Superficial and Deep Macula Vessel Density in Healthy, Glaucoma Suspect, and Glaucoma Eyes

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Conclusions: SCP vessel densities have better diagnostic accuracy for detecting glaucoma than DCP vessel densities. Although the diagnostic accuracy of the macula SCP is relatively modest, it is more informative than the DCP.

Key Words: glaucoma, superficial capillary plexus, deep capillary plexus, OCT-A

Glaucoma is a multifactorial optic neuropathy characterized by the loss of retinal ganglion cells (RGCs), leading to narrowing of the neuroretinal rim, excavation of the optic nerve head (ONH), and structural damage to the inner retina. About half of these RGCs are located within the center of the macula. Although the pathophysiology of glaucoma remains undetermined, it is hypothesized that vascular factors have a significant role in its pathogenesis. Optical coherence tomography angiography (OCT-A) is a noninvasive imaging technology that facilitates the visualization of retinal microvasculature using the dynamic motion of red blood cells. OCT-A has been used to investigate vessel density measurements defined as the percentage of area occupied by vessels containing measurable flowing blood. Recent studies involving glaucoma patients have shown that vessel density has similar diagnostic accuracy and is strongly correlated with retinal nerve fiber layer (RNFL) thickness measurements. It has also been demonstrated that vessel density is significantly correlated with the severity of visual field (VF) damage defined by VF mean deviation (MD).

Furthermore, OCT-A reportedly can detect retinal microvasculature dropout in eyes with no detectable VF damage. OCT-A has effectively been used to noninvasively visualize the different capillary layers in the perifoveal retina, leading to a better understanding of their connectivity, structure, and function, which has not previously been feasible without a histologic approach. Macular superficial capillary plexus vessel density (SCPV) measurements are commonly assessed and visualized using OCT-A. SCPV has been shown to decrease in patients with glaucoma. Furthermore, SCPV reportedly is positively correlated with retinal thickness. Few OCT-A studies have focused on deep capillary plexus vessel density (DCPV) measurements in glaucoma, in part due to the presence of projection artifacts, which arise from superficial retinal vessels and reflect in deeper layers. Fortunately, there are now automated methods for projection artifact removal.
that facilitate the assessment of the deeper layers by removing most of the superficial capillary plexus (SCP) flow projections while maintaining the deep capillary plexus (DCP) density.27,36–38

The SCP, which includes vasculature from the RNFL and GCL and consists of internal limiting membrane (ILM) and inner plexiform layer (IPL), freely interrelates with the DCP, which comprises the inner nuclear (INL) and outer plexiform (OPL) layers, resulting in a complex vascular network of the macula38 that often is affected in glaucoma patients. It is therefore important to investigate the deeper retinal changes in glaucoma, as RGC dendrites form synapses to the different glial cells located in the INL, which in turn connect to the cell bodies of the photoreceptors in the outer nuclear layer and OPL. Moreover, these neurons can directly or indirectly affect other synapsed neurons by retrograde or anterograde degeneration.39,40

In glaucoma patients with central VF loss, lower macular DCPVD was found to be associated with the worse visual function (eg, VF central scotomas), but without significant correlation with structural tissue thinning.41 Eyes with relatively better visual function had denser DCP when compared with functionally worse eyes. Moreover, macular DCPV was independently associated with central VF deterioration in normal-tension glaucoma patients even when macular ganglion cell layer thickness was included in the model.

Given that the SCP and DCP are anatomically anastomosed to form the macular vascular supply, it is important to understand how DCP is affected in healthy and glaucomatous eyes.

MATERIALS AND METHODS

Participants enrolled in the longitudinal Diagnostics Innovations in Glaucoma Study (DIGS),42–44 who underwent macular OCT-A (AngioVue: Optovue Inc., Fremont, CA) imaging were included in this cross-sectional study. The research protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of California, San Diego. Informed consent was obtained from all participants.

Participants

All participants underwent a comprehensive ophthalmic examination, including best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure (IOP) using Goldmann applanation tonometry, gonioscopy, pachymetry, dilated fundus examination, stereophotography of the optic disc and macula, and VF testing. Inclusion criteria at study entry were greater than 18 years of age, best-corrected visual acuity of 20/40 or better, and open angles on gonioscopy. Patients with a history of ocular trauma or intraocular surgeries (except for uncomplicated cataract and uncomplicated glaucoma procedures), coexisting retinal diseases, nonglaucomatous optic neuropathy, uveitis, or high myopia (axial length >26.5 mm) were excluded from this study.

