

# Flicker Light-Induced Retinal Vasodilation is Lower in Alzheimer's Disease

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# Financial Disclosure



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Others- None

# Introduction



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- The pathological process of Alzheimer's disease (AD) is thought to begin many years before the diagnosis of AD dementia.
- The “preclinical” phase of AD would provide a critical opportunity for therapeutic intervention.
- There is active research around the globe in search of suitable early biomarkers for Dementia. These include blood, CSF and several imaging modalities.
- What is missing?

**Whether these biomarkers are primary or secondary effects**

# Introduction-new perspective?



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- A growing body of evidence suggests that *pre-symptomatic* Alzheimer's disease (AD) may be detected in sensory organs.
- In animal studies, Impairment in the olfactory system, for example, has been shown to precede cognitive impairment in AD by a substantial period. Specifically, there is studies showing that denervation of the Olfactory bulb leads to decreased beta amyloid deposition in the brain [1].
- The same may hold true with current evidence suggesting that neurodegenerative activity in the retina precedes that of in the brain [2]. (beta amyloid deposition in the retina at 2.5 months vs brain at 5 months)
- Fortunately, retina and the brain share similar physiological and pathological properties. In fact it's the only organ in which its internal structure can be visualised. Thus, the retina provides a “window” to visualize the cerebral circulation and study AD-related changes.

[1] Bibari, O. *et al.* Denervation of the olfactory bulb leads to decreased A $\beta$  plaque load in a transgenic mouse model of Alzheimer's disease. *Curr. Alzheimer Res.* **10**, 688–96 (2013).

[2] Koronyo-Hamaoui, M. *et al.* Identification of amyloid plaques in retinas from AD patients and in vivo optical imaging of retinal plaques in a mouse model. *Neuroimage* **54**, S204–S217 (2011).



# We need more AD-specific biomarkers



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## Study 1

136 demented patients with AD and 290 age-gender-race-matched controls. Patients with narrower venular caliber, decreased arteriolar and venular fractal dimension and increased arteriolar and venular tortuosity were more likely to have AD [1].

## Study 2

AD was diagnosed in 519 and vascular dementia in 73 participants. Larger venular calibers were associated with an increased risk of dementia. The association remained significant after adjustment for stroke and cardiovascular risk factors. Smaller arteriolar calibers were also associated with an increased risk of vascular dementia, yet only when adjusted for venular calibers [2].

