## Functional & Structural OCT in Glaucoma

**David Huang, MD, PhD**  
Weeks Professor of Ophthalmic Research  
Prof. of Ophthalmology & Biomedical Engineering  
Casey Eye Institute,  
Oregon Health & Science University  
Portland, Oregon

**Financial Interests:**  
Dr. Huang has a significant financial interest in Carl Zeiss Meditec. Oregon Health & Science University (OHSU) and Dr. Huang have a significant financial interest in Optovue, a company that may have a commercial interest in the results of this research and technology. These potential conflicts of interest have been reviewed and managed by OHSU. Carl Zeiss Meditec, Inc.: patent royalty. Optovue, Inc.: stock options, patent royalty, grants, speaker honorarium.

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### OCT captures tissue function as well as structure

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<td><img src="image1" alt="Structural OCT" /></td>
<td><img src="image2" alt="Functional OCT" /></td>
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<td>Doppler shift (between consecutive A-scans)</td>
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</tbody>
</table>
Clinical Application

Structural Imaging in Glaucoma

Glaucoma affects 3 areas in the posterior segment of the eye:

- Cupping
- Rim loss
- Nerve fiber thinning
- Ganglion cell loss

David Huang, MD, PhD  www.COOLLab.net
SD-OCT and TD-OCT NFL profiles have similar glaucoma diagnostic accuracy

- Cirrus SD-OCT equivalent to Stratus TD-OCT
  - Chang RT et al. Ophthalmology 2009; 115:2294
  - Moreno-Montanes J et al. IOVS 2010; 51:335

- RTVue SD-OCT equivalent to Stratus TD-OCT

- OTI SD-OCT equivalent to Stratus TD-OCT
  - Cho et al. J Glaucoma 2011;20:15

- Spectralis SD-OCT better than HRT cSLO


SD-OCT NFL mapping may be better at detecting focal RNFL bundle defect

![Image](Image)

Jeoung, et al, IOVS 2010; 51:938
SD-OCT NFL reproducibility is better than TD-OCT: glaucoma tracking may be better with SD-OCT

- Cirrus SD-OCT better than Stratus TD-OCT
- RTVue SD-OCT better than Stratus TD-OCT
- Intersession Coefficient of Variation
  - 1.8% for FD-OCT
  - 3.6% for TD-OCT


---

SD-OCT disc analysis: BMO-MRW may enhance diagnostic accuracy

Chauhan et al. *Ophthalmology* 2013;120:535
OCT is used to map ganglion cell complex

GCC = Ganglion Cell Complex

GCC and NFL thicknesses have similar diagnostic accuracy

- GCC and NFL AROC are equivalent
  - Garas, et al, Eye (Lond) 2011;25:57-65

- GCC may have higher diagnostic accuracy in high myopes
  - Shoji, et al, IOVS 2011; 52:1098-1102
High-speed FD-OCT allows correlation of glaucoma disease patterns – Pre-Perimetric Glaucoma

David Huang, MD, PhD
www.AIGStudy.net

Macular GCC and peripapillary NFL are equal and complementary in diagnostic power

<table>
<thead>
<tr>
<th>Diagnostic Parameter</th>
<th>PG AROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCC-AVG (μm)</td>
<td>0.90</td>
</tr>
<tr>
<td>GCC-FLV (%)</td>
<td>0.92</td>
</tr>
<tr>
<td>GCC-GLV (%)</td>
<td>0.92</td>
</tr>
<tr>
<td>NFL-AVG (μm)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

GCC & NFL have similar diagnostic accuracy

Combining GCC, NFL, and disc data improves diagnostic accuracy

Huang JY et al., *J Glaucoma* 2011;20:87

RTVue FD-OCT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Overall Thickness (NFL+GCC)</td>
<td>32%</td>
<td>2.28 per 10 µm thinner</td>
<td>0.025</td>
</tr>
<tr>
<td>Combined FLV (NFL+GCC)</td>
<td>37%</td>
<td>1.35 per 1% higher</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vertical C/D Ratio</td>
<td>31%</td>
<td>1.39 per 0.1 higher</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Blue = GSDI
Green = NFL GLV (best single parameter)

NFL = nerve fiber layer
GLV = global loss volume
GCC = ganglion cell complex
FLV = focal loss volume
C/D = cup/disc

David Huang, MD, PhD [www.AIGStudy.net](http://www.AIGStudy.net)
GSDI Beats Any Single Variable