Participant’s eyes were divided into 3 diagnostic groups: healthy, glaucoma suspects, and glaucoma. Eyes from healthy individuals had IOP ≤21 mm Hg with no history of elevated IOP, normal-appearing optic discs with intact neuroretinal rim, and normal VF test results with the Humphrey Field Analyzer SITA standard 24-2 (Carl Zeiss Meditec, Dublin, CA) Swedish Interactive Thresholding Algorithm (pattern standard deviation within the 95% confidence limits and Glaucoma Hemifield Test results within normal limits). To be classified as a healthy subject, both eyes were required to meet the same criteria. The glaucoma suspect group included eyes with glaucomatous optic neuropathy (pre-perimetric glaucoma) or suspicious appearing optic nerves based on the review of stereoscopic ONH photographs, with or without high IOP (>21 mm Hg), and no evidence of repeatable glaucomatous VF damage. Eyes were classified as glaucomatous if they had at least 2 repeatable and reliable (≥33% fixation losses and false-negatives, and ≤33% false-positives) abnormal VF results with Glaucoma Hemifield Test outside normal limits or pattern standard deviation outside 95% normal limits with similar patterns of the glaucomatous defect as assessed by study investigators. A subject could have one eye in the glaucoma suspect group and the fellow eye in the glaucoma group. Glaucoma eyes were stratified into 3 severity groups based on 24-2 VF MD: (1) mild glaucoma: VF MD >−6 dB, (2) moderate glaucoma: VF MD between −6 and −12 dB, and (3) severe glaucoma: VF MD ≤−12 dB.45

OCT-A Image Acquisition

The Avanti AngioVue (OptoVue Inc.; software version 2017.1.0.151) was utilized to acquire HD 6×6 mm2 macula OCT-A scans. The scans consisted of merged Fast-X volume of 304 horizontal B-scans of 304 A-scans per B-scan and Fast-Y volume of 304 vertical B-scans of 304 A-scans per B-scan to minimize motion artifacts.

All vessel density measurements were acquired from the SCP (measured from the ILM to 10 μm below the IPL) and DCP (DCPVD) (measured from the INL to the OPL). Vessel density of the inner ring was measured in an annular region with an inner diameter of 1 mm and an outer diameter of 3 mm centered on the fovea for HD 6×6 mm2 scan size. Vessel density of the outer ring was measured in an annular region with inner and outer diameters of 3 and 6 mm, respectively for the larger scan.46,47 These measurements were automatically exported from the instrument. GCC (= RNFL+GCIPL) thickness measurements derived from the same scans were also included in the analysis.

All images included in this study were of good quality, based on qualitative review based on a standard protocol established by the University of California San Diego Image Data Evaluation and Analysis (IDEA) Reading Center. Images were considered of poor quality and excluded if they had a Scan Quality Index (SQI) of <4, signal strength index <48, poor clarity, motion artifacts, local weak signals due to floasters, off-centered fovea, and uncorrectable segmentation errors. In eyes with advanced glaucoma, a lower SQI score (SQI ≥3) was allowable as these patients tend to have a worse visual function within 10 degrees of fixation.48,49 In this study, 17 (20.0%) healthy eyes, 13 (33.3%) glaucoma suspect eyes, and 79 (32.9%) glaucoma eyes were excluded due to poor quality.

Projection Artifact Removal

Projection-resolved OCT-A DCP measurements have been described previously.27,36–38,50–52 In brief, projection artifacts from the DCP are automatically removed using OptoVue...
standard software, which is attained based on normalized OCT-A intensity (voxel-based) divided by OCT intensity. Depth cumulative OCT-A gradient intensity along the z-axis was used to differentiate in situ OCT-A nonprojection artifacts from projection artifacts by suppressing the projection artifacts to the background noise level. Only projection-resolved DCPVD measurements are reported.

