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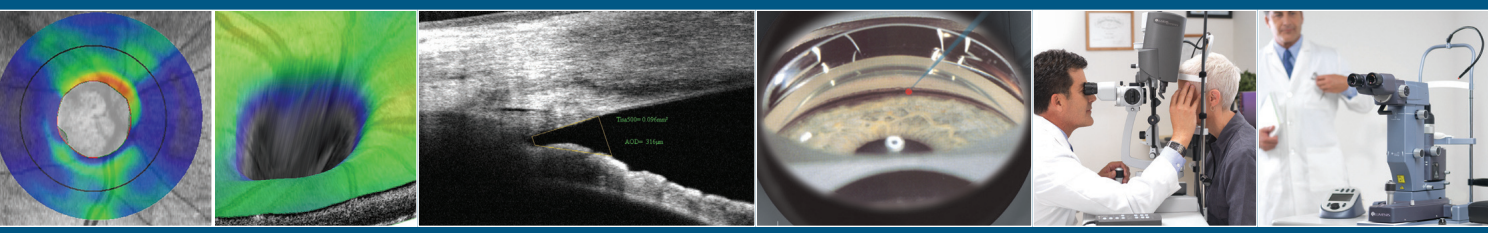
Cataract & Refractive Surgery TODAY

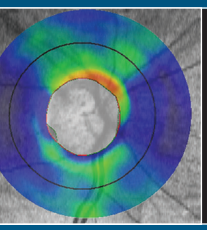
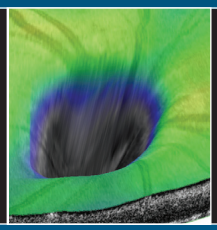
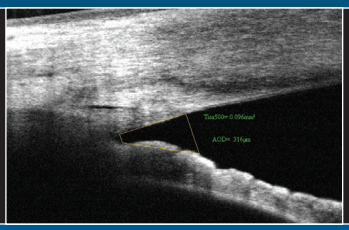
September 2009

Earlier Detection, Earlier Treatment, Better Outcomes



How advanced imaging and therapeutic strategies are helping glaucoma specialists preserve patients' vision.

Earlier Detection, Earlier Treatment, Better Outcomes

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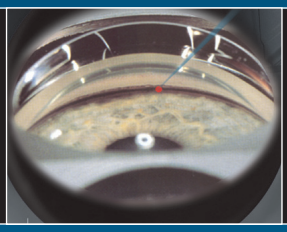

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Early Glaucoma: an Overview

Advanced technologies may help preserve patients' vision.

Ophthalmologists routinely use stereoscopic photography, scanning laser ophthalmoscopy, scanning laser polarimetry, and time-domain optical coherence tomography (OCT) to identify glaucomatous changes in the optic nerve and retinal nerve fiber layer (RNFL). Like any diagnostic technology, however, these imaging modalities have strengths and weaknesses that affect their utility for diagnosing and tracking the progression of glaucoma. Fortunately, ophthalmologists now have access to Fourier-domain OCT, an advanced technology that overcomes many of the limitations of time-domain OCT.

Advances in surgical therapy have also improved the management of glaucoma. For example, selective laser trabeculoplasty (SLT) reportedly has an excellent safety profile,[1] causes little to no damage to the trabecular meshwork, and is potentially repeatable.

In this supplement to *Cataract & Refractive Surgery Today*, David S. Greenfield, MD, and David Huang, MD, PhD, demonstrate the clinical utility of Fourier-domain OCT. Mark A. Latina, MD, the inventor of SLT, presents an overview of this surgical technique and discusses its place in the glaucoma treatment algorithm.

TIME-DOMAIN VERSUS FOURIER-DOMAIN OCT

"Time-domain OCT has limited clinical utility. Its dependence on mechanical scanning constrains the amount and quality of the acquired data," said Robert N. Weinreb, MD, in an interview with *CRSToday*. "It also is limited by a relatively slow scanning speed (400 A-scans per second), the use of software to interpolate between data points, difficulty imaging through opaque media, and the skill of the operator. All these factors can introduce artifacts and affect the scan's utility for detecting changes in the RNFL and the optic nerve."

In contrast, Fourier-domain OCT uses a stationary reference mirror to perform 26,000 A-scans per second. This high rate of acquisition produces detailed images.

SHIFTING PARADIGM

Under the traditional paradigm, the diagnosis of glaucoma depends on concurrent changes in ocular function (eg, visual fields) and structure (eg, thinning of the RNFL). An emerging paradigm states that changes in structure need not be accompanied by the loss of function to be indicative of glaucoma. Any technology that detects subtle structural changes in the optic nerve and RNFL, therefore, would be a valuable tool for diagnosing early glaucoma.

EARLY DETECTION, EARLY TREATMENT

Early diagnosis is just the first step in effectively managing glaucoma. The sooner clinicians initiate treatment, the longer patients are likely to retain functional vision.

