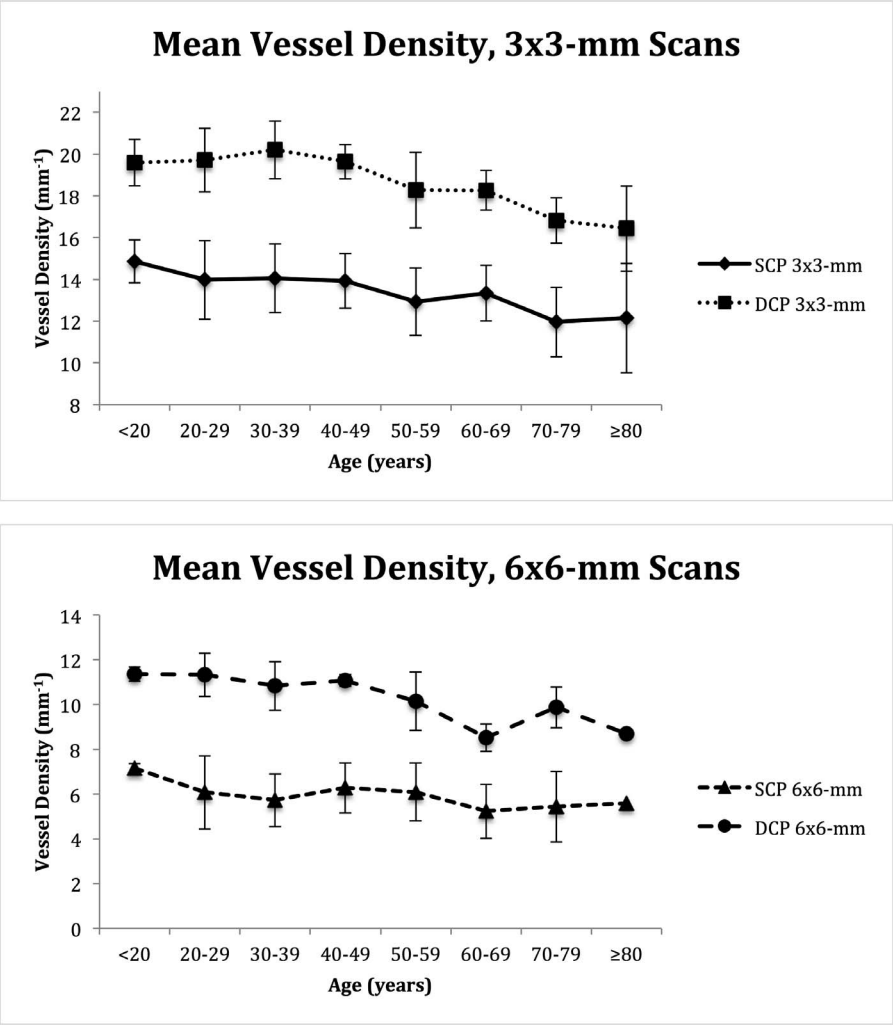

Figure 3. Line graphs show the relationship between mean vessel densities (mm^{-1}) and age in decades with error bars set to one standard deviation.

regard to normal retinal tissue perfusion than the caliber of those vessels, especially when interrogating a capillary plexus. OCTA images segmented at the level of the SCP clearly include large arteries and veins, which do not participate in oxygen and nutrient exchange in the retina. Therefore, calculations that take into account the caliber of retinal vessels, such as total vessel area per area of interest (percentage) via thresholded images,[14–16] or local fractal dimensions,[37] may overestimate retinal tissue perfusion.