Statistical Analysis

Patient and eye characteristics are presented as mean [95% confidence interval (CI)] for continuous data and count (%) for categorical data. Significance across groups was determined by analysis of variance and \( \chi^2 \) tests for continuous and categorical patient-level variables, with 2-sample \( t \) tests and \( \chi^2 \) tests used for pairwise comparisons. Linear mixed-effects models were used for continuous eye-level variables, with a random intercept included to account for within-patient correlation between eyes. A conditional \( F \) test was applied to these models to determine whether variation across the 3 disease groups was significant. To determine the significance of pairwise comparisons derived from the same models, \( t \) tests of the regression parameters and Satterthwaite approximation for degrees of freedom were used. Regression estimates for univariable and multivariable mixed models were calculated for whole image SCP and DCP from HD 6 × 6 mm\(^2\) scans. Variables in the univariable analysis with significance at \( P \)-value < 0.1 were included in the multivariable models.

Diagnostic accuracies for classifying healthy, glaucoma suspect, and glaucoma eyes were compared between SCPVD and DCPVD using age-adjusted and overall SQI-adjusted area under the receiver operating characteristic curve (AUC) for HD 6 × 6 mm\(^2\) scans, with CIs and hypothesis tests determined via a clustered bootstrap approach. We considered \( P \)-values < 0.05 to indicate statistical significance. All statistical analyses were performed using the R statistical software (version 3.5.2).

### RESULTS

Two hundred fifty-five eyes of 184 subjects consisting of 68 eyes from 44 healthy subjects, 26 eyes from 16 glaucoma suspects, and 161 eyes from 124 glaucoma patients were included. Of the 161 glaucoma eyes, 103 eyes had mild glaucoma, 33 eyes had moderate glaucoma, and 25 eyes had severe glaucoma. The healthy subjects were significantly younger [mean (95% CI): 53.3 (48.4, 58.2)] than the glaucoma suspect [60.8 (54.2, 67.3)] and glaucoma patients [70.2 (68.3, 72.1)] (\( P < 0.001 \)). Diabetes mellitus (DM) and hypertension (HTN) prevalence were significantly lower in healthy [DM: 0.0%, HTN: 34.1%] and glaucoma suspects [DM: 0.0%, HTN: 34.1%] compared with glaucoma patients [DM: 12.9%, HTN: 50.8%] (DM: \( P = 0.036 \), HTN: \( P = 0.041 \)).

Table 1 presents the patient and eye characteristics. The hemifield and parafoveal vessel densities had significant differences among the diagnostic groups. The SCPVD measurements between the suspect and glaucoma groups were not statistically significant between healthy and suspect eyes. Whereas differences in SCPVD measurements between the suspect and glaucoma eyes, as well as healthy and glaucoma eyes reached statistical significance (Table 2, Figs. 1, 2).

### TABLE 1. Patient and Eye Characteristics

|                      | Healthy | Glaucoma Suspect | Glaucoma | \( P \)       |
|----------------------|---------|------------------|----------|--------------|
| No. patients (eyes)  | 44 (68) | 16 (26)          | 124 (161)| <0.001†‡     |
| Age (y)              | 53.3 (48.4, 58.2) | 60.8 (54.2, 67.3) | 70.2 (68.3, 72.1) | <0.001†‡     |
| Sex                  |         |                  |          |              |
| Female               | 29 (65.9) | 11 (68.8) | 62 (50.0) | 0.101        |
| Race                 |         |                  |          |              |
| White                | 19 (43.2) | 9 (56.2) | 62 (50.0) | 0.430        |
| African              | 12 (27.3) | 2 (12.5) | 38 (30.6) |              |
| Asian                | 8 (18.2) | 4 (25.0) | 19 (15.3) |              |
| Others               | 5 (11.4) | 1 (6.2) | 5 (4.0) |              |
| Visual field 24-2 MD (dB) | -0.66 (-2.15, 0.83) | -0.91 (-3.37, 1.54) | -6.18 (-7.09, -5.27) | <0.001†‡     |
| Visual field 24-2 PSD (dB) | 1.6 (0.8, 2.5) | 1.9 (0.5, 3.3) | 6.0 (5.5, 5.5) | <0.001†‡     |
| IOP (mm Hg)          | 16.1 (14.9, 17.4) | 15.0 (13.0, 17.1) | 15.5 (14.7, 16.3) | 0.603        |
| CCT (µm)             | 541.6 (527.2, 556.0) | 539.3 (510.4, 557.4) | 542.4 (533.4, 551.3) | 0.804        |
| Axial length (mm)    | 24.5 (24.1, 24.9) | 24.6 (23.9, 25.2) | 24.6 (24.3, 24.8) | 0.966        |
| Diabetes             | 0 (0.0) | 1 (6.2) | 16 (12.9) | 0.036        |
| Hypertension         | 15 (34.1) | 4 (25.0) | 63 (50.8) | 0.041        |
| Scan Quality Index   | 8.0 (7.7, 8.4) | 7.3 (6.8, 7.8) | 7.0 (6.8, 7.2) | <0.001†‡     |

