Measurement of Blood Flow in the Retina and Optic Disc with OCT

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Financial Interests:
Dr. D. Huang has a significant financial interest in Optovue, a company that may have a commercial interest in the results of this research and technology. This potential individual conflict of interest has been reviewed and managed by OHSU.
Optovue, Inc.: stock options, patent royalty, grants, speaker honorarium & travel support
Carl Zeiss Meditec, Inc.: patent royalty

The leading causes of blindness are all associated with abnormal ocular circulation:

- Glaucoma
- Diabetic Retinopathy
- Macular Degeneration
A technique for rapid & accurate quantitation of total retinal blood flow is needed

Laser doppler flowmeter – time consuming

Fluorescein & ICG angiography - qualitative

Doppler ultrasound - inaccurate

Double circular scan transects all retinal branch vessels 12 times in 2 seconds

Semi-automated grading software was developed for Doppler OCT reading center

**Doppler OCT of Retinal Circulation (DOCTORC) software uses both double-circular and 3D volumetric scans**


Glaucoma, treated proliferative diabetic retinopathy, and optic neuropathy all reduce retinal blood flow

<table>
<thead>
<tr>
<th>Group (# of eyes)</th>
<th>Blood Flow (μl/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (20)</td>
<td>47.6 ± 5.4</td>
</tr>
<tr>
<td>Glaucoma (16)</td>
<td>34.1 ± 4.9 (p&lt;0.001)</td>
</tr>
<tr>
<td>NAION (7)</td>
<td>28.2 ± 8.2 (p&lt;0.001)</td>
</tr>
<tr>
<td>PDR (5)</td>
<td>15.8 ± 10.1 (p&lt;0.001)</td>
</tr>
</tbody>
</table>
Doppler OCT detects decreased blood flow in HIV microvasculopathy

<table>
<thead>
<tr>
<th></th>
<th>HIV (n=22)</th>
<th>Controls (n=23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Blood Flow$^a$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (μL/min)</td>
<td>38.2 ± 8.1</td>
<td>47.2 ± 7.0</td>
<td>0.0007</td>
</tr>
<tr>
<td>Median (range, [μL/min])</td>
<td>39.0 (22.7 to 53.5)</td>
<td>44.4 (38.1 to 62.4)</td>
<td></td>
</tr>
</tbody>
</table>

Courtesy of Drs. Partho Kalyani & Gary Holland (UCLA)

What is the role of blood flow in glaucoma?

- Elevated IOP
- Loss of retinal ganglion cells & nerve fibers
- Loss of visual field
- Decreased blood flow

David Huang, MD, PhD [www.AIGStudy.net]
Visual field, total retinal blood flow, and neural tissue loss were studied

Optovue RTVue Fourier-domain OCT system
Overall average thickness of the nerve fiber layer (NFL)
Overall average thickness of the ganglion cell complex (GCC)
Total retinal blood flow (Doppler software not yet FDA-approved)

Heidelberg Retina Tomograph (HRT3) confocal scanning laser ophthalmoscopy (cSLO) system
Optic nerve head rim area

Relationship among visual field, blood flow, and neural structure measurements in glaucoma. IOVS 2012; in press

Perimetric glaucoma and age-matched normal subjects in the Advanced Imaging for Glaucoma study cohort were studied

