Functional OCT for Glaucoma

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

Financial Interests:
OHSU and Dr. D. Huang have 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
Carl Zeiss Meditec, Inc.: patent royalty

OCT captures tissue function as well as structure

<table>
<thead>
<tr>
<th>Signal</th>
<th>Information</th>
<th>En Face</th>
<th>Cross Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflectance</td>
<td>Anatomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doppler shift (between consecutive A-scans)</td>
<td>Total retinal blood flow (global circulation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decorrelation (between consecutive B-scans)</td>
<td>Angiography (local circulation)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

David Huang, MD, PhD www.COOLLab.net
Total Retinal Blood Flow Calculation Using Double circular scan

Flow profile and direction determined on parallel sections

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

- \(\lambda\): wavelength
- \(\Delta f\): Doppler shift
- \(n\): refractive index
- Doppler angle \(\alpha = 90^\circ - \theta\)

Implemented on RTVue (Optovue, Inc.) 26 kHz spectral FD-OCT
Experimental software: off-label use of RTVue


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 ((\mu l/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>Model 1</td>
<td>Blood Flow</td>
<td>1.91</td>
<td></td>
<td>Rim Area</td>
<td>1.15</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>(&lt;0.001)</td>
<td></td>
<td></td>
<td>(0.006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>Blood Flow</td>
<td>1.62</td>
<td></td>
<td>NFL</td>
<td>2.56</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>(0.001)</td>
<td></td>
<td></td>
<td>(0.03)</td>
<td></td>
<td></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 link with 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

Hemispheric Retinal Blood Flow in Asymmetric Glaucoma

30 eyes of 30 subjects

<table>
<thead>
<tr>
<th></th>
<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

Total Retinal Blood Flow Using *En Face* Doppler OCT

Dual circular OCT scan requires both Doppler shift and angle for blood flow calculation.

*Doppler angle* *θ* measurement imprecise

*En face* Doppler OCT measurement of blood flow requires only Doppler shift.


---

Multi-Plane *En face* Doppler Measurement of Total Retinal Blood Flow

5 repeated volume scans in 3 seconds

Flow in each retinal vein is measured at optimal depth (optimal Doppler signal)

Implemented on RTVue-XR “Avanti” (Optovue, Inc.) 70 kHz spectral FD-OCT
Experimental software: off-label use of RTVue-XR

Ou Tan, PhD; David Huang, MD, PhD www.COOLLab.net
### Automated En face Doppler OCT Measurement of Total Retinal Blood Flow

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean± SD (µl/min)</th>
<th>Repeatability (CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (12 eyes)</td>
<td>33.9±4.9</td>
<td>8.6 %</td>
</tr>
<tr>
<td>Glaucoma (12 eyes)</td>
<td>25.9±5.7</td>
<td>8.4 %</td>
</tr>
</tbody>
</table>

#### Advantages of en face v. dual-circular Doppler OCT
- Fewer scans needed (1 v. 6)
- Automated measurement algorithm
- Improved repeatability

Ou Tan, PhD; David Huang, MD, PhD; John C. Morrison, MD. [Casey Eye Institute](http://www.caseyeinstitute.org)

---

![Split-Spectrum Amplitude Decorrelation Angiography (SSADA) with Ultrahigh-Speed OCT](image)

**OCT ANGIOGRAPHY**

David Huang, MD, PhD [www.COOLLab.net](http://www.COOLLab.net)
High-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)
- 5.3 µm axial resolution in tissue

Experimental system: not FDA-approved

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

---

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

David Huang, MD, PhD, Yali Jia, PhD  www.COOLLab.net
Solution: Split-Spectrum Amplitude Decorrelation (SSADA) Algorithm

8 high resolution OCT amplitude frame

32 low resolution OCT amplitude frame

28 decorrelation frame

M-B frames (N=8)

split spectrum (M=4)

averaged decorrelation

8 frames at one position now provides good angiography quality

Comparison of Angiography Algorithms

More continuous microvascular network

Full-Spectrum Amplitude Decorrelation

Split-Spectrum Amplitude Decorrelation


Less Noise
>2x SNR
OCT Angiography of the Optic Nerve Head – Layer by Layer

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

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

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!

Glaucoma reduced disc 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

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

ONH flow index

ONH flow index

Glaucoma reduces perfusion at multiple levels of optic nerve head

Retinal plane

Choroidal plane

Lamina cribrosa & sclera

Optic disc flow index vs. visual field

![Graph showing the relationship between optic disc flow index and visual field PSD (dB). The graph indicates a strong negative correlation (R = -0.84) with no overlap between normal and glaucoma groups.]


SSADA on Commercial OCT

- RTVue-XR “Avanti” (Optovue, Inc.)
- 70 kHz spectral FD-OCT
- 3x3 mm or 6x6 mm SSADA
- Orthogonal registration and merging of 2 consecutive scans
- 3.8 sec / scan

Experimental software: off-label use of RTVue-XR

David Huang, MD, PhD; Yali Jia, PhD  www.COOLab.net
**Pilot Study Subject Characteristics**

- **Normal**
  - 30 eyes of 30 subjects
  - Age: 56±11 years (mean ± SD)

- **Glaucoma**
  - 13 eyes of 13 subjects
  - 9 perimetric glaucoma, 3 pre-perimetric glaucoma
    and 1 glaucoma suspect.
  - Age: 70±10 years

---

**Variability of Peripapillary Retinal Flow (1x 1y registered OCT angiogram)**

**Normal Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Intra-visit repeatability N=30</th>
<th>Population variation N=30</th>
<th>Inter-operator reproducibility N=5</th>
<th>inter-visit reproducibility N=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow index</td>
<td>4.2%</td>
<td>9.9%</td>
<td>2.1%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Vessel density</td>
<td>2.3%</td>
<td>3.8%</td>
<td>1.1%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

Less variable than OCT NFL measurement!
Location of peripapillary retinal capillary dropout corresponded to visual field

Glaucoma reduced peripapillary retinal vessel density

AROC = 0.89

Glaucoma caused a -12.7% drop in peripapillary retinal vessel density

David Huang, MD, PhD; Yali Jia, PhD  www.COOLLab.net
Peripapillary vessel density was highly correlated with visual field

Parameters converted to dB scale by $10 \times \log_{10}\left(\frac{\text{value}}{\text{average value of the normal group}}\right)$

Conclusion

- Optic disc and peripapillary retinal microcirculation is reduced in glaucoma
- Pre-perimetric changes can be detected by quantitative OCT angiography
- OCT angiography with the SSADA algorithm may be a useful new tool in the evaluation of glaucoma
Grants & Material Supports

NIH Grant R01 EY023285 *Functional and Structural OCT for Glaucoma*

NIH Grant R01 EY013516 *Advanced Imaging for Glaucoma* [www.AIGStudy.net](http://www.AIGStudy.net)

Unrestricted grant from Research to Prevent Blindness

Grant & material support from Optovue, Inc.

[Image of a group of people with their names and affiliations]
Acknowledgements

MIT
Benjamin Potsaid, PhD
Jonathan J. Liu
Bernhard Baumann, PhD
Chen D. Lu
Woo Jhon Choi
James G. Fujimoto, PhD

Casey Eye Institute, OHSU
Glaucoma service
John C. Morrison, MD
Beth Edmunds, MD, PhD
Mansi Parikh, MD
Hana Takusagawa, MD
Shandiz Tehrani, MD

University Erlangen-Nuremberg
Martin F. Kraus
Joachim Hornegger, PhD

www.COOLLab.net