Retina Society Virtual Annual Meeting 2020

Impaired Layer Specific Retinal Vascular Reactivity Among Diabetic Subjects

Maxwell Singer[1], Bright S. Ashimatey[1], Xiao Zhou[2], Zhongdi Chu[2], Ruikang K. Wang[2], Amir H. Kashani[1,3]

[1]Department of Ophthalmology, Keck School of Medicine of the University of Southern California
[2]Department of Bioengineering, University of Washington
[3]USC Ginsberg Institute for Biomedical Therapeutics, Keck School of Medicine of the University of Southern California

Amir H. Kashani MD PhD

Associate Professor of Ophthalmology

USC Roski Eye Institute

USC University of Southern California

USC Roski Eye Institute
Keck Medicine of USC

Financial Disclosures

Commercial

- Carl Zeiss Meditec -- Research Funding, Honoraria and Travel
- Opternative -- Consultant
- Neurovision – Consultant
- Regenerative Patch Technologies – Research

Non-commercial

- University of Southern California
- National Eye Institute
- National Institute of Neurologic Diseases
- Research to Prevent Blindness

Conclusions

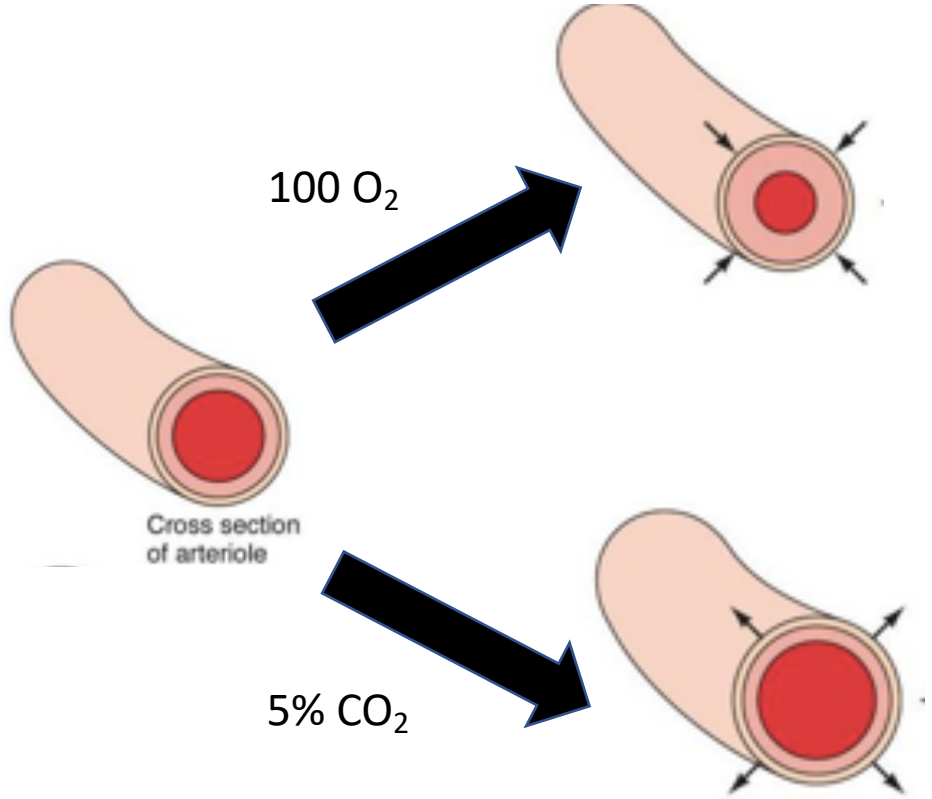
- We developed an *in vivo* OCTA based assay of human retinal capillary reactivity in response to physiologic changes in inhaled oxygen and carbon dioxide.

- Compared to non-diabetic controls we found significant attenuation or complete loss of capillary reactivity to hypercapnia and hyperoxia in both the superficial and deep retinal capillaries of subjects with diabetes and minimal to no diabetic retinopathy

- Our results were not changed when we included relatively large caliber arterioles or venules in our analysis. This suggests retinal vascular reactivity is mediated by changes in capillary properties.

