The “Double-Layer Sign” on Spectral-Domain Optical Coherence Tomography

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OBJECTIVE Characterize the presence of “Double-layer sign” on SD-OCT and discern it tomographic appearance in the spectrum of pachychoroidopathy disorders.

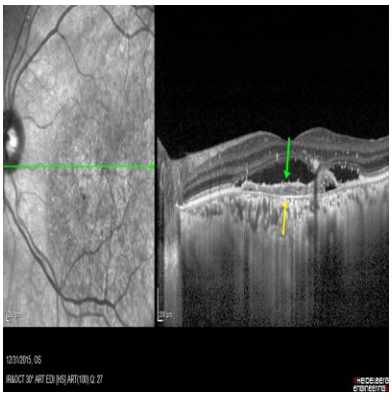
PURPOSE The “Double layer sign (DLS)” on SD-OCT, formed by shallow irregularly elevated RPE with underlying intact Bruch’s, is conceivably due to chronic choroidal hyperpermeability in pachychoroidopathy. The aim of our study was to evaluate and possibly differentiate between DLS seen in two pachychoroid variants– Polypoidal choroidal vasculopathy (PCV) and chronic central serous chorioretinopathy (CCSCR)

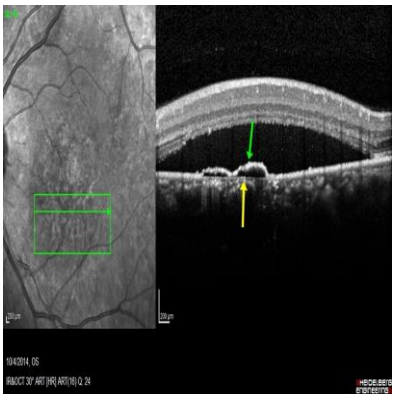
METHODS Retrospective analysis of seventy eyes with pachychoroidopathy who underwent multimodal imaging including enhanced-depth imaging optical coherence tomography (EDI-OCT), fundus autofluorescence, digital fluorescein angiography (DFA) and indocyanine green angiography (ICGA) on Spectralis OCT. Presence of PCV was confirmed on ICGA. Based on multimodal imaging, the eyes were categorized into two pachychoroid variants presenting with DLS - Polypoidal choroidal vasculopathy (PCV) and chronic central serous chorioretinopathy (CCSCR). Presence of DLS was scrutinized on SD-OCT and its detailed analysis was performed by a single masked grader. The sub-foveal choroidal thickness (SFCT) was measured too.

RESULTS 35 eyes each were present in PCV and CCSCR groups with CCSCR seen significantly more in males (p =0.005), in younger population (CCSCR: 55.66 ± 10.88 yrs; PCV: 62.89 ± 8.64 yrs; p < 0.001) and with significantly greater SFCT (CCSCR: 467.23 ± 97.13µ; PCV: 297.11 ± 82.47µ; p < 0.001). DLS sign was significantly associated with PCV (32/35 eyes; Sensitivity: 91.43%; Specificity: 68.57%; Positive Predictive Value [PPV]: 74.42%; Negative Predictive Value [NPV]: 88.89%) as compared to CSCR (11/35 eyes; Sensitivity: 31.43%; Specificity: 8.57%; PPV: 25.58%; NPV: 11.11%; p < 0.001). On meticulous evaluation of DLS feature, all 32 eyes of PCV with DLS had characteristic moderate hyperreflectivity in the space between the undulated RPE and Bruch's membrane. In contrast, the DLS seen in CCSCR showed uniform hyporeflectivity in all but one of the 11 eyes, while a single eye demonstrated moderate hyperreflectivity. Presence of hyperreflectivity in DLS was significantly associated with PCV (p < 0.001)

CONCLUSION Presence of DLS in pachychoroidopathy is significantly associated and favorably predictive of PCV as against CCSCR. In addition, occurrence of hyperreflectivity between the undulated RPE and intact Bruch's is a vital indicator of PCV while hyporeflectivity corresponded well to CCSCR. Moreover in pachychoroidopathy, younger age, male gender and thicker choroid correlates better with CCSCR than PCV.

TAKE HOME MESSAGE "Double layer sign" is found significantly more in PCV as compared to CCSCR with moderate hyporeflectivity between the RPE and Bruch's whereas in CSCR there is presence of uniform hyporeflectivity.





Evaluation of Choroidal Neovascularization Response to Anti-Vascular Endothelial Growth Factor Treatment With Quantitative OCT Angiography

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- David Wilson
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- Simon Gao

OBJECTIVE OCT angiography (OCT-A) is a non-invasive technique for imaging choroidal neovascularization (CNV) and determining CNV flow area, a novel metric for monitoring CNV treatment response.

PURPOSE To evaluate the utility of OCT-A generated CNV flow area to monitor CNV response to pro re nata (PRN) anti-vascular endothelial growth factor (anti-VEGF) treatment.