*Bold values indicate pairwise statistical significance (\( P < 0.05 \)).
†Healthy versus suspect.
‡Suspect versus glaucoma.
§CCT indicates central corneal thickness; dB, decibels; IOP, intraocular pressure; MD, mean deviation; PSD, pattern standard deviation.
similar trends as the whole image vessel density (Table 2, Figs. 1, 2).

Mean GCC thickness obtained from the HD 6×6 mm² scans was significantly greater in healthy eyes [all: 99.5 µm (96.3, 102.7 µm)] compared with glaucoma eyes [79.9 µm (78.0, 81.8 µm)] (P < 0.001). Mean GCC thickness was also significantly greater in glaucoma suspect [92.9 µm (87.6, 98.1 µm)] compared with glaucoma eyes [79.9 µm (78.0, 81.8 µm)] (P < 0.001). No statistically significant GCC thickness difference was found between healthy and glaucoma suspect eyes for the HD 6×6 mm² scans. This trend applies to all HD 6×6 mm² sectors (Table 3).

Univariable and multivariable regression analysis were completed to evaluate the association of SCP, DCP wiVD, and GCC measures with age, VF MD, IOP, overall SQI, HTN, and DM. In univariable analysis, SCP wiVD decreased with age, worsening VF MD, lower QI, and DM. VF MD had the strongest correlation with SCP wiVD (R² = 36.0) followed by age (R² = 22.6). A 1% decrease in HD 6×6 mm² SCP wiVD was associated with 1.61 dB (reciprocal of 0.62 from Table 4) decrease in MD. In contrast, a 1% decrease in HD 6×6 mm² DCP wiVD was associated with a 3.33 dB (reciprocal of 0.30 from Table 4) decrease in MD. Univariable analysis for GCC had similar trends to SCP. Multivariable analysis showed a significant association between SCP wiVD, DCP wiVD, and GCC measurements and age, VF MD, and SQI (Table 4).

As DM can influence SCPVD in glaucoma and GCC decreased with DM in the univariable analysis, we repeated the statistical analysis after excluding DM patients (data not shown). These results were very similar to those that included the DM patients. Age-adjusted and SQI-adjusted diagnostic accuracies were higher for GCC and SCPVD than DCPVD measurements. Specifically, the diagnostic accuracy for differentiating between healthy and glaucoma eyes was best for

| Table 2. Mean (95% Confidence Interval) Vessel Density by Classification From High-density 6×6 mm² Scans |
|---|---|---|---|---|
| Scan Layer | Sector | Healthy Eyes | Glaucoma Suspect Eyes | Glaucoma Eyes | Adjusted P |
| Superficial capillary plexus | Whole image (wivD) | 49.7 (48.3, 51.2) | 46.0 (43.6, 48.4) | 40.9 (40.0, 41.8) | < 0.001*† |
| Superior hemiﬁeld | 49.9 (48.4, 51.4) | 46.1 (43.7, 48.6) | 41.5 (40.6, 42.4) | < 0.001*† |
| Inferior hemiﬁeld | 49.6 (48.0, 51.1) | 45.8 (43.2, 48.4) | 40.3 (39.4, 41.3) | < 0.001*† |
| Inner parafovea | 52.2 (50.6, 53.8) | 49.5 (46.8, 52.1) | 45.0 (44.8, 46.0) | < 0.001*† |
| Outer parafovea | 50.2 (48.7, 51.7) | 46.1 (43.6, 48.6) | 41.2 (40.2, 42.1) | < 0.001*† |
| Deep capillary plexus | Whole image (wivD) | 50.6 (48.9, 52.4) | 47.3 (44.4, 50.1) | 45.7 (44.6, 46.7) | 0.916 |
| Superior hemiﬁeld | 50.8 (49.1, 52.5) | 47.6 (44.8, 50.4) | 46.0 (45.0, 47.1) | 0.970 |
| Inferior hemiﬁeld | 50.4 (48.6, 52.3) | 46.9 (43.9, 50.0) | 45.3 (44.2, 46.4) | 0.824 |
| Inner parafovea | 54.9 (53.6, 56.3) | 53.0 (50.8, 55.2) | 51.6 (50.8, 52.4) | 0.968 |
| Outer parafovea | 51.8 (49.9, 53.7) | 48.2 (45.1, 51.4) | 46.4 (45.2, 47.5) | 0.929 |