- OCTA based retinal vascular reactivity assessment in humans is feasible and may play a useful role in detecting impaired capillary function before onset of clinically apparent diabetic retinopathy

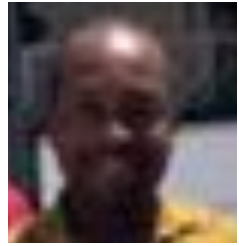
Retinal Vascular Reactivity To Inhaled Gas Mixtures



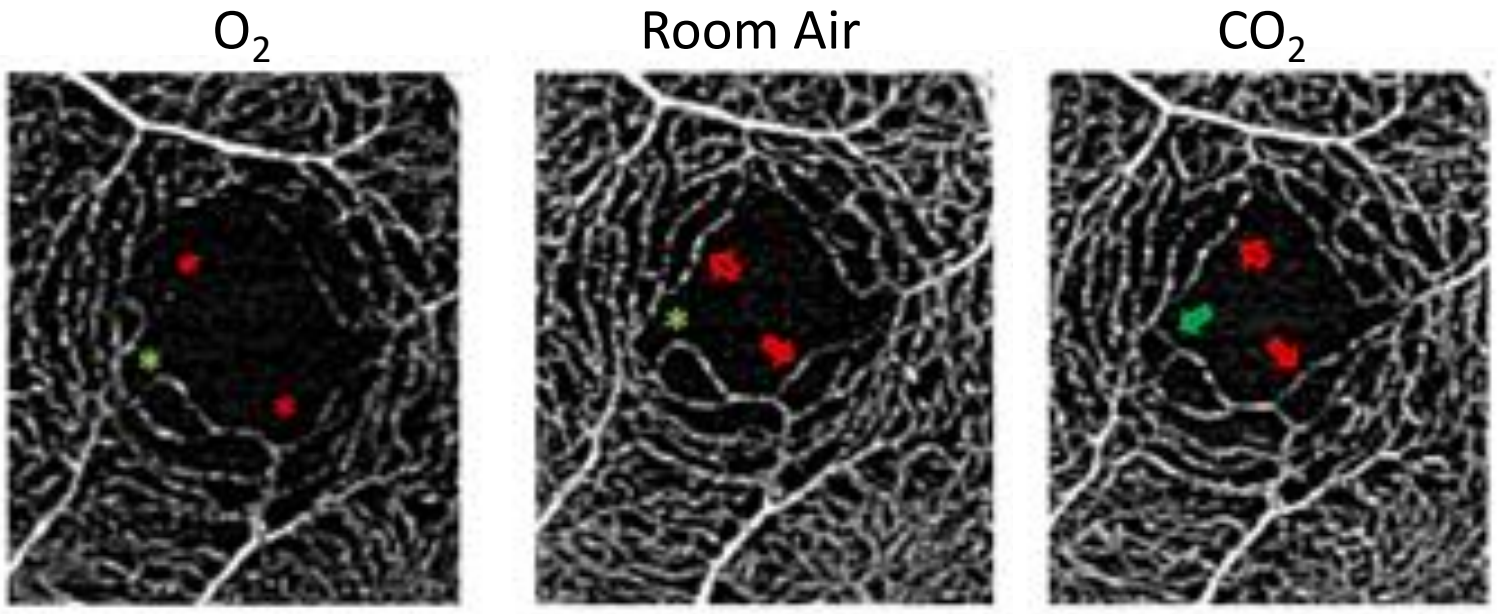
Vascular tissue is designed to modulate blood flow in response to physiologic stimuli such as changes in inhaled oxygen and carbon dioxide

In 2019 we published a novel method of assessing changes in retinal vascular reactivity to physiologic manipulations of inhaled oxygen and carbon dioxide.