In the analysis of 3 × 3-mm scans, our results show a decrease in mean vessel density between subjects 40 to 49 years of age and those 50 to 59 years of age that is trending toward significance in the SCP ($P = 0.097$) and is statistically significant ($P = 0.033$) in the DCP (Fig. 3). Furthermore, a statistically significant decrease in mean vessel density exists in both the SCP ($P = 0.029$) and DCP ($P = 0.003$) in a comparison of subjects 60 to 69 to subjects 70 to 79 years of age. We also analyzed the 3 × 3-mm scan data by comparing larger near-tertile age groups, that is, subjects 35 years of age or less, 36 to 64 years of age, and 65 years of age or older. We found statistically significant decreases in SCP and DCP vessel density between the lowest and middle tertiles ($P = 0.007$ in SCP; $P = 0.002$ in DCP) and between the middle and highest tertiles ($P = 0.035$ in SCP; $P = 0.001$ in DCP). This is the first study to validate an age-dependent change in the retinal capillary plexus vessel density. The FAZ area was not found to be statistically different between any of these tertiles at either the SCP or DCP. Larger data sets analyzing healthy eyes from all age groups and ethnicities will be necessary in order to develop screening guidelines to detect variations in vessel density which could serve as an early indicator of change secondary to AMD or retinal vascular diseases that commonly affect older patients.

In the current study we found no statistical difference between males and females in the mean vessel density of the SCP or DCP in both 3 × 3-mm and 6 × 6-mm OCTA scans. The annual decrease in vessel density at the level of the SCP was greater for males at 0.0528 mm^{-1} (0.34%) per year than for females at 0.0344 mm^{-1} (0.23%) per year with 3 × 3-mm scans. In the DCP the annual decreases in vessel density were similar for both sexes at 0.0557 mm^{-1} (0.26%) per year for males and 0.0578 mm^{-1} (0.27%) per year for females. These results support those in the study by Yu et al.,[14] showing that annual decreases in the parafoveal vessel area density of the full retinal thickness were greater in male than in female subjects.[15]

The mean FAZ area was found to be 0.289 ± 0.108 mm^2 and 0.614 ± 0.200 mm^2 in the SCP and DCP, respectively, demonstrating a twofold increase in FAZ area at the level of the deep plexus. In both males and females, the horizontal GLD was greater than the vertical GLD at the level of both capillary plexuses, which is consistent with findings by Shahlaee et al.[23]

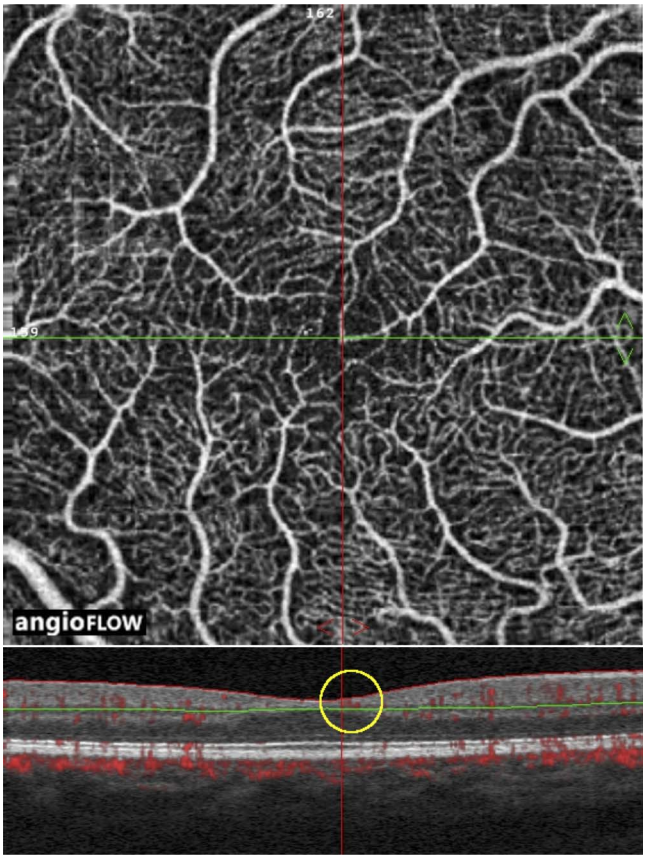

FIGURE 4. OCTA 3 × 3-mm scan segmented to show the superficial retinal capillary plexus (*top*) showing minimal or nearly absent foveal avascular zone in a healthy 18-year-old female with visual acuity of 20/20. Coregistered OCT B-scan (*bottom*) taken at the level of the *green horizontal line* in the OCTA above, with *red cross sectional* angiography overlay highlighting blood flow. Note the normal appearance of the foveal pit depression despite vessels encroaching on and passing through the fovea (*circle*).

