The Next Generation MIOCT System: Real Time Volumetric Intraoperative Optical Coherence Tomography With 4D Visualization of Surgical Maneuvers

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OBJECTIVE To introduce the next generation, high speed (400kHz) microscope integrated optical coherence tomography system that provides real time volumetric "4D" visualization via heads-up stereoscopic display

PURPOSE Ophthalmic surgery is performed through an en-face surgical microscope that provides limited depth information. With limited depth information comes limited precision in delicate retinal surgical maneuvers such as subretinal therapy delivery.

METHODS A commercially available Enfocus MIOCT scanner (Leica Microsyst; Wetzlar, Germany) was modified for 1050nm light and high speed, ScannerMax (Pangolin; Orlando, FL) galvos. The OCT engine used either a 100 kHz or 400 kHz swept source laser (Axsun Technologies; Bilerca, MA) with a center wavelength of 1050nm. Custom GPU based software performed real time OCT acquisition, processing, and display. OCT volumes were rendered in real time using a modified GPU based ray casting algorithm. A Truevision (Goleta, CA) 3D visualization system was used to provide heads up visualization of the surgical field and OCT data on a 3D TV (fig. 1). Mock surgical maneuvers were performed in ex-vivo porcine eyes.

RESULTS Imaging with 100 kHz source (2.71 Hz volume rate) was performed during the

creation of a retinal bleb in ex-vivo porcine eyes. Although the needle was obscured by the retina on the en-face microscope view, 4D MIOCT provided clear visualization of the needle within the bleb and under the surface of the retina. In sperate mock surgical procedures the MIOCT system with the 400 kHz source (8.68 Hz volume rate) was used to image sub retinal cysts. The higher volume rate and heads up visualization enabled the surgeon to monitor the dynamics of the tool tissue interaction and manipulate the cysts. Using MIOCT guidance, the surgeon was able to use the surgical tool to combine the cysts.

CONCLUSION We demonstrate the use of new generation, high speed (400kHz), MIOCT system with real time volumetric "4D" visualization via heads-up stereoscopic display in mock surgical maneuvers in porcine eyes. The 4D MIOCT system allows for more precise manipulation of delicate retinal tissue or subretinal therapy delivery. The system is ready for translation into human ophthalmic microsurgery.

HUMAN RESEARCH Yes: Approved by institutional review board

Wide-Field Swept-Source Optical Coherence Tomography Angiography Versus Fluorescein Angiography for Detecting Diabetic Retinopathy

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- Yifan Lu
- Jay C Wang, MD
- Dean Eliott, MD
- David M Wu, MD, PhD
- Deeba Husain, MD
- Leo A. Kim, MD, PhD
- Demetrios Vavvas, MD, PhD

OBJECTIVE To compare different scan protocols of wide-field swept-source optical coherence tomography angiography (WF SS-OCTA) versus fluorescein angiography (FA) for detecting diabetic retinopathy (DR).

PURPOSE Diabetic retinopathy is a common cause of irreversible vision loss worldwide, and early and accurate detection is critical to appropriate treatment and management of DR. How traditional imaging with FA compares with novel techniques such as WF SS-OCTA with and without ultra-wide field color fundus photography (UWF CFP) for detecting DR lesions has not been previously studied.