Retinal Vascular Reactivity Assessment via OCTA



Full Thickness OCTA of Normal Human Subject Breathing Various Gas Mixtures

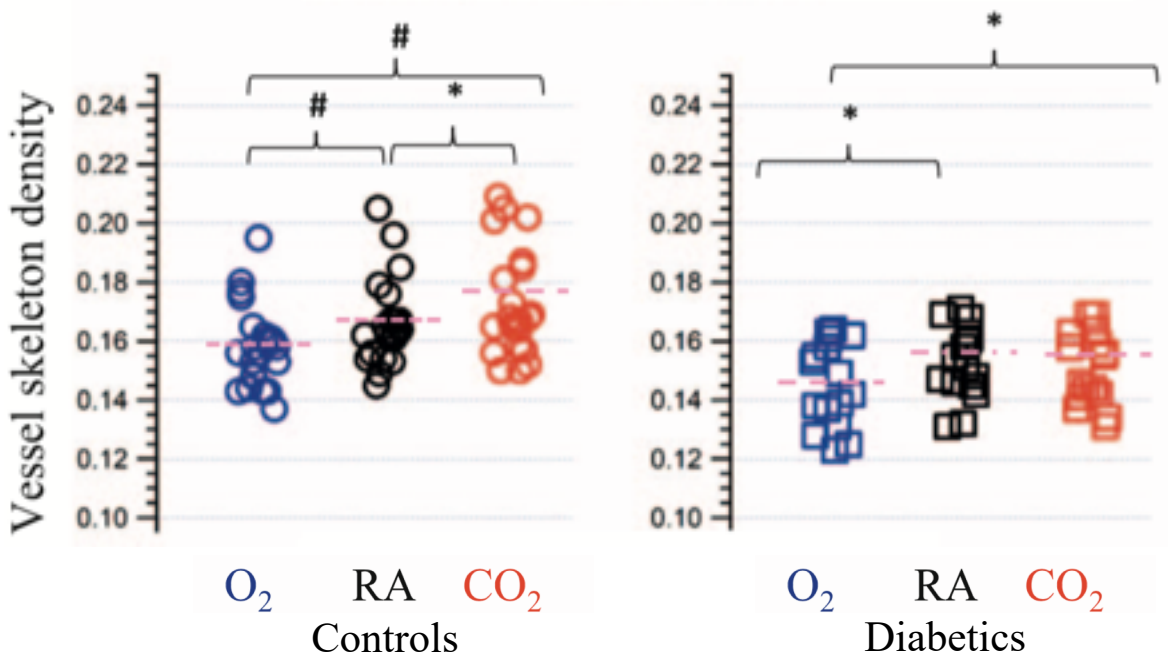


Ashimatey BS, Green KM, Chu Z, Wang RK, Kashani AH. "Impaired Retinal Vascular Reactivity in Diabetic Retinopathy as Assessed by Optical Coherence Tomography Angiography." *Investigative Ophthalmology & Visual Science* 60, no. 7 (June 3, 2019): 2468–73.

Impaired Retinal Vascular Reactivity in Diabetic Retinopathy as Assessed by Optical Coherence Tomography Angiography

Retinal vascular reactivity in diabetic subjects is impaired.

Impairment is more profound to hypercarbia than hyperoxia



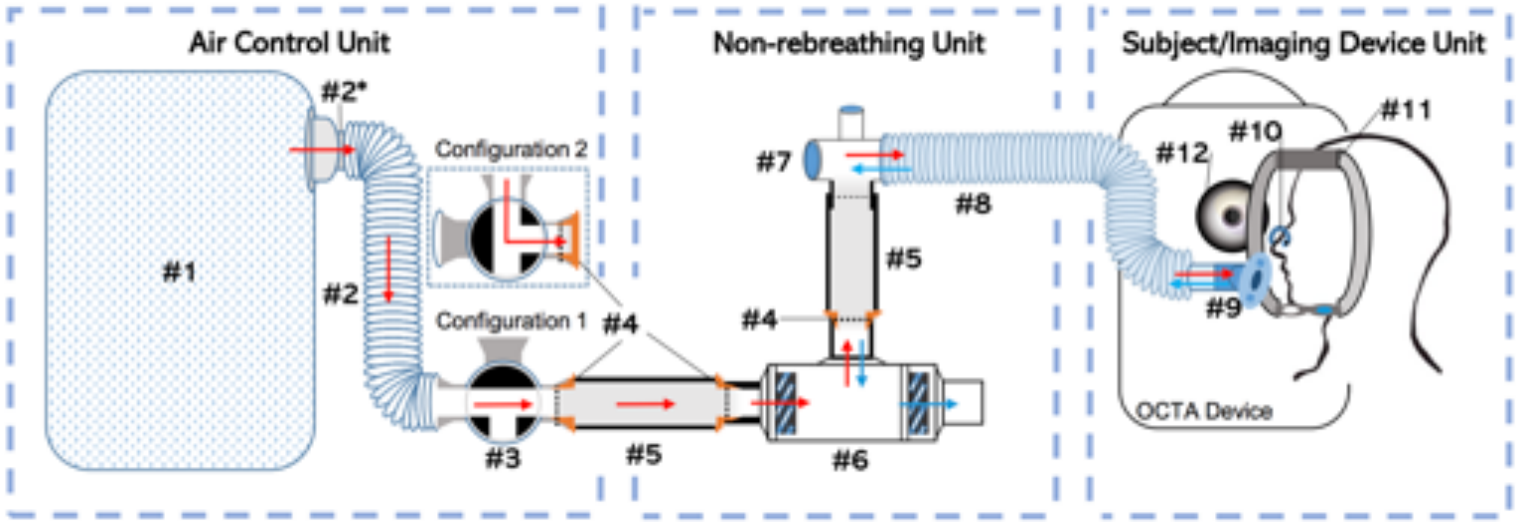
Ashimatey BS, Green KM, Chu Z, Wang RK, Kashani AH. "Impaired Retinal Vascular Reactivity in Diabetic Retinopathy as Assessed by Optical Coherence Tomography Angiography." *Investigative Ophthalmology & Visual Science* 60, no. 7 (June 3, 2019): 2468–73.