## Lack of Specificity and Sensitivity

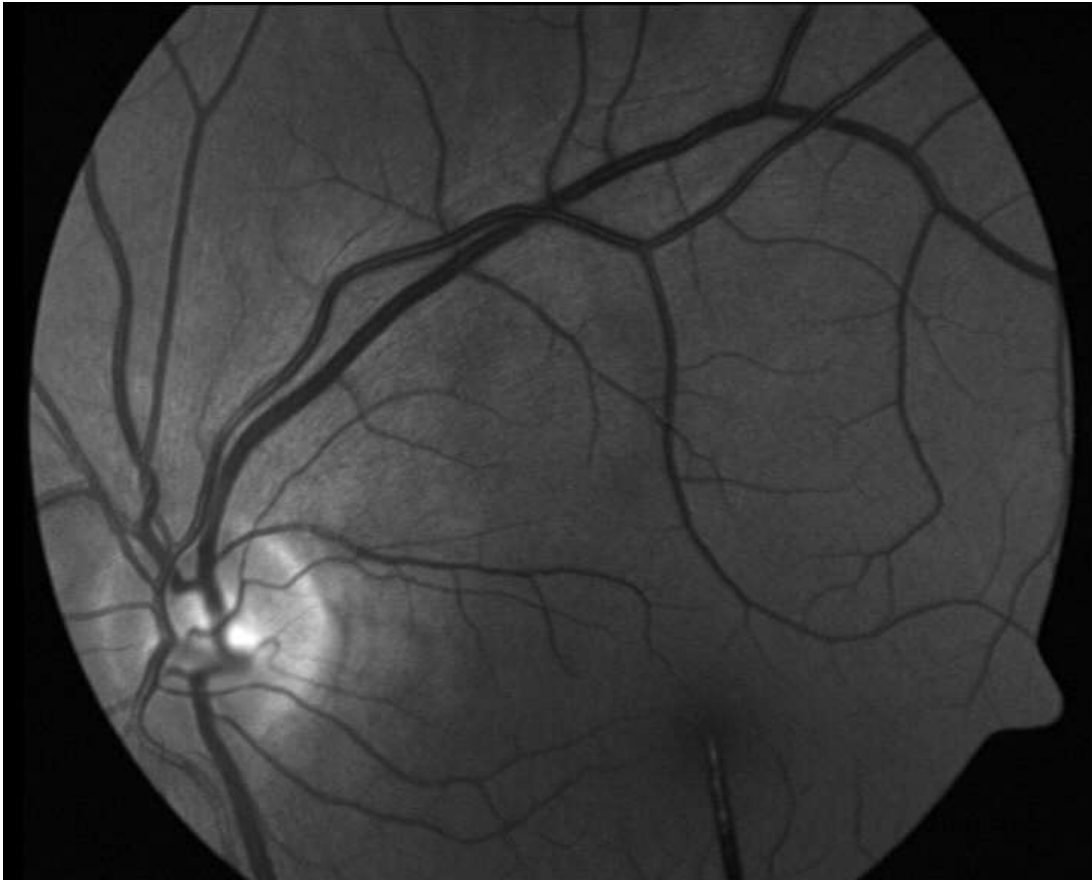
[1] Cheung, et al. (2014). Microvascular network alterations in the retina of patients with Alzheimer's disease. *Alzheimer's & Dementia* 10(2), 135–42

[2] De Jong, F. J., et al (2011). Retinal vascular caliber and risk of dementia: the Rotterdam study. *Neurology*, 76(9), 816–21.

# Dynamic Analysis



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*Indices measurable:*

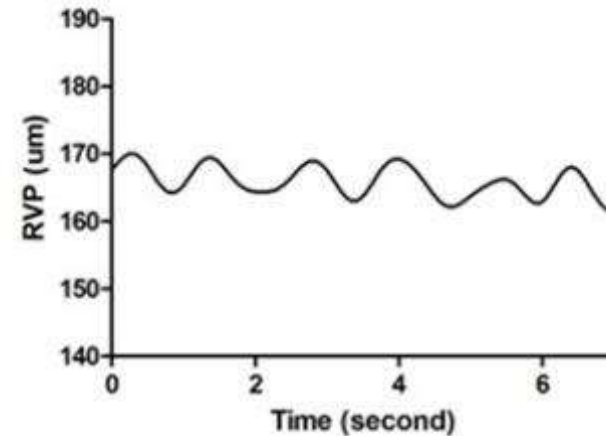
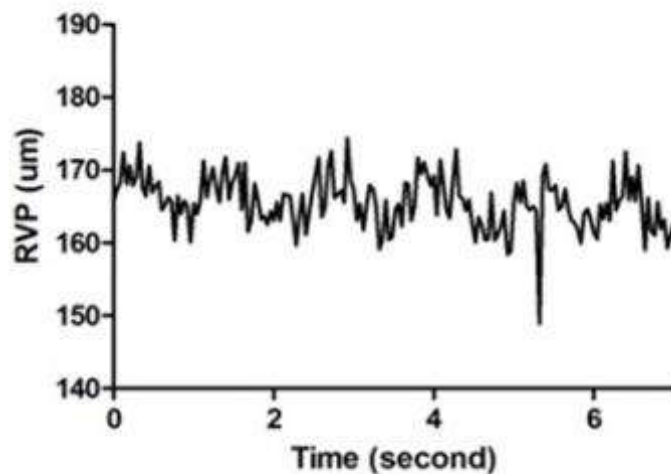
1. Pulse Wave Velocity  
(Measure of Vessel  
Stiffness)
2. Pulsatility Index
3. Retinal Vasodilation  
response