Bold values indicate mixed model statistical significance (P < 0.05).
*Healthy versus glaucoma.
†Suspect versus glaucoma.
wivD indicates whole image vessel density.

FIGURE 1. Examples of optical coherence tomography angiography vessel density maps for superficial capillary plexus (SCP) and deep capillary plexus (DCP) high-density 6×6 mm² scans in healthy, suspect, and glaucoma eyes showing the inner and outer sectors (inner ring: inner diameter of 1 mm and outer diameter of 3 mm centered on the fovea; outer ring: annular region with inner and outer diameters of 3 and 6 mm).
GCC [0.86 (0.73, 0.94)], followed by SCPVD [0.80 (0.66, 0.91)] and DCPVD [0.44 (0.30, 0.57)]. Both GCC and SCPVD had significantly better diagnostic accuracy than DCPVD (both P < 0.001), while no significant difference in AUC was found between GCC versus SCPVD (P = 0.21) (Table 5, Fig. 3). The inner and outer sectors had similar patterns to the whole image. For the inner sector, the diagnostic accuracy for differentiating between healthy and glaucoma eyes was best for GCC [0.79 (0.65, 0.89)], followed by SCPVD [0.70 (0.53, 0.85)] and DCPVD [0.43 (0.30, 0.57)]. Both GCC and SCPVD had significantly better diagnostic accuracy than DCPVD (both P < 0.001). No significant difference in AUC was found between GCC versus SCPVD (P = 0.26). For the outer sector, the diagnostic accuracy for GCC [0.86 (0.73, 0.93)], SCPVD [0.79 (0.64, 0.91)], and DCPVD [0.45 (0.30, 0.59)]. Both GCC and SCPVD had significantly better diagnostic accuracy than DCPVD (both P < 0.001). No significant difference in AUC was found between GCC and SCPVD (P = 0.20) (Table 5, Figs. 1, 3).

The diagnostic accuracy for differentiating between glaucoma suspects and glaucoma was not significantly better for GCC [AUC: 0.77 (0.57, 0.91)] or SCPVD [AUC: 0.71 (0.57, 0.89)] than DCPVD [AUC: 0.54 (0.34, 0.80)] (P = 0.46, GCC vs. SCPVD; P = 0.12, GCC vs. DCPVD; P = 0.09, SCPVD vs. DCPVD) (Table 5, Fig. 3). AUCs for GCC and SCPVD were also similar to DCPVD measurements for differentiating suspect from healthy eyes (Table 5, Fig. 3). The inner and outer sectors had similar patterns to the whole image (Table 5, Figs. 1, 3).

**DISCUSSION**

The present study evaluated the diagnostic accuracy of SCPVD and projection artifact-resolved DCPVD measurements of the HD 6×6 mm² macular OCT-A scans in normal, glaucoma suspect, and glaucomatous eyes. Our results, consistent with previous reports, suggest that SCPVD has similar diagnostic accuracy to GCC and both have better diagnostic accuracy than DCPVD for differentiating between healthy and glaucoma eyes.