Purpose

To investigate layer specific and vessel caliber specific retinal vascular reactivity in healthy controls and subjects with mild non-proliferative diabetic retinopathy (NPDR) or no diabetic retinopathy (DR).

Methods: Gas Delivery System

OCTA acquired using SS-OCTA system (Carl Zeiss PLEX Elite 9000) during room air, 5% CO_2, or 100% O_2 delivery



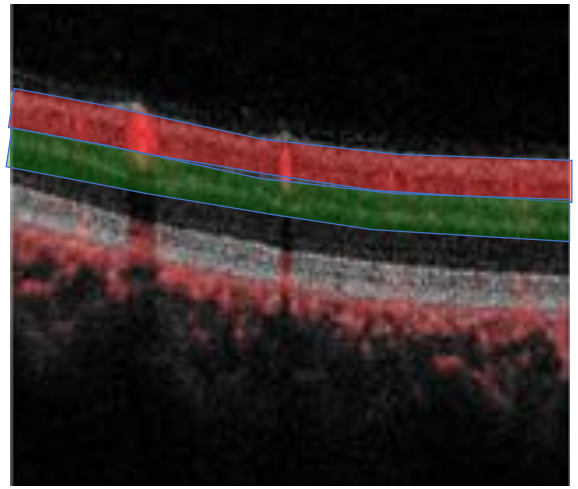
Kushner-Lenhoff A, Ashimatey, BS, Kashani AH., "Retinal Vascular Reactivity as Assessed by Optical Coherence Tomography Angiography." *Journal of Visualized Experiments: JoVE*, no. 157 (March 26, 2020).

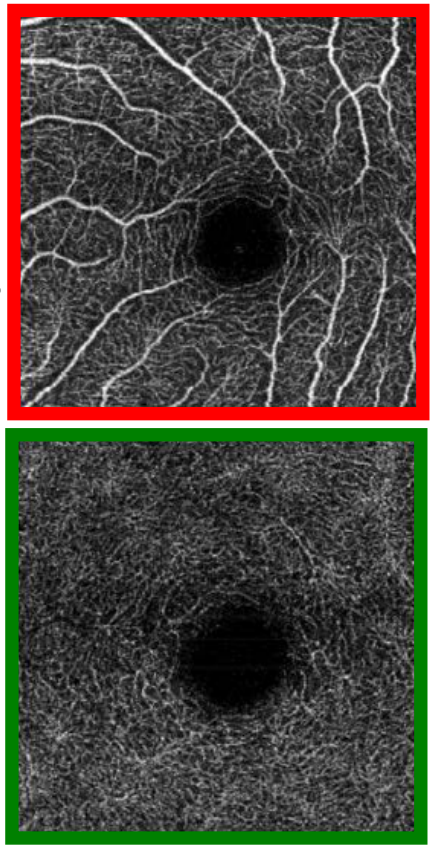
Methods: Scan Segmentation

3x3mm OCTA acquired using SS-OCTA system (Carl Zeiss PLEX Elite 9000)