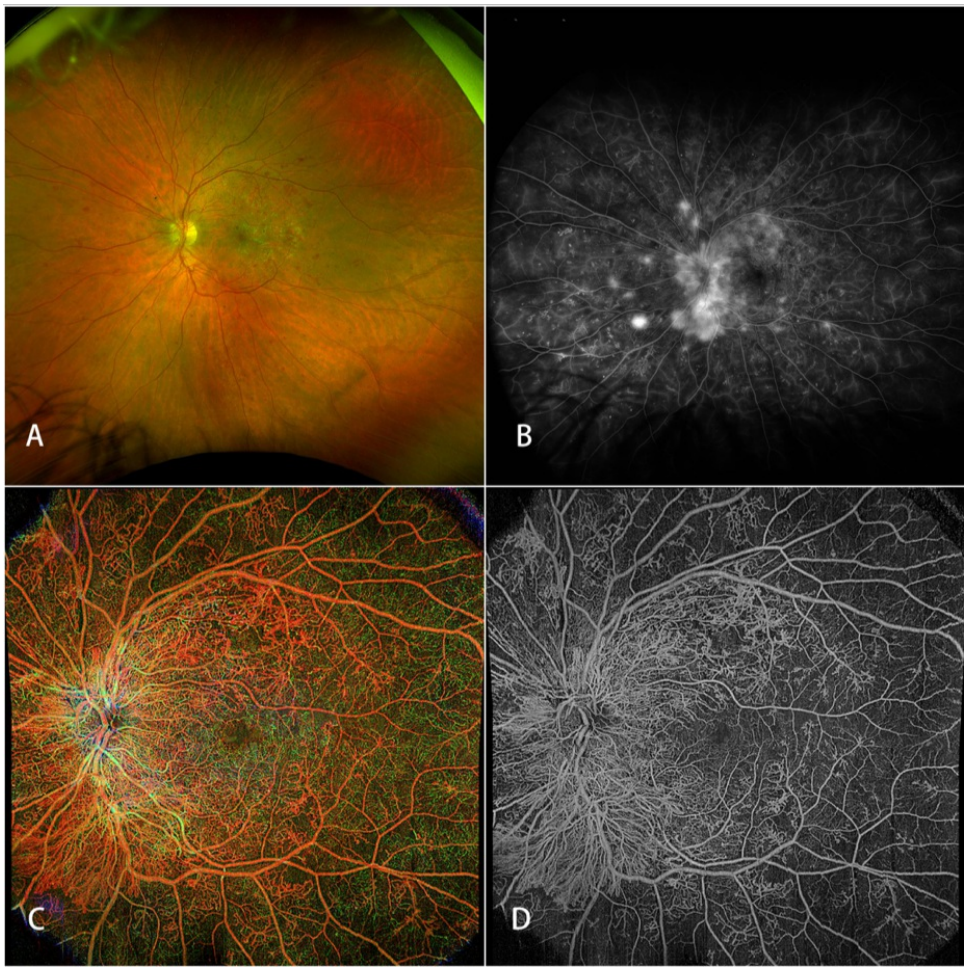
METHODS Prospective, observational study at Mass Eye and Ear from December 2018 to July 2019. Diabetic patients with proliferative, non-proliferative, and no DR were included. WF SS-OCTA with the following scan protocols were used: Angio 6mm×6mm and Angio 12mmx12mm centered on fovea and optic disc and Montage 15mm×9mm. UWF CFP and FA were taken by a 200 degree, single capture retinal imaging system. Images were independently evaluated by two graders for microaneurysms (MAs), intraretinal microvascular abnormalities (IRMA), neovascularization elsewhere (NVE) and

neovascularization of the disc (NVD), venous beading (VB), and nonperfusion areas. Statistical analyses were performed using SPSS 25.0.

RESULTS One hundred and seventy-six eyes in 119 participants were included in this study. The detection rate of NVE or NVD on Angio 6mm×6mm centered on fovea and optic disc was two thirds of that on Montage 15mm×9mm ($P<0.05$). Furthermore, the Angio 12mm×12mm centered on the fovea and optic disc scan combination had comparable detection rates to Montage 15mm×9mm for all DR lesions ($P>0.05$). When we compared different scans of WF SS-OCTA with FA, Montage 15mm×9mm and Angio 12mm×12mm centered on the fovea and optic disc had a comparable detection rate for all types of DR lesions ($P>0.05$) except VB. In addition, a high degree of agreement was found in Angio 12mm×12mm centered on the fovea and optic disc combined with UWF CFP ($\kappa=0.851$) compared with FA, as well as Montage 15mm×9mm combined with UWF CFP ($\kappa=0.704$) compared with FA.