# Equipment



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- We use Dynamic Vessel Analyzer (DVA) to capture dynamic properties of retinal vessels
- DVA records at 25 Hz.
- We then filter the recordings and extract the amplitude of the pulsations

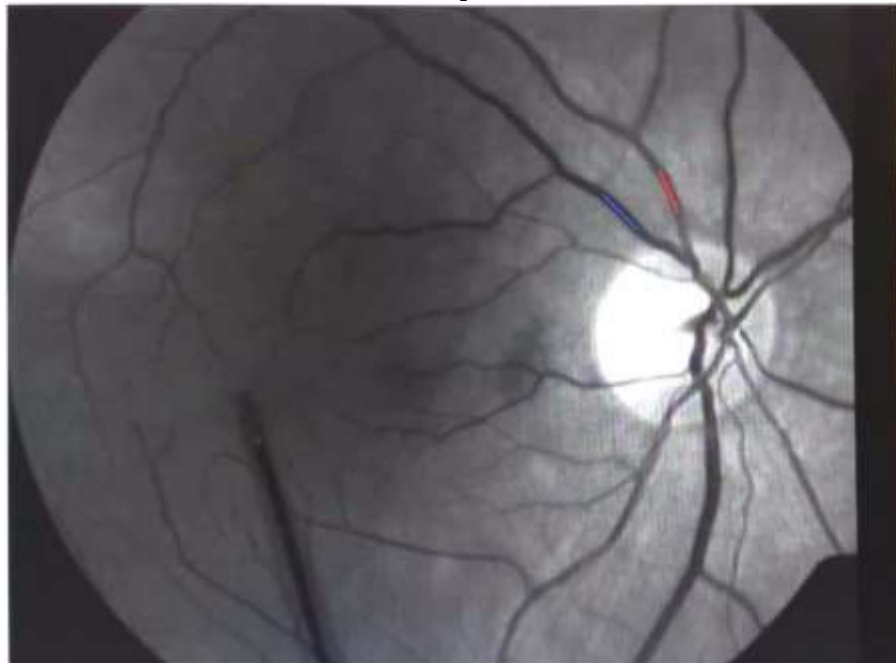


# Endothelial Dysfunction



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- Retinal vasodilation is a normal physiological response to flicker light stimulation.
- This phenomenon is recognised as a function of increased retinal ganglion cell activity and nitric oxide (NO) release to provide additional oxygen to meet the increased requirements of metabolically active cells in the retina.
- To measure Endothelial Dysfunction (Edf), DVA uses the illumination light of the fundus camera which is reflected by the retina and blood vessels.