Automated segmentation of SRL and DRL performed

Segmentation was manually reviewed for each subject





Methods: Morphometric Measures

$$\text{Vessel Skeleton Density (VSD)} = \frac{\sum_{(i,j)}^{n} L_{(i,j)}}{\left(\sum_{(i,j)}^{n} X_{(i,j)}\right)}$$

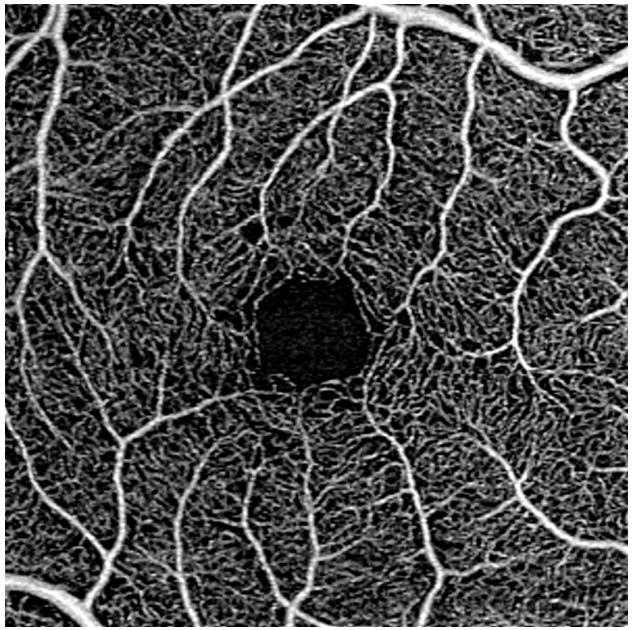
where $L_{(i,j)}$ represents pixels occupied by blood vessel length (white pixels in the skeletonized image) and $X_{(i,j)}$ are all pixels in the skeletonized image

$$\text{Vessel Area Density (VAD)} = \frac{\left(\sum_{(i,j)}^{n} B_{(i,j)}\right)^2}{\left(\sum_{(i,j)}^{n} X_{(i,j)}\right)^2}$$

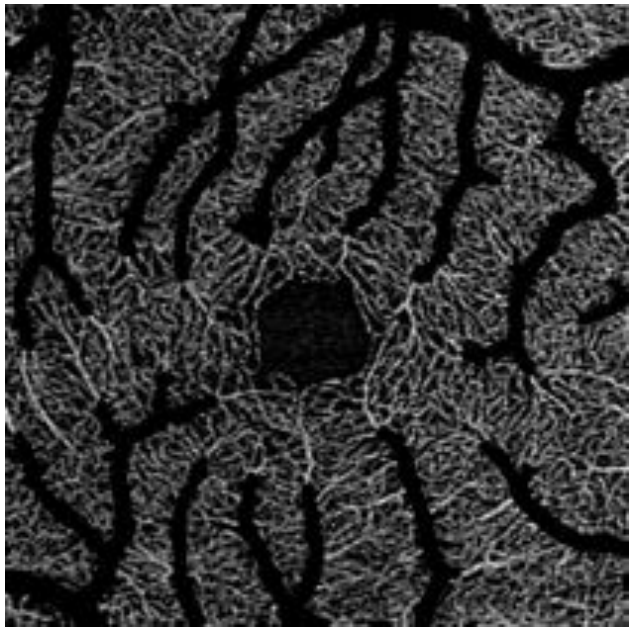
where $B_{(i,j)}$ represents pixels occupied by blood vessels (white pixels in the binarized image) and $X_{(i,j)}$ are all pixels in the binarized image.

Kim AY, Chu Z, Shahidzadeh A, Wang RK, Puliafito CA, Kashani AH. "Quantifying Microvascular Density and Morphology in Diabetic Retinopathy Using Spectral-Domain Optical Coherence Tomography Angiography." *Investigative Ophthalmology & Visual Science* 57, no. 9 (01 2016): OCT362-370.