CONCLUSION WF SS-OCTA imaging was useful for detecting DR lesions. The Angio 12mm × 12mm centered on fovea and optic disc may be the optimal balance between speed and accuracy for DR evaluation in a busy clinical practice. Angio 12mm × 12mm centered on fovea and optic disc combined with UWF CFP may be a better choice to follow severe non-proliferative and proliferative DR patients.

HUMAN RESEARCH Yes: Approved by institutional review board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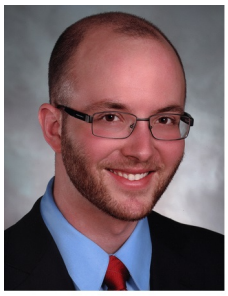
Swept Source Optical Coherence Tomography Angiography Analysis of Intraretinal Microvascular Abnormalities



- Thomas A Mendel, MD, PhD
- Kimberly Baynes, BSN, RN, COA
- Sumit Sharma, MD
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OBJECTIVE Demonstrate utility of swept source optical coherence tomography angiography (ssOCTA) for quantification of intraretinal microvascular abnormalities (IRMAs).

PURPOSE IRMAs can be difficult to detect clinically, often obscured by other pathology of diabetic retinopathy. ssOCTA may serve to differentiate IRMAs quantitatively from the background retinal vasculature.

METHODS This is a retrospective review of consecutive patients with diabetic retinopathy who had ssOCTA performed (Zeiss Plex Elite). Widefield 12 x 12 ssOCTAs were used to create montage images. ssOCTA images were analyzed using ImageJ (Fiji version), comparing the region identified clinically as IRMA with control areas in a different quadrant of the same retina. Flow density (area of flow/area of retina), and flow length density (area of contiguous branching flow/area of retina) were calculated in both regions of interest. Corresponding fluorescein angiograms were also evaluated. Control regions were compared to IRMAs to determine if a distinct digital signature of IRMAs could be developed.

RESULTS 200 patients with diabetic retinopathy were enrolled in an IRB approved study, resulting in 8 patients with observable IRMAs on exam and ssOCTA. IRMAs were evaluated and demonstrated a mean superficial retinal flow density of 18.56%, significantly less than that of control areas at 31.10% ($p = 0.02$). IRMAs demonstrated a mean superficial retinal flow length density of 15.58%, similar to that of control areas at 13.67% ($p = 0.74$). The

IRMAs were noted clinically demonstrated a range of leakage on FA, from none to prominent leakage.

CONCLUSION ssOCTA is a useful tool to characterize and quantify IRMAs in diabetic retinopathy. Different IRMAs demonstrated different degrees of leakage, as has been noted previously. IRMAs were analyzed and determined to have significantly decreased flow density compared to control areas in the same retina, with similar flow length density measurements. On closer examination, IRMAs tended to develop in microregions of the retina, which were sometimes adjacent to areas of nonperfusion. This resulted in less background flow and more consolidated flow through the IRMA itself, thus reducing flow density in a given area. As the IRMAs themselves increased the branched flow length density, this made up for the decrease in background branched flow length density, thus rendering IRMA areas similar to control areas in that regard. The ability to quantify and characterize IRMAs with ssOCTA will provide the clinician with a valuable point-of-care tool to identify subtle microvascular changes without the need for vascular access and traditional fluorescein angiography. Combining ssOCTA information in the clinical viewing systems in use today may give the clinician additional vital information about disease progression. This work provides a proof of concept for the development of IRMA quantification in future OCTA development.

