PROJECT TITLE: Spectral Domain-Optical Coherence Tomography Angiography of Posterior Segment Diseases

IDENTIFYING WORDS: spectral domain optical coherence tomography, optical coherence tomography angiography, noninvasive imaging, retinal disease, age-related macular degeneration, diabetic macular edema, diabetic retinopathy, retinal vascular occlusion, macular telangiectasia, glaucoma, optic neuropathies, choroidal diseases, uveitis, ocular inflammatory diseases

PRINCIPAL INVESTIGATOR: Priyatham S. Mettu, M.D.

MEDICALLY RESPONSIBLE: Priyatham S. Mettu, M.D.

PROJECT USES IONIZING RADIATION: No

PROJECT INVOLVES USE OF DURABLE POWER OF ATTORNEY: No

MULTI-INSTITUTIONAL PROJECT: No

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SUMMARY

Optical coherence tomography (OCT) is an optical ranging and imaging technique that provides high-resolution, micrometer-scale depth imaging in clinical ophthalmology. For the posterior segment of the eye, it allows rapid acquisition of cross-sectional posterior segment images that approximate tissue histology. While OCT has revolutionized diagnostic capability and advanced the development of therapeutics in the clinic for posterior segment diseases (defined as diseases of the retina, choroid, uveal tract, and optic nerve, including glaucoma), current commercially available OCT imaging units cannot provide information on retinal vasculature and physiologic perfusion. Angiography is the current gold-standard imaging modality for assessment of the retinal blood vessels. Angiography utilizes injection of an intravenous dye, a light source emitting light at the specific excitation wavelength of the dye, and a specially equipped camera that images at the specific emission wavelength of the dye. While generally well tolerated by most patients, angiography does have a few drawbacks: it requires several minutes for image acquisition typically on a separate imaging system, and patients can occasionally experience side effects of the intravenous dye, including nausea, discomfort, and rarely, anaphylaxis.

Several retinal imaging companies are developing the next generation of OCT technology: OCT angiography (OCT-A). OCT-A allows noninvasive, high-resolution imaging of the microvasculature of the retina and choroid (the vascular plexus subjacent to the retina), without the need for intravenous dye administration. OCT-A platforms currently under development include both spectral domain (SD) and swept-source (SS) based technologies. Whereas SS-based OCT-A utilizes a longer wavelength (~1060 nm) light source, SD-based units use the same light source used in commercially available and FDA-cleared OCT units on a modified platform. These include the AngioVue OCT-A unit (Optovue, Inc., Fremont, CA), the AngioPlex OCT-A unit (Zeiss, Inc., Dublin, CA), and the Spectralis SP-X1601 OCT-A (Heidelberg Engineering, Franklin, MA). These units utilize novel software algorithms that allow for detection of motion in the blood vessel lumen by measuring the variation in reflected OCT signal amplitude between consecutive cross-sectional scans. Each of these units can generate high-quality angiograms of both the retina and choroid, with images of the smallest retinal vessels (capillaries) in normal healthy control participants. In this proposed prospective interactive clinical study, we will use the AngioVue unit, the AngioPlex unit, and the Spectralis SP-X1601 OCT-A unit to image patients and characterize vascular abnormalities that are present in the setting of posterior segment diseases.

1.0 BACKGROUND

OCT is an optical ranging and imaging technique first described in 1991 that has since been used successfully to provide high-resolution, micrometer-scale depth imaging in clinical ophthalmology (and other fields). It can be thought of as the optical analogue of ultrasound imaging. For the ocular posterior segment, OCT provides rapid acquisition of high-resolution, cross-sectional images of the posterior segment that approximate tissue histology. In vivo imaging of the posterior segment with OCT has thus dramatically improved clinicians' diagnostic capabilities, allowing earlier and more accurate diagnosis of disease and more precise assessment of response to therapies over time.

While OCT provides important information on posterior segment anatomy, it is currently limited in its ability to provide information on retinal and choroidal vasculature and blood flow. Angiography is the current gold-standard imaging modality for retinal and choroidal vascular imaging. Angiography involves intravenous injection of a fluorescent dye (typically either fluorescein or indocyanine green for the retinal or choroidal vessels, respectively) that circulates through the body. A light source emitting light at the specific excitation wavelength of the dye is placed in front of the patient's eye, and a camera equipped with a filter corresponding to the emission wavelength of the dye is then used to image vessel morphology and retinal perfusion, either through still images or a short movie. Angiography provides physiologic information about the posterior segment that complements the anatomical information provided by OCT. While generally well tolerated by most patients, angiography does have drawbacks: it often requires the use of a separate imaging system, it requires several minutes for image acquisition, and it involves intravenous injection of a dye. Patients occasionally experience side effects of intravenous dye administration, including nausea, discomfort, and rarely, anaphylaxis.