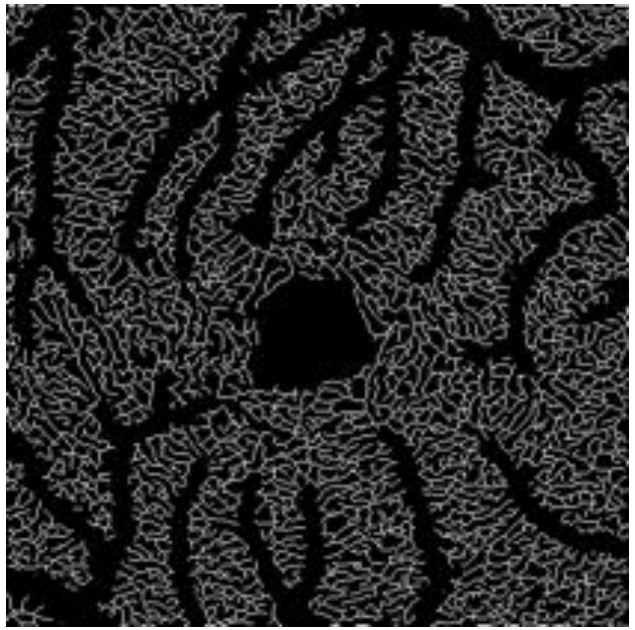
Methods: Large Vessel Exclusion



Original Image



Original Image with
Large Vessel Removal



Skeletonized Image with
Large Vessel Removal

(Singer M et al., in submission)

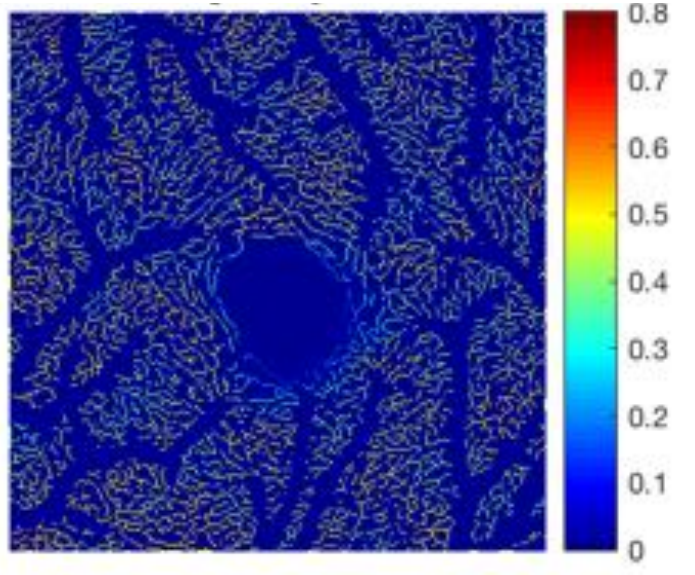
Results: Subject Demographics

	Disease Classification	
	Controls	Diabetics
Number (Subjects)	41	22
Age	53.0 ± 18.9	53.7 ± 16.7
Female Gender	20 (48.8%)	9 (40.9%)
Hypertension	10 (24.4%)	6 (27.3%)
Severity of diabetic retinopathy	N/A	15 no DR, 7 mild NPDR

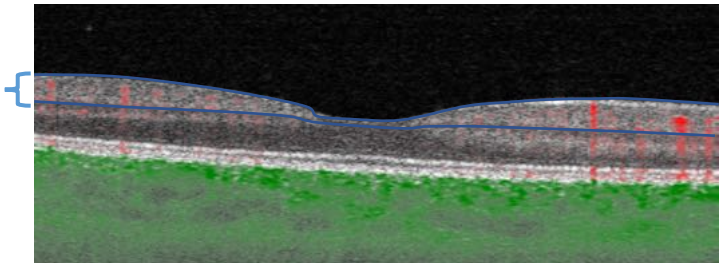
(Singer M et al., in submission)