HUMAN RESEARCH Yes: Approved by institutional review board

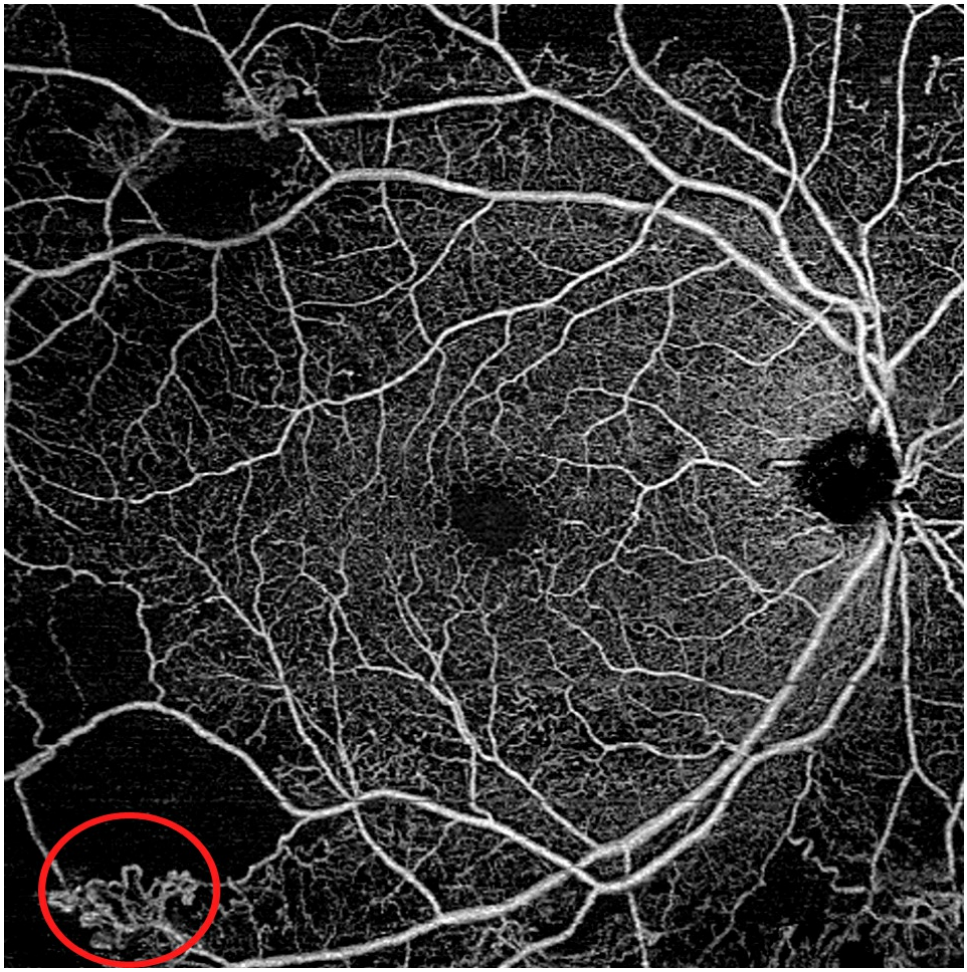

Figure 1 – Example ssOCTA image revealing IRMA adjacent to region of non-perfusion.

Wide-Field Swept-Source Optical Coherence Tomography Angiography Versus Ultra-Wide Field Color Fundus Photo for Detecting Diabetic Retinopathy

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- Ying Cui, M.D.
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- John B. Miller, MD

OBJECTIVE To compare wide-field swept-source optical coherence tomography angiography (WF SS-OCTA) with ultra-wide field color fundus photo (UWF CFP) for detecting diabetic retinopathy (DR) lesions.

PURPOSE Diabetic retinopathy is a major cause of vision loss worldwide. Creating an efficient and accurate screening method for detecting DR would help minimize the burden of diabetic eye disease, but the optimal screening method has not yet been determined.

METHODS A prospective, observational study at Mass Eye and Ear from December 2018 to July 2019. Patients with proliferative, non-proliferative, and no diabetic retinopathy were included. Patients were imaged with Montage 15mm×9mm in a 100 kHz SS-OCTA instrument (Plex® Elite 9000, Carl Zeiss Meditec Inc., Dublin, CA). UWF CFP were taken by a 200 degree, single capture retinal imaging system. Images were independently evaluated by two graders for the presence of microaneurysms (MAs), intraretinal microvascular abnormalities (IRMA), neovascularization elsewhere (NVE), and neovascularization of the optic disc (NVD). All statistical analyses were performed using SPSS 25.0.