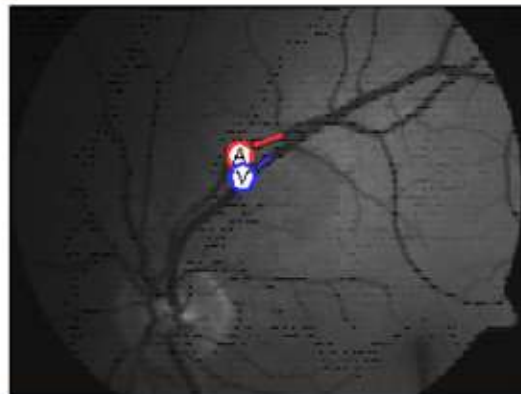
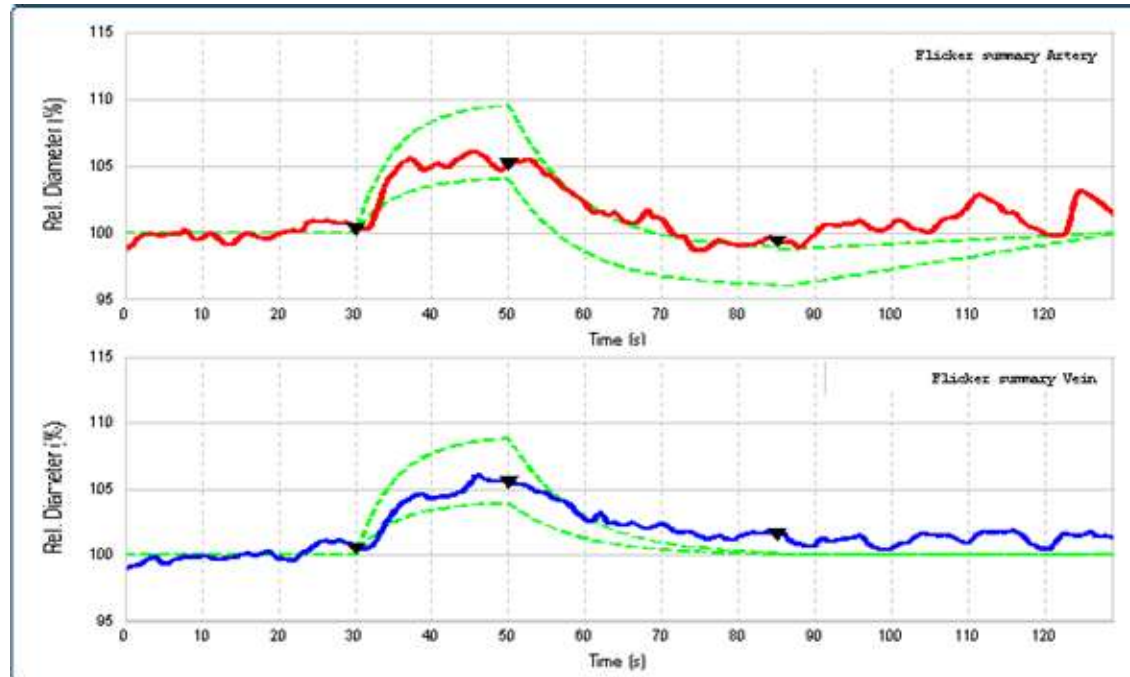




# Endothelial Dysfunction



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Artery	<Local>	Normal Mean	Normal STD
Value (MU)	128.55	-	-
Valid (%)/Cycles	75.7 / 3	>30	-
Max. Dil. (%)	+5.2	+6.9	±2.8
Max. Constr. (%)	-0.7	-2.7	±1.4
Peak Value (%)	+5.9	+9.6	±3.0
Vein	<Local>	Normal Mean	Normal STD
Value (MU)	165.55	-	-
Valid (%)/Cycles	76.6 / 3	>30	-
Max. Dil. (%)	+5.5	+6.5	±2.5