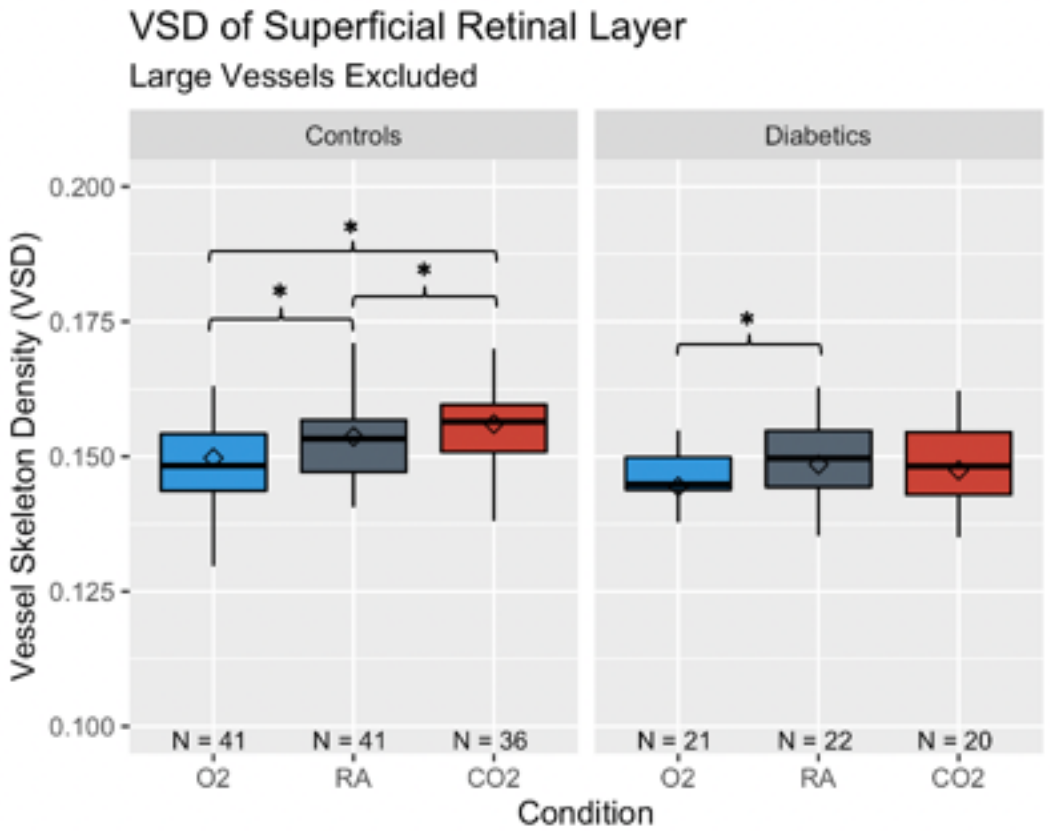
Results: Superficial Retinal Layer

Retinal vascular reactivity to CO_2 is absent in superficial retinal layer of diabetic subjects



Superficial Retinal Layer

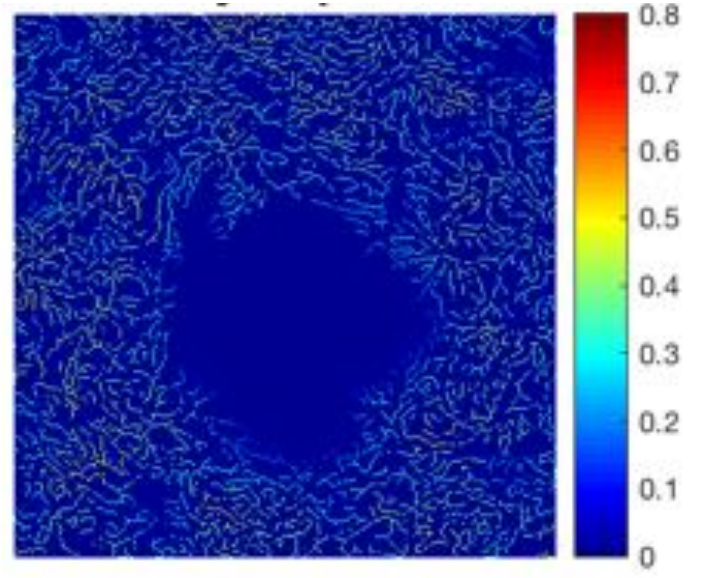




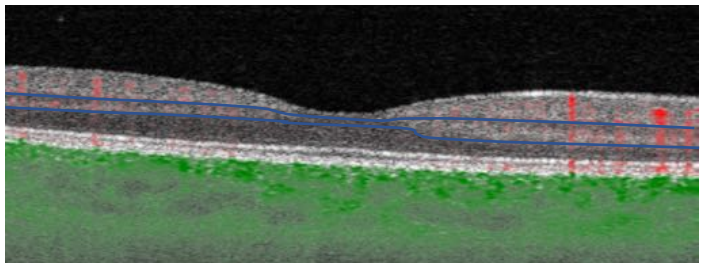
(Singer M et al., in submission)