RESULTS One hundred and fifty-two eyes in 101 participants were included in the study. The average age was 54.26±13.40 years and average diabetes duration was 17.81±10.93 years. Eighty eyes had diabetic macular edema and 81 eyes were treatment naïve at the time of imaging. UWF CFP was better at detecting MAs than Montage 15 mm×9mm using WF SS-OCTA (88.2% vs. 80.3%, P<0.05). However, the detection rate of IRMA on Montage 15 mm×9mm was higher than UWF CFP (69.1% vs. 44.1%, P<0.05). Furthermore, Montage 15mm×9mm had better performance in detecting NVE/NVD compared with UWF CFP (39.5% vs. 30.3%, P<0.05).

CONCLUSION WF SS-OCTA (Montage 15 mm×9mm) was clinically useful in detecting MAs, IRMAs, and NVD/NVE although SS-OCTA image covers a smaller area than UWF CFP.

HUMAN RESEARCH Yes: Approved by institutional review board

Artificial Intelligence Algorithm May Improve Performance of Retinal Specialists in Detection of Retinal Fluid on OCT in AMD: AREDS2 10-Year Study

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OBJECTIVE Comparison of performance between (i) retinal specialists and (ii) artificial intelligence (AI)-based Notal OCT Analyzer (NOA), in detecting retinal fluid in SD-OCT macular scans from eyes with AMD

PURPOSE In neovascular AMD, retreatment decisions are based mostly on qualitative assessments of retinal fluid presence by retinal specialists. This is highly time-consuming and accuracy may be suboptimal. AI software algorithms that help identify the presence, location, and quantity of fluid could therefore be highly useful in clinical practice, as diagnostic aids

METHODS In this prospective study, SD-OCT scans were acquired from all Age-Related Eye Disease Study 2 10-year follow-on (AREDS2-10Y) participants with Cirrus or Spectralis devices. Masked investigators graded each scan for intraretinal and subretinal fluid. The same scans underwent masked grading by (i) NOA, and (ii) reading center (RC) graders, used as ground truth. The primary outcome measure was accuracy

RESULTS 1,127 eyes (651 participants) were eligible (mean age 80 y). 50% required RC senior adjudication for fluid presence. Retinal fluid was present in 370 eyes. For detecting retinal fluid, the AREDS2-10Y investigators' performance was: accuracy 0.805 (95% CI 0.780-0.828), sensitivity 0.468 (0.416-0.520), and specificity 0.970 (0.955-0.981). NOA performance was: 0.851 (0.829-0.871), 0.822 (0.779-0.859), 0.865 (0.839-0.889). For

intraretinal fluid, investigator performance was 0.815 (0.792-0.837), 0.403 (0.349-0.459), 0.978 (0.966-0.987); NOA performance was 0.877 (0.857-0.896), 0.763 (0.713-0.808), 0.922 (0.902-0.940). Comparing the investigator true positive (n=173) and false negative (n=197) cases, the mean NOA-calculated fluid volume was 156 vs 33 nl (p<0.001), with fluid present in 32% vs 11% B-scans (p<0.001)

CONCLUSION In this large and challenging sample of OCT scans, retinal specialists had imperfect accuracy in detecting retinal fluid, with low sensitivity. This was particularly true for intraretinal fluid and low fluid volume. AI detection achieved a higher level of accuracy. This software tool could assist physicians in detecting retinal fluid, which is important for retreatment and prognostic tasks in AMD