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal</th>
<th>Glaucoma</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>27</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Eyes, n</td>
<td>27</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>62.1 ± 9.0</td>
<td>61.4 ± 8.7</td>
<td>0.73</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>1 (4)</td>
<td>3 (7)</td>
<td>0.99</td>
</tr>
<tr>
<td>Systemic Hypertension, n (%)</td>
<td>10 (37)</td>
<td>15 (36)</td>
<td>0.84</td>
</tr>
<tr>
<td>Systemic Antihypertensive Medication, n (%)</td>
<td>4 (15)</td>
<td>11 (23)</td>
<td>0.56</td>
</tr>
<tr>
<td>Intraocular Pressure (mmHg)</td>
<td>14.3 ± 2.1</td>
<td>13.5 ± 2.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>82.5 ± 8.6</td>
<td>80.3 ± 8.0</td>
<td>0.32</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>130.3 ± 17.1</td>
<td>124.6 ± 12.0</td>
<td>0.12</td>
</tr>
<tr>
<td>Diastolic Ocular Perfusion Pressure (mmHg)</td>
<td>68.6 ± 8.9</td>
<td>66.8 ± 7.5</td>
<td>0.41</td>
</tr>
<tr>
<td>Systolic Ocular Perfusion Pressure (mmHg)</td>
<td>116.4 ± 17.6</td>
<td>111.1 ± 11.1</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Relationship among visual field, blood flow, and neural structure measurements in glaucoma. IOVS 2012; in press
Total retinal blood flow and vascular caliber were reduced in glaucoma subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Glaucoma</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Retinal Blood Flow (μl/min)</td>
<td>45.5 ± 9.5</td>
<td>34.9 ± 8.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Arterial Area (mm²)</td>
<td>0.033 ± 0.0077</td>
<td>0.028 ± 0.0074</td>
<td>0.006</td>
</tr>
<tr>
<td>Venous Area (mm²)</td>
<td>0.047 ± 0.012</td>
<td>0.041 ± 0.0086</td>
<td>0.01</td>
</tr>
</tbody>
</table>


Blood flow was highly correlated with visual field, but not with structural parameters

**Spearman’s correlation coefficient R**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Visual Field MD (dB)</th>
<th>Blood Flow (dB)</th>
<th>cSLO Rim Area (dB)</th>
<th>OCT NFL (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Flow (dB)</td>
<td>0.48 (&lt;0.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cSLO Rim Area (dB)</td>
<td>0.34 (0.02)</td>
<td>-0.02 (.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCT RNFL Thickness (dB)</td>
<td>0.37 (0.01)</td>
<td>0.19 (0.23)</td>
<td>0.36 (0.02)</td>
<td></td>
</tr>
<tr>
<td>OCT GCC Thickness (dB)</td>
<td>0.20 (0.20)</td>
<td>0.03 (0.84)</td>
<td>0.31 (0.04)</td>
<td>0.68 (&lt;0.01)</td>
</tr>
</tbody>
</table>

- All values in dB scale normalized against 27 normal eyes.
- Age, blood pressure, intraocular pressure, and ocular perfusion pressure were not significantly correlated VF, blood flow, or structural measures

Visual field loss was independently correlated with both blood flow and neural tissue loss

Multivariate regression and analysis of variance for visual field mean deviation (MD)

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Variable 1</th>
<th>Slope (p)</th>
<th>$R^2$</th>
<th>Variable 2</th>
<th>Slope (p)</th>
<th>$R^2$</th>
<th>Total $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Blood Flow</td>
<td>1.91 (&lt;=0.001)</td>
<td>0.26</td>
<td>Rim Area</td>
<td>1.15 (0.006)</td>
<td>0.10</td>
<td>0.36</td>
</tr>
<tr>
<td>Model 2</td>
<td>Blood Flow</td>
<td>1.62 (0.001)</td>
<td>0.24</td>
<td>NFL</td>
<td>2.56 (0.03)</td>
<td>0.09</td>
<td>0.33</td>
</tr>
</tbody>
</table>

- All values in dB scale normalized against 27 normal eyes.
- Age, blood pressure, intraocular pressure, and ocular perfusion pressure were not significant factors when added to the multivariate models

Blood flow is >2 times as important as structural variables in explaining the variation in visual field deviation


Blood flow has a direct effect on visual function independent of neural structural loss

Elevated IOP → Decreased blood flow → Loss of retinal ganglion cells & nerve fibers → Loss of visual field

David Huang, MD, PhD www.AIGStudy.net
OCT Split-Spectrum Amplitude-Decorrelation Angiography (SSADA)

David Huang, MD, PhD
Yali Jia, PhD

Ultrahigh-Speed Swept-Source OCT

Developed by MIT Optic & Quantum Electronic Group (Fujimoto) and OHSU Center for Ophthalmic Optics and Lasers (Huang)

**Performance features:**
- 100,000 axial scans/sec
- 1050 nm tunable laser (deep penetration)
- 6 μm axial resolution in tissue
OCT amplitude-decorrelation angiography uses intrinsic contrast – no dye injection!