As previously reported, the FAZ borders were more clearly delineated at the level of the SCP than at the level of the the DCP.[11,38] Because split-spectrum amplitude-decorrelation angiography measurements are derived from changes in reflections and backscattering of light, the larger vessels of the SCP often resulted in projection artifacts that were visualized at the level of the DCP, obscuring the FAZ borders at that level.[15,23] Careful comparison between the retinal layers was needed at times to resolve the FAZ borders of the deep plexus. Our results showed FAZ areas were not significantly different between males and females in the SCP ($P = 0.174$) or the DCP ($P = 0.383$). These results support the findings of Samara et al.,[11] who demonstrated no differences in FAZ area between males and females. Across all subjects, our results showed a positive correlation of the FAZ area with increasing age in the SCP. This is in contrast to Samara et al.[11] but consistent with Shahlaee et al.[23]

A reproducibility analysis was performed in a subset of 27 eyes (24%) in order to confirm the reliability of vessel density and FAZ dimension calculations on OCTA images. The results from this analysis validated the reproducibility of capillary density and FAZ measurements made on 3 × 3-mm OCTA scans. For 6 × 6-mm scans, however, the results demonstrated a statistically significant change in DCP vessel density at follow-up. This indicates further investigation is needed to validate the ability of the RTVue-XR Avanti device to accurately resolve the deep retinal capillary plexus in 6 × 6-mm OCTA scans.

Of note, three healthy subjects without history of albinism or nystagmus showed minimal or potentially absent FAZs despite the presence of a normal foveal pit and preserved visual function. Previously, Marmor et al.[39] studied four patients who showed absence or near absence of the FAZ in the setting of fovea plana. In these patients, vessels were seen crossing the foveal center on fundus photos and fluorescein angiography, and multifocal electroretinography responses were within normal limits and with normal waveforms across the fovea and posterior pole. The authors concluded that neither the FAZ nor the foveal pit is critical to development of cone lengthening and spatial packing that presumably results in higher visual resolution. Dolz-Marco et al.[40] reported OCTA findings from three patients with fovea plana, demonstrating fusion of the SCP and DCP, absence of an FAZ, and flattening of the foveal pit. In our study, by coregistering the OCTA scans with OCT B-scans from the same location, we observed normal foveal pits with widened outer nuclear layers and cone outer segment lengthening despite minimal or absent FAZ (Fig. 4). Because each subject maintained normal visual acuity, it was determined that they were normal variants and were included in the final analysis. These results support the conclusion of Marmor et al.[39] that the FAZ is not critical for the normal structural development of the high visual acuity fovea or foveal pit.

Despite continued advancement in OCTA technology, we acknowledge some limitations in our study. As SSADA technology relies on the detection of blood flow, any movement of the patient's head or eyes during image acquisition resulted in varying degrees of motion artifact and decreased image quality. These complications were noted more often in the extremes of age groups. In addition, projection artifact of the large vessels of the SCP onto deeper retinal layers may have lead to artificially increased values of vessel density in the DCP.[41] More advanced algorithms that remove or correct for these types of artifacts will greatly improve the accuracy with which OCTA can identify vessels in their native location. This imminent advancement will permit a more real and distinct separation of superficial, intermediate, and deep retinal capillary plexuses and will vastly improve the reliability of measurements in both normal and pathological eyes. Finally, this study only used one trained reader to measure the dimensions of the FAZ. Previous studies have shown that manual identification of the FAZ using OCTA is reliable and accurate in the SCP but may vary in the DCP due to projection artifact obscuring the FAZ borders.[23] Even with these limitations, the results from this study are noteworthy as they include data from subjects in nearly every decade of life.

Age-matched measurements of the SCP and DCP in normal eyes provide important standardized values and may allow more accurate diagnosis and management of retinal vascular disorders. By continuing to perform OCTA analysis of healthy eyes across the lifespan, we hope to eventually establish normative data for vessel density and FAZ dimensions in both the superficial and the deep retinal capillary plexuses to aid in the early diagnosis of macular pathology and the preservation of vision into old age.

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