<table>
<thead>
<tr>
<th>Region</th>
<th>Best Variable</th>
<th>AUC</th>
<th>Sensitivity at 95% Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFL</td>
<td>GLV</td>
<td>0.919</td>
<td>68.5%</td>
</tr>
<tr>
<td>GCC</td>
<td>FLV</td>
<td>0.912</td>
<td>72.3%</td>
</tr>
<tr>
<td>Disc</td>
<td>Vertical CDR</td>
<td>0.873</td>
<td>62.4%</td>
</tr>
<tr>
<td>GSDI</td>
<td>n/a</td>
<td>0.942</td>
<td>81.7%</td>
</tr>
</tbody>
</table>

Glaucomatous right eye of a 63 year old male:
GSDI=0.96, P<1%

Baseline GCC predicts likelihood of visual field progression

```
-- GCC FLV > 5% volume loss
- GCC FLV < 5% volume loss

P < 0.01

5% 40%
```

David Huang, MD, PhD  www.AIGStudy.net
**SD-OCT provides more repeatable measurements that may be useful for glaucoma tracking**

95 Percentile Cutoff for Intervisit Change in Overall Average Thickness in Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>NFL</th>
<th>GCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD-OCT (Stratus)</td>
<td>-9.9%</td>
<td></td>
</tr>
<tr>
<td>SD-OCT (RTVue)</td>
<td>-5.6%</td>
<td>-5.1%</td>
</tr>
</tbody>
</table>

**Subject 108 Perimetric Glaucoma OS**

[Images of retinal images showing hemorrhage and rim thinning at baseline, 1 year, and 2 years]

David Huang, MD, PhD [www.AIGStudy.net](http://www.AIGStudy.net)
Humphrey VF Glaucoma Progression Analysis

No Change

TD-OCT (Stratus) Serial Analysis

No Change
**SD-OCT (RTVue) NFL Glaucoma Progression Report**

<table>
<thead>
<tr>
<th>Time</th>
<th>Baseline</th>
<th>6 month</th>
<th>1 year</th>
<th>2 year</th>
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<tbody>
<tr>
<td>NFL avg</td>
<td>91.6</td>
<td>90.3</td>
<td>91.8</td>
<td>87.3</td>
</tr>
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</table>

4.7% loss

Non-Significant Progression

**SD-OCT (RTVue) GCC Glaucoma Progression Report**

<table>
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<th>Baseline</th>
<th>6 month</th>
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<th>2 year</th>
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<tbody>
<tr>
<td>GCC avg</td>
<td>83.1</td>
<td>79.5</td>
<td>82.2</td>
<td>73.6</td>
</tr>
</tbody>
</table>

11.4% loss

Significant Progression
High-speed OCT wide-field imaging will further enhance detection of focal glaucomatous loss

VF defect

100 kHz SS-OCT

NFL Reflectance

Rim defect

NFLThickness Map GCC Thickness Map

Ganglion cell complex thinning

NFL defect

New Frontier

Functional OCT

David Huang, MD, PhD www.AIGStudy.net
The leading causes of blindness are all associated with abnormal ocular circulation:

**Glaucoma**
**Diabetic Retinopathy**
**Macular Degeneration**

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**OCT captures tissue function as well as structure**

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Structural OCT

Functional OCT
Total Retinal Blood Flow Calculation Using Double circular scan

\[ \text{Flow} = \int_{\text{vessel area}} \frac{\lambda \Delta f \, dx}{2n \sin(\alpha)} \]

\( \lambda \): wavelength
\( \Delta f \): Doppler shift
\( n \): refractive index
\( \alpha \): Doppler angle

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

<table>
<thead>
<tr>
<th>Group (# of eyes)</th>
<th>Blood Flow ((\mu l/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>

Total retinal blood flow and vascular caliber were reduced in glaucoma subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal (27 subjects)</th>
<th>Glaucoma (42 subjects)</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>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>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>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.


Hemispheric Retinal Blood Flow in Asymmetric Glaucoma

<table>
<thead>
<tr>
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<th>Abnormal Hemifield</th>
<th>Normal Hemifield</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF Sensitivity (1/La)</td>
<td>535 ± 340</td>
<td>874 ± 352</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Retinal Blood Flow (µL/min)</td>
<td>15.3 ± 5.4</td>
<td>19.3 ± 8.4</td>
<td>0.03</td>
</tr>
<tr>
<td>NFL (µm)</td>
<td>87.0 ± 20.2</td>
<td>103.7 ± 20.6</td>
<td>0.002</td>
</tr>
<tr>
<td>GCC (µm)</td>
<td>77.6 ± 12.1</td>
<td>83.6 ± 10.1</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Decreased blood flow not an artifact of IOP or glaucoma drops.