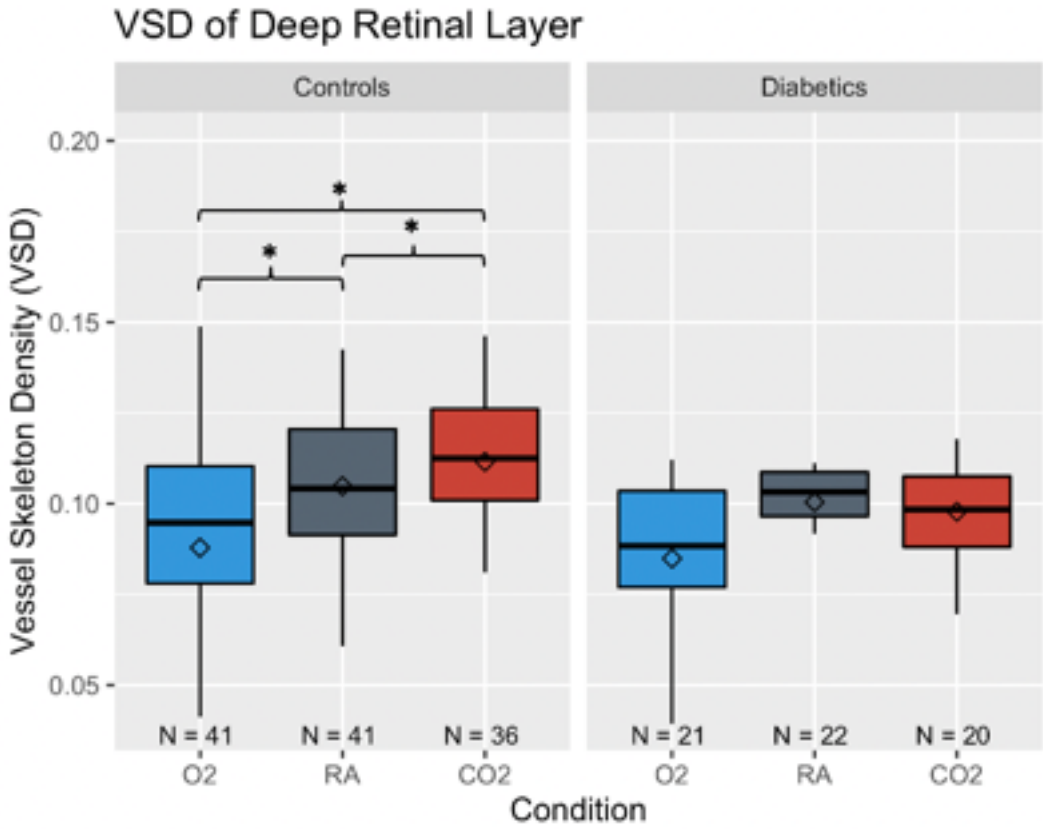
Results: Deep Retinal Layer

Retinal vascular reactivity to CO_2 and O_2 is impaired in deep retinal layer of diabetic subjects



Deep
Retinal Layer





(Singer M et al., in submission)

Conclusions

- We developed an *in vivo* OCTA based assay of human retinal capillary reactivity in response to physiologic changes in inhaled oxygen and carbon dioxide.
- Compared to non-diabetic controls we found significant attenuation or complete loss of capillary reactivity to hypercapnia and hyperoxia in both the superficial and deep retinal capillaries of subjects with diabetes and minimal to no diabetic retinopathy
- Our results were not changed when we included arterioles or venules in our analysis. This suggests retinal vascular reactivity is mediated by changes in capillary properties.
- OCTA based retinal vascular reactivity assessment in humans is feasible and may play a useful role in detecting impaired capillary function before onset of clinically apparent diabetic retinopathy

(Singer M et al., in submission)

USC University of Southern California

Acknowledgements

USC Roski Eye Institute
Keck Medicine of USC

Lab Members:
Bright S. Ashimatey, PhD

Collaborators:
Xiao Zhou
Zhongdi Chu, PhD
Ruikang K. Wang, PhD

ARI Network
Luis de Sisternes
Stephanie Magazzeni

Funding Sources:
Tai Family Research Scholars Fund
NIH R01EY030564
NIH K08EY027006
Research Grants Carl Zeiss Meditec
Unrestricted Departmental Grant
From Research To Prevent Blindness