Most OCT-A studies have focused on visualizing SCPVD without putting much emphasis on calculating DCPVD measurements in glaucoma, in part due to the

**TABLE 3.** Mean (95% Confidence Interval) Ganglion Cell Complex Thickness by Classification From High-density 6×6 mm² Scans

| Sector               | Healthy Eyes | Glaucoma Suspect Eyes | Glaucoma Eyes | Adjusted P |
|----------------------|--------------|-----------------------|---------------|------------|
| All (field)          | 99.5 (96.3, 102.7) | 92.9 (87.6, 98.1) | 79.9 (78.0, 81.8) | < 0.001** |
| Superior hemifield   | 98.8 (95.3, 102.2) | 91.7 (86.0, 97.4) | 80.9 (78.8, 82.9) | < 0.001** |
| Inferior hemifield   | 100.2 (96.7, 103.7) | 94.1 (88.3, 99.8) | 78.7 (76.6, 80.9) | < 0.001** |
| All (inner ring)     | 107.4 (103.3, 111.5) | 100.7 (94.0, 107.5) | 88.3 (85.8, 90.8) | < 0.001** |
| All (outer ring)     | 99.1 (95.8, 102.3) | 92.5 (87.1, 97.9) | 79.3 (77.3, 81.2) | < 0.001** |

Bold values indicate mixed model statistical significance (P < 0.05).

*Healthy versus glaucoma.

†Suspect versus glaucoma.
existence of projection artifacts, which now can largely be removed using automated algorithms while maintaining the DCPVD. However, several studies demonstrate as we illustrate in Figure 4, the persistent presence of these artifacts even with the use of the projection artifact removal software and show that the likelihood of these artifacts is higher in eyes with pathologies.52,56

To date, few studies have compared the diagnostic accuracies of SCPV and projection artifact-resolved DCPVDs in glaucoma and healthy eyes, Specifically, Shin et al53 compared SCPV and DCPVDs using the AngioPlex OCT-A device (Carl Zeiss Meditec) and a large scan size (6×6 mm²) in 51 healthy and 41 glaucoma eyes and concluded that SCPV measurements were better than DCPVD (AUC: 0.78 vs. 0.67) for classifying healthy and glaucoma eyes. Lommatzsch et al54 utilized the AngioVue and a 3×3 mm² scan size in 50 healthy and 85 glaucoma eye and also found that SCPV measurements were better than DCPVD when comparing healthy and glaucoma eyes (AUC: 0.78 vs. 0.70). Takusagawa et al55 analyzed an additional layer (intermediate capillary plexus) in addition to the SCP and DCP and concluded that SCPVD has the highest accuracy in detecting glaucoma. Our study confirms these results in HD scans and is unique in that it also compares these measurements in healthy and glaucoma eyes with the HD scan measurements in glaucoma suspect eyes.

SCPVD and macular GCC thickness measurements, which both decrease over time in healthy and glaucomatous eyes,60,61 are obtained from the ILM to the IPL. In contrast, the DCPVD is measured from the INL to the OPL, and whether the deeper retinal changes in glaucoma remain controversial. A recent spectral domain optical coherence tomography study investigated the deeper retinal changes in glaucoma and found that INL thickness was negatively correlated with VF severity as defined by MD, which was thought to be due to reactive response of the glial or neuronal cells in the INL during the progression of glaucoma.40

Consistent with previous studies,54,62,63 vessel density was found to be lower, especially in SCP in glaucoma patients and glaucoma suspects than healthy subjects.

### Table 5

| Scan Layer                  | Sector                        | Healthy vs. Glaucoma | Healthy vs. Suspect | Suspect vs. Glaucoma |
|-----------------------------|-------------------------------|----------------------|---------------------|----------------------|
| Superficial capillary plexus| Whole image                   | 0.80 (0.66, 0.91)    | 0.64 (0.42, 0.81)   | 0.71 (0.57, 0.89)    |
|                            | Inner parafovea               | 0.70 (0.53, 0.85)    | 0.57 (0.40, 0.74)   | 0.66 (0.53, 0.85)    |
|                            | Outer parafovea               | 0.79 (0.64, 0.91)    | 0.64 (0.41, 0.80)   | 0.69 (0.54, 0.88)    |
| Deep capillary plexus       | Whole image                   | 0.44 (0.30, 0.57)    | 0.49 (0.32, 0.65)   | 0.54 (0.34, 0.80)    |
|                            | Inner parafovea               | 0.43 (0.30, 0.57)    | 0.45 (0.28, 0.61)   | 0.55 (0.34, 0.78)    |
|                            | Outer parafovea               | 0.45 (0.30, 0.59)    | 0.48 (0.31, 0.65)   | 0.55 (0.33, 0.81)    |
| Ganglion cell complex       | Whole image                   | 0.86 (0.73, 0.94)    | 0.61 (0.39, 0.78)   | 0.77 (0.57, 0.91)    |
|                            | Inner parafovea               | 0.79 (0.65, 0.89)    | 0.55 (0.32, 0.70)   | 0.74 (0.57, 0.90)    |
|                            | Outer parafovea               | 0.86 (0.73, 0.93)    | 0.60 (0.41, 0.78)   | 0.76 (0.58, 0.91)    |