Sehi, M et al., Retinal Blood Flow in Glaucomatous Eyes with Single Hemifield Damage. Submitted for publication.
Blood flow has a direct link with visual function independent of neural structural loss

1. Elevated IOP
2. Loss of retinal ganglion cells & nerve fibers
3. Loss of visual field
4. Decreased blood flow

Split-Spectrum Amplitude Decorrelation Angiography (SSADA) with Ultrahigh-Speed OCT

OCT ANGIOGRAPHY
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)
- 5.3 µm axial resolution in tissue

Potsaid B, et al., Optics Express 2010; 18:20029

**OCT amplitude-decorrelation angiography uses intrinsic contrast – no dye injection!**

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

SSADA improves signal to noise ratio of flow detection

Full Spectrum

Split Spectrum

Less Background Noise

Clear Vessels

Comparison of Angiography Algorithms

More continuous microvascular network

Full-Spectrum Amplitude Decorrelation

Split-Spectrum Amplitude Decorrelation

Less Noise

>2x SNR

Motion error can be removed with 3D registration of x-fast and y-fast scans

Kraus et al. Biomedical Optics Express 2012; 3:1182

Yali Jia, PhD, David Huang, MD, PhD www.AIGStudy.net
3D OCT angiography of optic nerve head

SSADA algorithm used

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

Reflectance (Structure) Decorrelation (Flow)

Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. Optics Express 2012; 20:4710

OCT Angiography of the Optic Nerve Head – Layer by Layer

SSADA algorithm used

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

Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. Optics Express 2012; 20:4710
Variability of Disc Flow Index
(2x 2y registered OCT angiogram)

Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>Intra-Visit Repeatability (n = 4)</th>
<th>Inter-Visit Reproducibility (n = 4)</th>
<th>Inter-Subject Variability (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.2%</td>
<td>4.2%</td>
<td>5.0%</td>
</tr>
</tbody>
</table>

Less variable than OCT NFL measurement!

Pilot Study Subject Characteristics

- **Normal**
  - 24 eyes of 24 subjects
  - Age: 52±10 years (mean ± SD)

- **Glaucoma**
  - 11 eyes of 11 subjects
  - 8 perimetric glaucoma, 3 pre-perimetric glaucoma
  - Age: 68±10 years

David Huang, MD, PhD, John Morrison, MD, Yali Jia, PhD  www.AIGStudy.net
Glaucoma reduced ONH flow index

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Glaucoma</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual field</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean deviation (dB)</td>
<td>0.20 ± 0.87</td>
<td>-3.28 ± 4.12</td>
<td>0.003</td>
</tr>
<tr>
<td>Pattern standard deviation (dB)</td>
<td>1.43 ± 0.20</td>
<td>4.44 ± 3.12</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Structure (cSLO)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rim area (mm²)</td>
<td>1.55 ± 0.34</td>
<td>1.13 ± 0.25</td>
<td>0.007</td>
</tr>
<tr>
<td>Cup/Disc area ratio</td>
<td>0.11 ± 0.10</td>
<td>0.37 ± 0.17</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>Blood flow</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disc flow index</td>
<td>0.161 ± 0.008</td>
<td>0.121 ± 0.026</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Numbers displayed are mean ± population standard deviation; cSLO, scanning laser ophthalmoscopy

* Wilxson rank sum

Glaucoma caused a -25% drop of blood flow in optic disc

David Huang, MD, PhD, John Morrison, MD, Yali Jia, PhD  www.AIGStudy.net

OCT Angiography Showing Reduced ONH Blood Flow in Pre-Perimetric Glaucoma

<table>
<thead>
<tr>
<th>Normal (OS)</th>
<th>Preperimetric Glaucoma (OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>PFG</td>
</tr>
<tr>
<td>Disc Photo</td>
<td>OCT Angiography</td>
</tr>
</tbody>
</table>

ONH flow index = 0.159

ONH flow index = 0.125

David Huang, MD, PhD, John Morrison, MD, Yali Jia, PhD  www.AIGStudy.net
ONH flow index vs. visual field

No overlap between normal and glaucoma

R = -0.84

Difference between normal and glaucoma not due to age, cup/disc ratio or rim area
Summary & Conclusions

• ONH microcirculation is reduced in glaucoma
• Pre-perimetric changes can be detected by quantitative OCT angiography
• ONH flow index can be measured with high repeatability (1.2% CV) and high reproducibility (4.2% CV)
• Variability is small among normals: 5.0% CV
• OCT angiography with the SSADA algorithm may be a useful new tool in the evaluation of glaucoma

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 (3-4 mm)
  – Larger field with higher speed
• No visualization of leakage and stain
  – But can visualize fluid space and thickening

David Huang, MD, PhD, www.COOLLab.net

David Huang, MD, PhD, www.AIGStudy.net
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