Several retinal imaging companies are developing the next generation of OCT technology: OCT angiography (OCT-A). OCT-A allows noninvasive, high-resolution imaging of the microvasculature of the retina and choroid (the vascular plexus subjacent to the retina), without the need for intravenous dye

administration. OCT-A platforms currently under development include both spectral domain (SD) and swept-source (SS) based technologies. Whereas SS-based OCT-A utilizes a longer wavelength (~1060 nm) light source, SD-based units use the same light source used in commercially available and FDA-cleared OCT units on a modified platform. These include the AngioVue OCT-A unit (Optovue, Inc., Fremont, CA), the AngioPlex OCT-A unit (Zeiss, Inc., Dublin, CA), and the Spectralis SP-X1601 OCT-A (Heidelberg Engineering, Franklin, MA). These units utilize novel software algorithms that allow for detection of motion in the blood vessel lumen by measuring the variation in reflected OCT signal amplitude between consecutive cross-sectional scans. Each of these units can generate high-quality angiograms of both the retina and choroid, with images of the smallest retinal vessels (capillaries) in normal healthy control participants. In this proposed prospective interactive clinical study, we will use the AngioVue unit, the AngioPlex unit, and the Spectralis SP-X1601 OCT-A unit to image patients and characterize vascular abnormalities that are present in the setting of posterior segment diseases, as defined as diseases of the retina, choroid, uveal tract, and optic nerve, including glaucoma.

2.0 OBJECTIVE OF THE STUDY

The objective of this study is to image posterior segment vascular alterations in patients with posterior segment diseases using the AngioVue OCT-A system, the AngioPlex OCT-A system, and the Spectralis SP-X1601 OCT-A system and understand the information images captured on all three systems provide.

3.0 STUDY DESIGN AND METHODS

3.1 Experimental Design: This project is being conducted under abbreviated IDE, since this study was initially approved in 2015 for use of the AngioVue prior to the FDA clearance of the AngioVue unit, and because the Spectralis SP-X1601 remains investigational. Following acquisition of consent, study participants will undergo imaging of both eyes with the AngioVue unit (approximately 60 seconds/eye), the AngioPlex unit (approximately 60 seconds/eye), and the Heidelberg Spectralis unit (approximately 60 seconds/eye), per standard operating protocol for each unit. Imaging is noncontact, and pharmacologic dilation will not be used for the purposes of this study. In most instances, study participants will undergo

only a single imaging session on all three units on a single day, though participants will receive a break of approximately five minutes between imaging sessions. The cumulative time imaged on all three units will result in a total light source exposure that will remain well below the ANSI standards for safe maximal permissible exposure limits. However, potential participants will be asked to consent for additional imaging sessions (up to 12) that may occur over the course of subsequent future visits to the clinic. Additionally, study participants will be asked to consent to prospective collection of clinical and demographic data, to correlate findings of OCT-A imaging to subsequent clinical course.

3.2 Participant Selection: Participants will be identified from patients presenting for ophthalmologic consultation at the Duke Eye Center and/or one of its satellite clinical locations. All adults (age 18 or older) meeting study criteria (as detailed in Section 4.0) will be asked to participate. A care provider known to the patient will introduce the study and his/her ophthalmologist will be asked for prior approval before the study is discussed with the patient. Following this, members of the study staff will approach potential study participants.

3.3 Sample Size: The total planned enrollment for this pilot study is approximately 100 participants, to allow for the inclusion of a sufficient number of participants with several different posterior segment diseases.

3.4 Baseline Evaluation: Prior to study enrollment, potential participants must have had a previous examination that documents the presence of posterior segment diseases (including but not limited to age-related macular degeneration, diabetic retinopathy, diabetic macular edema, glaucoma, retinal vein occlusion, idiopathic macular telangiectasias, uveitis, and optic neuropathies).

3.5 Study Evaluation: If the participant meets the criteria for study inclusion and consent is obtained following full explanation of the research, study participants will undergo OCT-A imaging of both eyes, per standard operating protocol for imaging.

4.0 INCLUSION / EXCLUSION CRITERIA

4.1 Inclusion Criteria:

a) Capable and willing to provide consent

b) History of clinically diagnosed posterior segment diseases, including but not limited to age-related macular degeneration, diabetic retinopathy, glaucoma, retinal vein occlusion, macular telangiectasias, and diabetic macular edema, uveitis, and optic neuropathies.

c) At least 18 years of age

4.2 Exclusion Criteria:

a) Unable or unwilling to give consent

b) Under 18 years of age

4.3 Inclusion of Women and Minorities: Posterior segment diseases encompass a broad array of demographics, though they tend to be slightly more common in older individuals. No specific gender predominance is expected for such a diverse group. Study participants will be actively recruited from each gender. The target enrollment will be approximately 100 participants. Every effort will be made to include individuals of African-American and Hispanic racial/ethnic backgrounds, particularly given the high incidence of diabetic retinopathy in these individuals. Participants will not be compensated for participation.