AUC indicates area under the receiver operating characteristic curve; CI, confidence interval.
Furthermore, SCPVD was consistently lower than the DCPVD in all eyes, notably in glaucomatous eyes. This finding is expected because the RNFL and GCL, which are structurally damaged in glaucomatous eyes, receive blood from the SCP. In addition, the SCP is believed to have more vascular changes (ie, blood flow regulation) than the DCP in glaucoma. Alternatively, more advanced glaucoma with less perfusion to the SCP may allow more vessels to be visible in the DCP, which creates a paradoxical trend showing higher perfusion in the deeper layers as the disease progresses. We also know that DCP microvasculature dropout detected qualitatively was associated with the...

FIGURE 3. Age-adjusted and image Scan Quality Index–adjusted area under the receiver operating characteristic curves (AUCs) comparing superficial capillary plexus (SCP) and projection artifact-resolved deep capillary plexus (DCP) HD 6 mm² vessel density measurements in healthy, suspect, and glaucoma eyes. GCC indicates ganglion cell complex.

FIGURE 4. Examples of optical coherence tomography angiography images for superficial capillary plexus and deep capillary plexus HD 6×6 mm² scans in healthy, suspect, and glaucoma eyes showing the presence of remaining projection artifacts in deep capillary plexus slabs (arrows). DCPVD indicates deep capillary plexus vessel density; SCPVD, superficial capillary plexus vessel density.
disease severity in glaucoma suspects, and the presence of gamma zone peripapillary atrophy, and higher VF progression rates in glaucoma patients.

The vessel density of the outer sector had a trend of higher diagnostic accuracy compared with the vessel density of the inner sector of the HD 6×6 mm² when differentiating the 3 different groups. A previous study by our research group compared the diagnostic accuracy of the inner area of the 3×3 mm² with the outer area of non-HD 6×6 mm² and concluded that the outer area was better than the inner area when classifying healthy and mild glaucoma eyes, whereas classification was similar when classifying healthy and moderate to severe glaucoma eyes.

Our study has several limitations. First, the projection artifact removal algorithm does not remove all artifacts. Several eyes showed remaining artifacts in the deeper layer after projection artifact removal (Fig. 4). As different projection artifact removal algorithms are implemented, it is important to understand the strengths and limitations of the various algorithms and how they differ in their ability to remove these artifacts. Second, the sample size of the glaucoma suspect was smaller than the healthy and glaucoma groups and may limit our ability to detect significant differences. Third, a relatively larger proportion of glaucoma and suspect eyes were excluded due to poor quality scans which may reduce the generalizability of the results. We also did not compare the GCC/SCP thickness to the DCP due to lack of deep layer thickness data using the current software. In addition, topical glaucoma and systemic medications might influence the vessel density and the effects of different medications and possible changes in medications are not easily evaluated in a cross-sectional study design. Longitudinal studies are needed to test the influence of changes in medications on SCPVD and DCPVD measurements.

In conclusion, DCPVD measurements may not provide critical diagnostic information for glaucoma management as these measurements performed relatively poorly at differentiating between healthy, glaucoma suspect and glaucoma eyes compared with SCPVD and GCC. The DCPVD results may be influenced by the imperfect ability of the algorithm to remove all the artifacts. These results suggest that SCPVD and GCC measurements are more informative than DCPVD for the detection and management of glaucoma.

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