HUMAN RESEARCH Yes: Approved by institutional review board

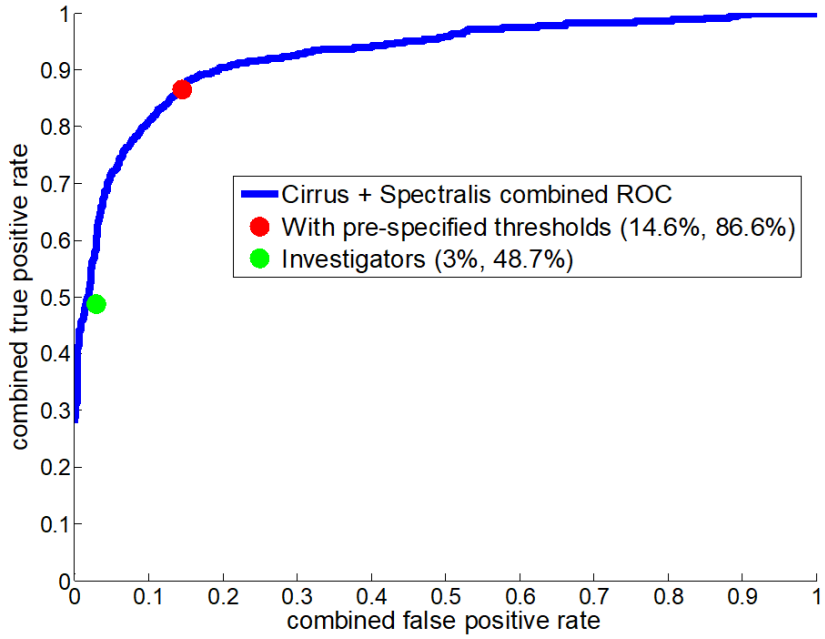

Figure 1. ROC curve of NOA in detecting retinal fluid; AUC = 0.925; retinal specialists' performance (green dot)

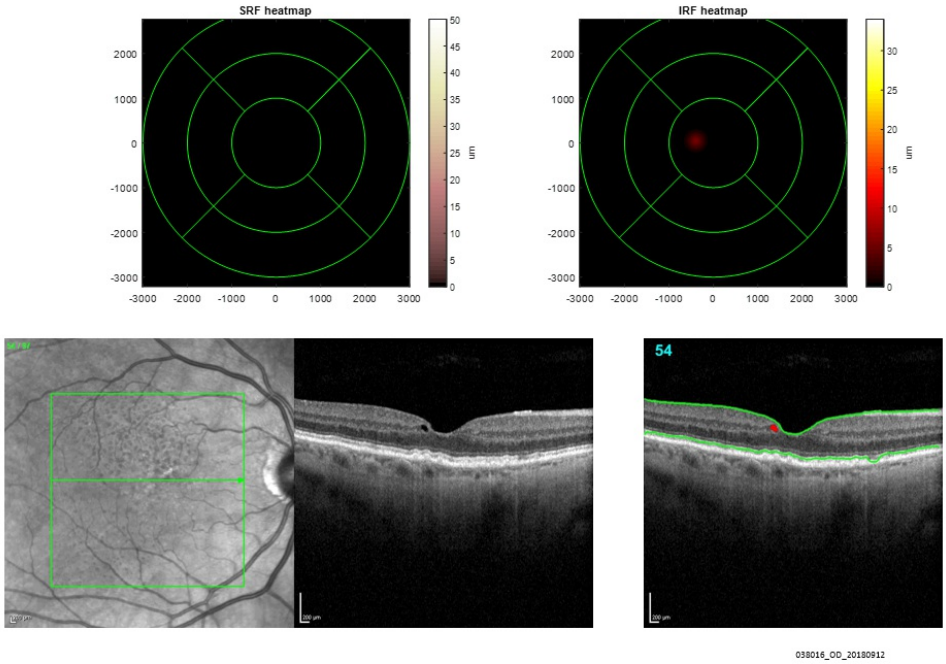

Figure 2. OCT scan with low volume intraretinal fluid: missed by retinal specialist but correctly detected by NOA (red)

Obstructive Sleep Apnea and Its Treatment Alter Choroidal Thickness in Patients With Central Serous Chorioretinopathy

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- Nadim M Rayess, MD

OBJECTIVE To explore the association of obstructive sleep apnea and its treatment on choroidal thickness in patients with central serous .