# This Study



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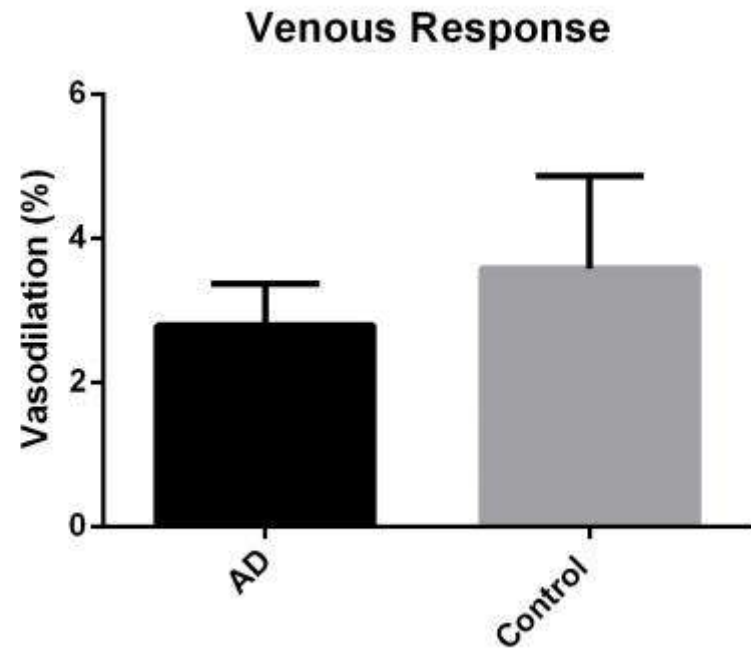
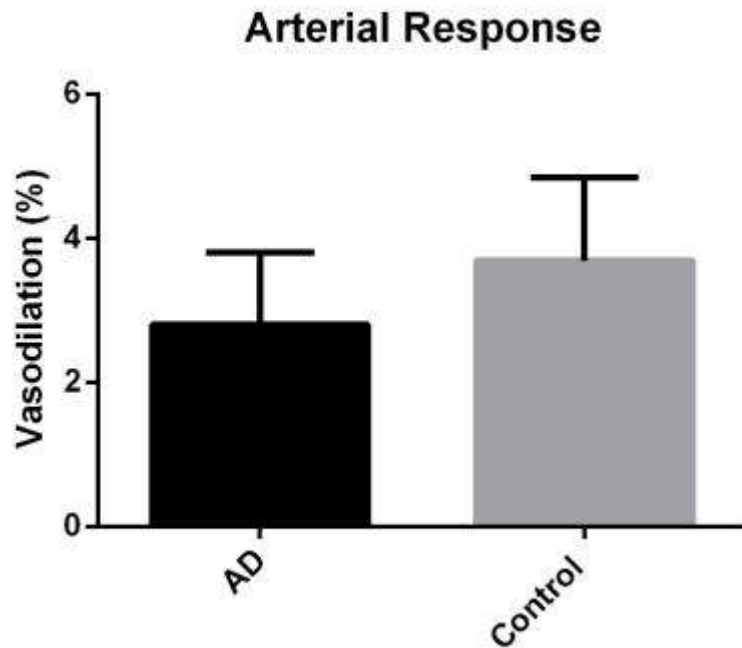
- 42 subjects including 19 diagnosed with AD (10 male, age  $72 \pm 6$  yrs) and 23 healthy controls (12 male, age  $67 \pm 10$  yrs) were included.
- Following initial eye assessment, pupils of all subjects were dilated with Tropicamide 1%. Intraocular Pressure (IOP) was measured using Goldman tonometry.
- Resting calibers of selected retinal vessel segments were recorded in measurement units (MU).
- Maximum percentage dilations during flicker stimulation were calculated from baseline calibers using the Dynamic Vessel Analyzer.

# Results

The arterial and venous response to flicker induced light showed a significantly lower vasodilation in the AD group compared with controls :