TARGETED/PLANNED ENROLLMENT: Approximately 100 participants			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	4%	4%	8%
Not Hispanic or Latino	46%	46%	92%
Ethnic Category Total of All Participants*	50%	50%	100%
Racial Categories			
Native American/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	10%	10%	20%
White	40%	40%	80%
Racial Categories: Total of All Participants*	50%	50%	100%

5.0 PARTICIPANT MONITORING AND DATA COLLECTION PLAN:

Clinically indicated care will be provided to all participants as required. All imaging will be obtained according to established imaging protocols, by study personnel who have received necessary training in the safe and appropriate use of the OCT-A imaging devices. Data analysis will occur at the conclusion of the study using descriptive methods.

5.1 Statistical Considerations: We have planned on an enrollment of 100 participants to allow for the inclusion of a sufficient number of individuals with several different posterior segment vascular diseases at varying stages in the disease course. No prior clinical studies exist to guide our study sample size. We will use descriptive statistics to analyze data derived from the OCT-A images.

6.0 HUMAN PARTICIPANT PROTECTION

6.1 Safety and Confidentiality: No long-term safety concerns are anticipated as a result of study interventions. Imaging will not require contact with the eye. As prolonged intense light exposure can be harmful, this device will not be used for ocular examination under prolonged circumstances. The brightness settings will not exceed what is needed to provide clear visualization of the target structures. Additionally, the intensity of light directed into the patient's eye will be limited to the minimum level which is necessary for diagnosis. Dr. Mettu and his study staff will monitor for any safety events on a regular basis. After hours contact information will be provided to all study participants in case of an adverse event.

The AngioVue unit (Optovue) is comprised of the commercially available and FDA-cleared RTVue conventional SD-OCT imaging platform that has been modified to incorporate a novel imaging algorithm. Both the hardware and the imaging algorithm software of the AngioVue unit have been FDA

cleared, and the AngioVue unit is now commercially available (as of early 2016). This study was initially IRB approved in late 2015 under an abbreviated IDE, with non-significant risk (NSR) designation.

The AngioPlex unit (Zeiss) incorporates optical micro angiography algorithms that utilize amplitude and phase OCT signal data to deliver the high quality angiography images of the retina and choroidal vascular beds. The AngioPlex unit has received FDA clearance for use in clinical practice.

The Spectralis SP-X1601 OCT-A system uses the same light source used in commercially available and FDA approved OCT unit. Heidelberg has developed the SP-X1601 software which utilizes a novel algorithm to produce high quality angiography images on the Spectralis platform. While the Spectralis hardware of the platform is FDA cleared for use in clinical practice, the SP-X1601 software is investigational.

Each OCT system stores its scans locally within an internal hard drive, and all units will be stored securely with the Clinical Research Unit of the Duke Eye Center. However, confidentiality of the scans/files on the OCT device will be maintained by use of a unique study identifier (without medical record number, date of birth, or other PHI), effectively rendering the data de-identified on the local drive. The internal hard drive associated with the system will only be accessible by study personnel. Password-protected portable hard drives used to transfer and store de-identified OCT images for offline analysis; these hard drives will be "wiped" upon completion of this study.

Collected clinical data, including a single master list to relink the study ID to the participant, will be stored on password-protected, hard drive-encrypted computers in the Department of Ophthalmology. Only the investigators and approved study personnel will have access to these files. Once all data analyses are complete, the master list of study IDs will be deleted and overwritten to permanently de-identify all collected data for that study.

6.2 Participant Consent: A consent form has been developed that describes the nature of the research, the risk/benefit ratio, and the voluntary nature of participant involvement. Consent will be obtained directly from the participant in a private location within the clinic by the study PI, study coordinator, or other study

staff. Participants will be given a verbal explanation of the research and then will be granted ample time to read the consent form or have the consent read to them if necessary, and they will be permitted to ask questions. The consent and imaging will occur on the same day as the participant's visit to the clinic in order to limit transportation and logistical hardships, unless otherwise requested by the participant. Individuals unwilling to provide signed consent will not be enrolled.

6.3 Risks and Benefits: The risks of the study are as outlined above, for all study participants. Participants will not receive compensation and may not directly benefit from the study; however, this study will test a novel imaging modality that may improve the experience of future patients and could serve as the basis for future studies of OCT-A, with the overall goal of optimizing efficiency of care delivery for patients with posterior segment diseases.

6.4 Discomforts and Inconveniences: Expected discomforts and inconveniences of this study are related to the time required of the study participants for imaging. Dr. Mettu and study staff will monitor for any unanticipated adverse events arising from participation in this study; however, Duke University, the study physicians, and study staff will make no commitment to provide monetary compensation or free medical care to participants in the event of a study-related injury.

7.0 ETHICS

We will perform this trial in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws. Additionally, we will conduct the trial in accordance with the Declaration of Helsinki.

8.0 CHANGES TO THE PROTOCOL

Any change or addition to this protocol will only be completed with a written protocol amendment submitted to the IRB.