8 consecutive OCT scans at each position (M-B-scan Mode, N=8)

Problem: 8 frames at one position do not provide sufficient angiography quality

Solution: Split-Spectrum Amplitude Decorrelation (SSADA) Algorithm

8 frames at one position now provides good angiography quality
Intentional lowering of OCT resolution to optimize flow detection

Full-Spectrum

Split-Spectrum

Coherence length \( \Delta z = \frac{0.44 \lambda_0^2}{\Delta \lambda} \)

resolution cell (full width half amplitude) \( (\Delta x = \Delta y = 18 \mu m, \Delta z = 6 \mu m) \)

Orbital pulsation \( \rightarrow \) Z motion

Blood flow \( \rightarrow \) X, Y motion

More sensitive to noise than flow

Modified isotropic resolution cell \( (\Delta x = \Delta y = \Delta z' = 18 \mu m) \)

More channels of flow information
Less axial motion noise

Comparison of Cross-Sectional Decorrelation Angiograms

High Noise

Faint Blood Vessels

Low Noise

Clear Blood Vessels

Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. Optics Express 2012; 20:4710
**En face Projection Angiogram**

*Image showing 3D rendering of an en face projection angiogram with labels for maximum and en face projection.*

Yali Jia, PhD, David Huang, MD, PhD [www.AIIGStudy.net](http://www.AIIGStudy.net)

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**Comparison of Angiography Algorithms**

*Images showing a comparison of full-spectrum and split-spectrum amplitude decorrelation angiography, highlighting a more continuous microvascular network and less noise with >2x SNR.*

OCT angiography is 3 dimensional

SSADA algorithm used

3x3x3 mm OCT 3D angiography acquired in a 3-second scan

Reflectance (Structure) Decorrelation (Flow)


OCT Angiography of the Optic Nerve Head – Layer by Layer

SSADA algorithm used

3x3x3 mm OCT 3D angiography acquired in a 3-second scan

OCT Angiography Showing Reduced ONH Blood Flow in Glaucoma

![Disc Photo](image1)

<table>
<thead>
<tr>
<th>Normal (OD)</th>
<th>Preperimetric Glaucoma (OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image2" alt="Disc Photo" /></td>
<td><img src="image3" alt="OCT Angiography" /></td>
</tr>
</tbody>
</table>

Average flow index = 0.188 ± 0.003
Average flow index = 0.098 ± 0.006

David Huang, MD, PhD, John Morrison, MD, Yali Jia, PhD  [www.AIGStudy.net](http://www.AIGStudy.net)

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OCT Angiography (SSADA) v. Fluorescein/ICG Angiography

**OCT Advantages**
- 3 dimensional
  - Easily separates disc, retinal, and choroidal circulations
  - Sections & projections along any plane
- Quantitative
  - Flow index
- No injection
  - No vomiting or anaphylactic reaction

**OCT Disadvantages**
- Small field (3 mm)
  - Field will increase with higher speed
- No visualization of leakage and stain
  - But can visualize fluid space and thickening

David Huang, MD, PhD [www.AIGStudy.net](http://www.AIGStudy.net)
Applications of OCT Angiography & Doppler OCT

- Diabetic Retinopathy:
  - Assess capillary dropout & macular ischemia
  - Visualize Neovascularization in 3D
  - Evaluate global reduction in blood flow
- Age-related macular degeneration
  - Assess choroidal ischemia
  - See flow in choroidal neovascular membrane
- Glaucoma
  - Evaluate global reduction in blood flow
  - Evaluate reduced disc perfusion
  - Evaluate reduced macular ganglion cell perfusion
- Diagnosis, prognosis, tracking, assessing treatment effectiveness

David Huang, MD, PhD  [www.AIGStudy.net](http://www.AIGStudy.net)
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www.COOLLab.net