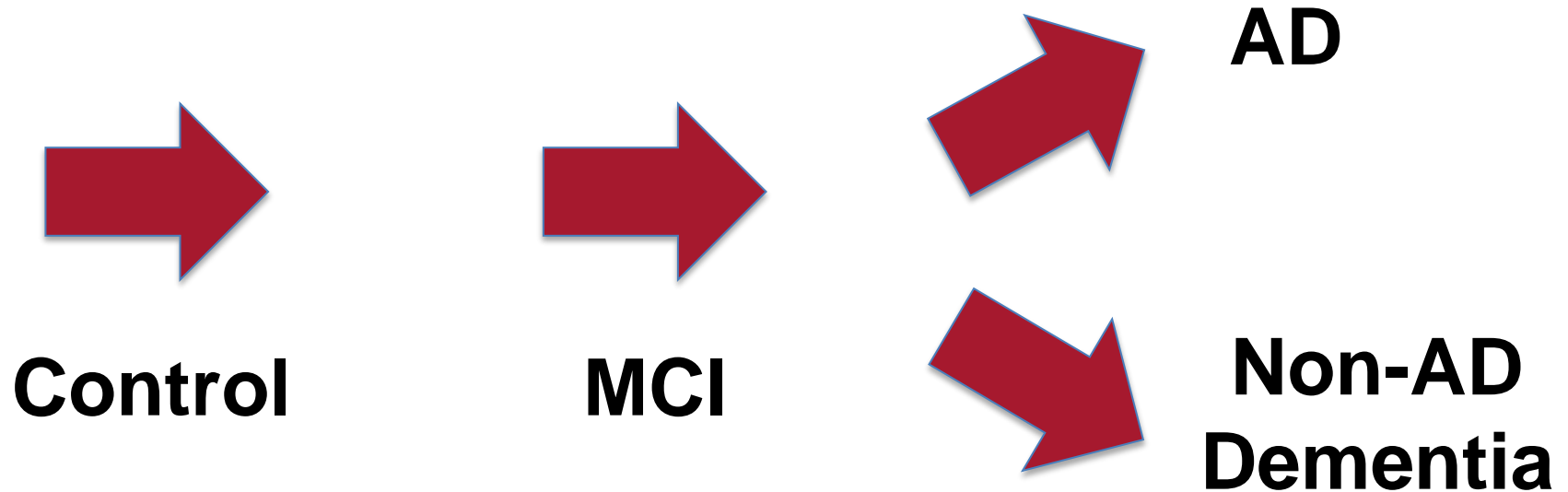
**Artery:**  $2.8 \pm 1\%$  vs.  $3.7 \pm 1\%$  ( $p < 0.01$ )

**Vein:**  $2.7 \pm 0.6\%$  vs.  $3.6 \pm 1\%$  ( $p < 0.05$ )



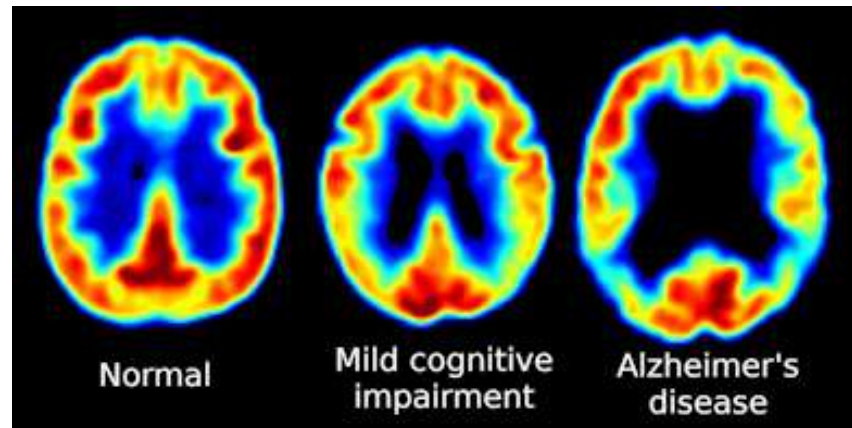


## Determine Specificity of Retinal Measurements



# What's Next

- Recruited 100 pre-AD patients (on-going collaborative study with Prof. Ralph Martins)
- MRI and FDG PET scans along with all retinal scans
- Longitudinal study