PURPOSE An association between obstructive sleep apnea (OSA) and central serous chorioretinopathy (CSC) has been reported in the literature. Additionally, choroidal thickness (CT) is altered in both CSC and OSA and has been examined in each disease separately. We propose an association of OSA, stratified by diagnosis, severity, and treatment status, on CT in patients with CSC.

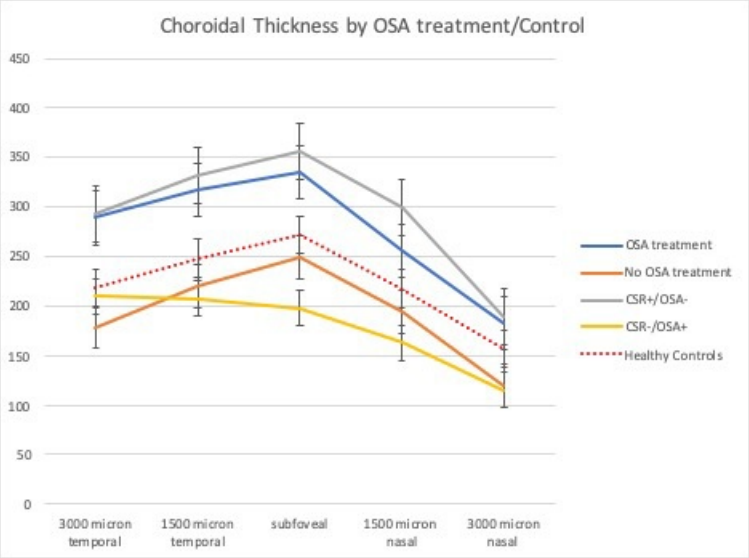
METHODS In an IRB-approved, retrospective observational study, we identified all patients in the STAnford Research Repository (STARR) with a diagnosis of CSC with OSA, who were seen at the Byers Eye Institute from 2011 to 2019. Age- and sex-matched controls with either CSC or OSA alone were also identified. Eyes with gradable OCT scans were included and we collected clinical information, OSA severity and treatment status. CT was measured at five points (subfoveal; 1500- and 3000-microns nasal and temporal to fovea) by two independent and masked graders. ANOVA and Tukey tests were used to compare mean CT among patient groups.

RESULTS A total of 65 patients met study inclusion criteria, divided among the CSC with OSA cohort (N=22) and the 2 control groups of CSC and OSA alone (N=20 and N=23, respectively). The mean subfoveal CT (SFCT) were significantly different across the 3 groups: OSA-only was the thinnest, followed by CSR with OSA, and CSR-only was the thickest (198 mm, 302mm, and 356 mm, respectively, $p < .001$). Similar differences were observed for CT measurements at all five points. When stratified by treatment status, SFCT was significantly higher in CSC patients with treated OSA versus those with untreated OSA (335 mm vs. 249 mm, respectively, $p < .001$), but still lower than CSC-alone. In patients with CSC and OSA, there was a positive association of OSA Apnea-Hypopnea Index (AHI), a marker of disease severity, and increased SFCT ($p = .02$). CT thickness grading reached an interclass correlation coefficient of 95% with a less than 10 mm difference for any given measurement.

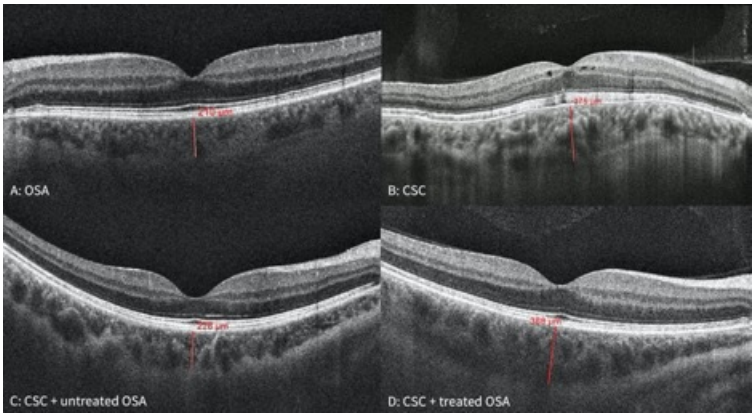
CONCLUSION Subfoveal CT is significantly different in patients with OSA alone, CSC with OSA, and CSC alone. In patients with CSC and OSA, OSA treatment is associated with choroidal thickening. This suggests a role for OSA evaluation in known CSC patients with