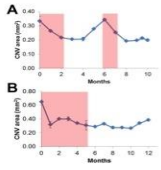
METHODS Prospective study of 10 eyes from 10 patients with treatment naïve CNV that underwent OCT-A scans at baseline and monthly visits while under a PRN anti-VEGF treatment regimen. A minimum of six monthly follow-up visits was required. Spectral OCT (RTVue-XR Avanti, Optovue) and the split-spectrum amplitude-decorrelation angiography algorithm was used to compute blood flow. Semi-automated quantification of CNV flow area was assessed by summing pixels with detectable flow in the outer retinal/RPE slab (between Bruch's membrane and outer plexiform layer). Two scans were acquired at each visit and within-visit repeatability was assessed by coefficient of variation (CV).

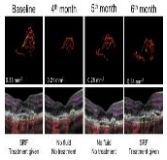
RESULTS Within-visit CNV area repeatability was 7.8%. Six of 10 eyes showed reduction in CNV flow area ranging from 9%-83%. In one eye, CNV flow area decreased after three monthly treatments; during subsequent visits treatment was withheld and CNV

flow area increased preceding fluid accumulation on structural OCT (Fig. 1A) (Fig. 2). In another example, CNV flow area decreased after five consecutive injections, then remained stable without treatment (Fig. 1B). Four eyes showed an increase in CNV flow area while under consecutive monthly treatments. Of these, one was due to subretinal hemorrhage resulting in incomplete initial CNV flow area measurement. The second was due to poor initial signal strength intensity that improved after cataract surgery that occurred while under anti-VEGF treatment. The final two eyes had large predominantly serous pigment epithelial detachments (PED); as the PED collapsed with treatment, the CNV became more visible and CNV flow area increased.

CONCLUSION CNV flow area can be semi-automatically measured with excellent repeatability. This metric can be useful in monitoring treatment response. In some cases, increase in CNV area may precede recurrence of fluid on structural OCT, serving as an earlier indicator for the need for treatment.

TAKE HOME MESSAGE OCT angiography is a non-invasive approach to visualize and quantify choroidal neovascularization (CNV). CNV flow area is a novel metric to monitor CNV growth and CNV response to treatment.





HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

Qualitative and Quantitative Spectral Domain OCT Angiography (SD-OCTA) of Diabetic Retinopathy

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OBJECTIVE To demonstrate the utility of OCT Angiography in the evaluation of diabetic retinopathy.

PURPOSE The purpose of this study is to non-invasively evaluate retinal perfusion and quantify the density and morphology of retinal vasculature in patients with diabetic retinopathy (DR) using SD-OCTA.

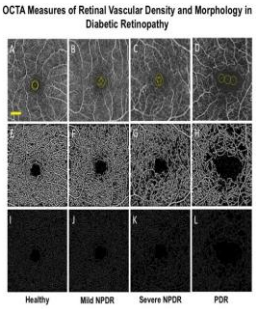
METHODS This was a retrospective, cross-sectional, observational study of adult subjects recruited at the USC Eye Institute. OCTA was performed on at least 98 eyes of 58 patients with DR and at least 20 eyes of 10 healthy subjects. 3 x 3mm scans of the fovea were acquired with a prototype SD-OCTA system using an intensity-based optical microangiography decorrelation algorithm. Quantification of the density and morphology of foveal retinal perfusion was performed in superifical and deep retinal layers using a custom program to assess skeleton density (SD), vessel density (VD), fractal dimension (FD), and vessel diameter index (VDI) in non-segmented and segmented OCTA slabs.

RESULTS SD, VD, and FD progressively decreased and VDI progressively increased in eyes with increasing severity of DR compared to healthy eyes regardless of OCTA segmentation. Significant differences between mild nonproliferative diabetic retinopathy (NPDR) and severe NPDR or proliferative DR could be detected depending on segmentation. Statistical analyses were performed using the Student's *t*-test or

analysis of variance (ANOVA) with post hoc Tukey Honest Significant Difference (HSD) tests for multiple comparisons. A *P*-value of less than 0.05 was accepted as significant. In addition, a generalized estimating equations model (GEE) was also used to analyze associations between the OCTA measures and disease status within each OCTA layer. This nonparametric logistic regression analysis adjusted for age, gender, and correlated data due to inclusion of both eyes in patients with bilateral disease. This model confirmed the association of decreasing SD, VD, FD with increasing severity of DR.

CONCLUSION SD-OCTA of the central macula can quantify several parameters that are representative of retinal perfusion and vascular morphology.These parameters can provide objective assessment of overall disease severity in patients with DR. Progressively decreasing skeleton density, vessel density, and fractal dimension, as well as increasing vessel caliber on macular OCTA indicates worsening severity of DR.

TAKE HOME MESSAGE OCT Angiography of the central macular field (3x3mm) may be a useful method of quantitatively assessing the overall severity of diabetic retinopathy.



HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

Quantitative Microscopic Validation of OCT Angiography Using Adaptive Optics Scanning Light Ophthalmoscope Fluorescein Angiography (AOSLO-FA)

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OBJECTIVE To compare the quantitive and qualitative results obtained using commercial OCT Angiography(Optovue SSADA) and an ultrahigh resolution Adaptive Optics SLO Fluorescein Angiography instrument.

PURPOSE OCTA is the latest high-resolution imaging technique for noninvasive quantitative visualization of retinal microvasculature but it is difficult to compare to conventional fluorescein angiography. We used AOSLO-FA in a side-by-side comparison with OCTA on healthy and diseased eyes to evaluate their quantitative and qualitative similarities and differences.

METHODS 6 patients with diabetic retinopathy, branch retinal vein occlusion, or sickle cell retinopathy and 3 controls were imaged using a commercial OCTA system (Optovue Avanti RTVue-XR) and our laboratory AOSLO-FA. A 10x10° OCTA full vessel layer scan and a 6x6° AOSLO-FA montage centered at the fovea were obtained for each eye. Foveal

avascular zone (FAZ) area, perimeter, and acircularity were measured. Vessel density at 3 annular regions of interest (ROI)100, 200, & 300 μm away from the FAZ margin was computed as the total vessel length divided by ROI area. Paired t-tests were used to assess statistical significance. Images were compared for differences in vessel patterns and deletions.

RESULTS OCTA demonstrated excellent qualitative and quantitative agreement with AOSLO-FA as well as no statistically significant difference in FAZ perimeter, acircularity, and vessel density at all 3 ROIs. FAZ area showed a very small but statistically significant difference (OCTA 0.38±0.27 vs AOSLO-FA 0.38±0.28 mm^2; p=0.02). A few vessel segments seen on AOSLO-FA did not appear on OCTA and vice versa. OCTA, as all clinical instruments, has a lateral resolution 10 times lower than AOSLO-FA (20 micron vs. 2 micron) and is prone to artifacts due to eye movement, which are removed by the intensive post-processing algorithms employed with AO. OCTA surpasses AOSLO FA in clinical application given its shorter scan time, near immediate image reconstruction and the ability to delineate multiple capillary layers in a single scan.

CONCLUSION OCTA shows excellent agreement with ultrahigh resolution AOSLO-FA around the fovea of both healthy and diseased eyes with minor quantitative and qualitative differences. These results help support the validation of OCTA as a significant advance in noninvasive quantitative clinical angiography. Larger longitudinal studies will be needed to validate its predictive capabilities.

TAKE HOME MESSAGE OCT Angiography shows excellent quantitative and qualitative agreement with ultrahigh resolution Adaptive Optics SLO-FA and has distinct practical advantages.


HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

Analysis of Vascular Dilation and Tortuosity Using the ROPtool

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OBJECTIVE To evlauate the accuracy of the ROPtool, a computer program, in identifying Plus Disease in ROP.

PURPOSE ROPtool is a software program that analyzes dilation and tortuosity of vessels. To validate this program vessels were assessed by two methods; (1) tortuosity assessment by a computer program (ROPtool), and (2) assessment by a lay reader compared with assessment by a panel of 3 retinopathy of prematurity (ROP) experts for remote clinical grading of vascular abnormalities such as plus disease.

METHODS A total of 335 fundus images of prematurely born infants were obtained by neonatal intensive care unit nurses. Eighty-four images with varying degrees of vascular dilatation, tortuosity, or both were graded by a panel of 3 ROP experts and 251 images with no evidence of vascular abnormalities. Digital images were sent to an experienced lay reader who graded them for vascular abnormalities. The same images were analyzed using the ROPtool. The ROPtool measurements were graded and compared with expert panel grades with a receiver operating characteristic (ROC) curve. The area under the ROC curve was calculated for the ROPtool. Sensitivity and specificity were computed for the lay reader.

RESULTS Compared to expert readers, ROPtool had excellent accuracy for detection of vascular abnormalities suggestive of plus disease. ROPtool's tortuosity assessment had an area under the ROC curve of 0.917. Using a threshold value of 4.97 for the second most tortuous quadrant, ROPtool's sensitivity was 91% and its specificity was 82%. Additionally, the lay reader's results showed excellent sensitivity and good specificity when compared with those of the expert graders. Lay reader sensitivity and specificity were 99% and 73%, respectively, and had high reliability (k, 0.87) in repeated measurements.

CONCLUSION This data confirms that modalities to enhance remote reading of images to detect vascular abnormalities are reliable in regard to teleophthalmology for remote management of ROP. Additionally, the use of teleophthalmology with remote reading for efficient delivery of high-quality care and to detect infants requiring bedside examination is feasible with advances in image management.

TAKE HOME MESSAGE Computer analysis of digital images may be a useful tool in the advancement of teleophthalmology. Threshold measurements of vascular tortuosity and dilation aid in the identification of Plus Disease.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board