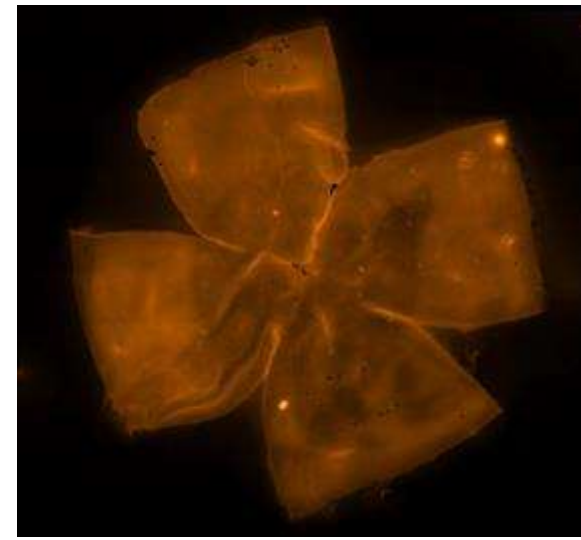
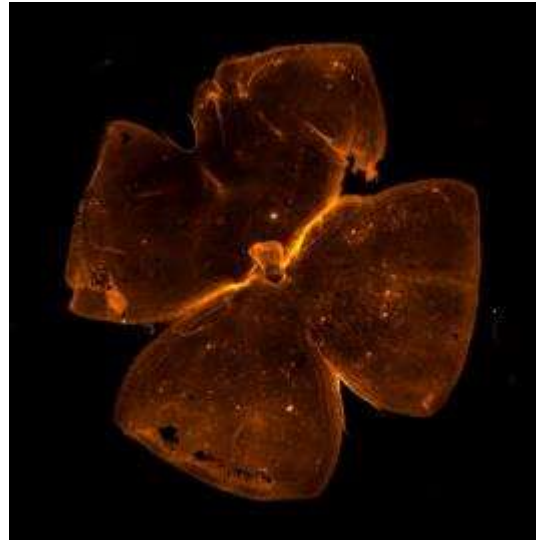
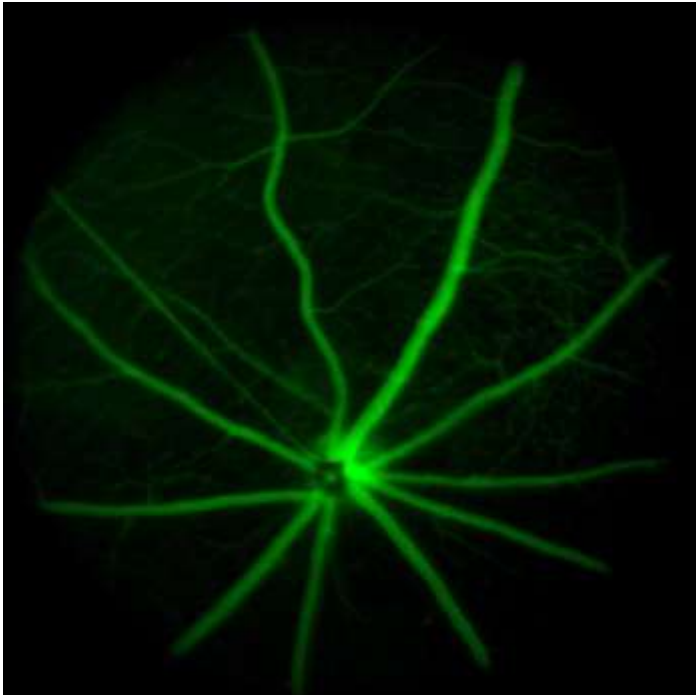
# What's Next



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## Animal Studies (APP/PS1)

- Measure dynamic properties of retinal vessels in conjunction with brain degeneration
- Measure beta amyloid deposition in the retina vs. brain and then Compare with vascular properties



# Conclusions



- Dynamic changes of retinal vessels can be used as a biomarker for preclinical AD
- Endothelial dysfunction along with increased mechanical force on vessels (increased pulsatility) may play a significant role in the early stages of AD.
- The co-morbidity with other diseases needs further investigation. e.g; a few studies have shown that AD patients have a 3 fold increase in glaucoma development.
- We are investigating whether this is a primary or secondary phenomenon

# Acknowledgments

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