atypically thin CT

HUMAN RESEARCH Yes: Approved by institutional review board



Subfoveal choroidal thickness and at 1500- and 3000-microns nasal and temporal to fovea in patients with OSA only (yellow), CSR with OSA stratified by treatment (blue with treatment, orange without treatment), CSR alone (gray), and previously published healthy control data by Manjunath et al. (red dotted). ** Healthy control data from and extrapolated to 3000 microns



Composite of sample OCT with subfoveal choroidal thickness measurement markers for the four cohorts – A: OSA only, B: CSC only, C: OSA+CSR without treatment, and D: OSA+CSR with treatment

Swept Source OCT Angiography in Vitreomacular Traction - Natural Follow-up Versus Vitreoretinal Surgery

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OBJECTIVE To determine changes in swept source OCT Angiography and visual acuity in the natural follow up versus surgical results in vitreomacular traction.

PURPOSE Vitreomacular traction (VMT) was defined as perifoveal vitreous cortex detachment, coexisting with macular cortex attachment and associated with retinal anatomical changes. The aim of this study was the analysis of retinal and choroidal vasculature in swept source OCT Angiography (SS-OCT A) in patients with natural course of vitreomacular traction syndrome as well as patients scheduled for surgery

METHODS Retrospective analysis of patients with the diagnosis vitreomacular traction who had at least two OCT Angiography examination in our database. Group A included non- treated patients with an at least 12 months follow-up. Group B included patients examined before and after surgical intervention. In all eyes a complete ophthalmic examination, swept source OCT and SS-OCT A was performed. We measured central retinal thickness (CRT), central choroidal thickness (CCT), width of traction and the area of the fovea avascular zone in superficial (sFAZ) and deep retina (dFAZ) vessels layer. During surgery core vitrectomy and ILM peeling (membrane blue) was performed.

RESULTS 38 eyes were included into this retrospective analysis In group A 24 patients were observed for 15 months. Traction spontaneously detached in 5/24 eyes (20%). In multivariate analysis spontaneous vitreous detachment was associated with the width of traction ($p<0.05$). The mean width of traction in eyes with complete spontaneous detachment was 396.8µm and 962 µm in eyes in which the traction remained visible. In one eye a lamellar macular hole was created after traction spontaneously relieved. A positive

correlation between dFAZ and CRT increased over time in group A ($p<0.05$). Hyporeflective areas were noted in all eyes at the choriocapillaries level. In group B, in 14 eyes, we noted a decrease of CRT ($p=0.01$) after surgery. CCT did not significantly change. The sFAZ and dFAZ area decreased after surgery ($p<0.05$). Multiple regression analysis revealed that initial visual acuity depends on initial central retinal thickness ($p<0.05$) and initial central choroidal thickness ($p<0.05$). Final visual acuity was better in eyes with primary focal vs. broad traction (according to the VMT study group). Hyporeflective areas noted at the choriocapillaries level decreased after surgery.

CONCLUSION The sFAZ and dFAZ decreased after vitrectomy with ILM peeling but not in eyes after spontaneous release of traction. It might suggest that long- persisting traction might influence superficial and deep retinal vasculature. In all cases of VMTS a hyporeflective artifact associated with traction is visible in the choriocapillaries layer. It disappears when traction is released.

HUMAN RESEARCH Yes: Approved by institutional review board