"Three decades after the introduction of laser trabeculoplasty, this procedure is recognized throughout the world as a viable therapy for most patients with open-angle glaucoma," said Dr. Weinreb. "In fact, SLT is so safe, well-tolerated, and effective that it no longer is reserved only for those patients who have been advanced to maximal tolerated medical therapy." Although careful clinical studies and economic analyses are needed to understand the value of SLT, Dr. Weinreb added, he believes that clinicians can comfortably justify using SLT as first- or second-line treatment for some patients.[2]

CONCLUSION

When used together, Fourier-domain OCT and SLT may advance ophthalmologists' understanding of glaucoma and significantly affect how they diagnose and treat this disease in the future. ■

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Detecting and Managing Early Glaucoma

Fourier-domain OCT provides insights into structural changes that precede the loss of vision.

BY DAVID S. GREENFIELD, MD

Glaucoma is a neurodegenerative disease of the optic nerve that presents to the practitioner at various stages of a continuum that is characterized by accelerated retinal ganglion cell death, subsequent axonal loss and optic nerve damage, and eventual visual field loss.[1]

The initial changes in the optic nerve and retinal nerve fiber layer (RNFL) are often asymptomatic and undetectable with standard automated perimetry (SAP) and optic disc photography. Since glaucoma is a progressive disease, this suggests that awaiting overt signs of disease involves accepting some irreversible damage and probable progression.

Computerized imaging technologies provide objective and quantitative measures of the optic nerve and RNFL. Imaging provides an effective means of establishing baseline documentation, defining the stage of glaucoma severity, measurement of optic disc size, and assists the clinician with early glaucoma diagnosis and detection of progression.[2] During the past several years, there has been an explosion of information that utilizes imaging technologies to differentiate normal from abnormal, improve precision, and increases resolution and image registration. The development and commercialization of high-speed Fourier-domain optical coherence tomography (OCT) offers higher speed and resolution than time-domain OCT, along with the ability to perform three-dimensional imaging of posterior segment structures. This report highlights examples in which Fourier-domain OCT imaging (RTVue; Optovue, Inc., Fremont, CA) adds to clinical care by providing adjunctive information that facilitates the early glaucoma diagnosis, risk assessment, and monitoring disease progression.

IMPACT OF EARLY GLAUCOMA DIAGNOSIS

Glaucoma produces irreversible optic nerve injury. As optic nerve damage progresses, severe visual dysfunction and blindness may ensue in a small group of patients. A study performed in Olmsted County, Minnesota, reported that ocular hypertensive patients under treatment followed for 20 years had a 14% cumulative probability of progression to unilateral blindness.[3] Using a mathematical model for estimating the risk of glaucoma progression based upon randomized clinical trial data and population-based studies, data suggest that, in untreated patients, the estimated risk of progression from ocular hypertension to unilateral blindness is 1.5% to 10.5%.[3] In treated patients, the estimated risk of progression is 0.3% to 2.4% over 15 years.[1] The impact of delayed treatment upon the rate of progression of ocular hypertension to glaucoma is the subject of a follow-up study of the Ocular Hypertension Treatment Study (OHTS). This trial seeks to examine long-term differences between patients who received treatment early (medical group) compared with later (observation group).

> "Computerized imaging technologies provide objective and quantitative measures of the optic nerve and RNFL."

RISK ASSESSMENT

Established risk factors for the progression of ocular hypertension to glaucoma include increased age, IOP, cup-to-disc ratio, optic disc hemorrhage, and reduced central corneal thickness.[4] The Confocal Scanning Laser Ophthalmoscopy (CSLO) ancillary study to the OHTS reported that, when the optic disc is not classified by expert review of stereoscopic photographs as glaucomatous and the standard visual field is normal, certain optic disc features obtained using baseline CSLO imaging are associated with the development of primary

(All images courtesy of David S. Greenfield, MD.)

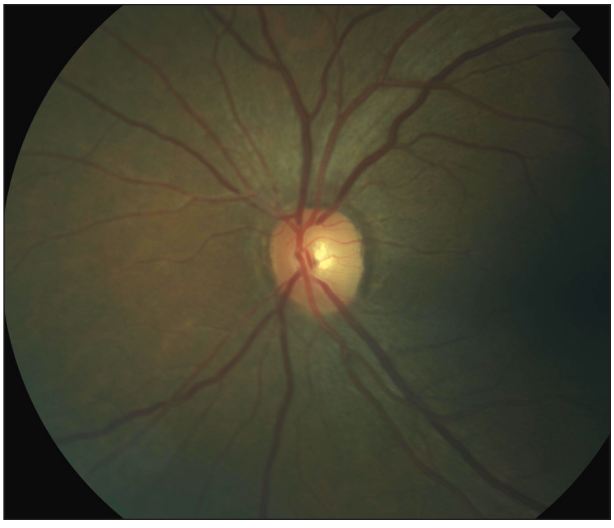

Figure 1. A fundus photograph of the patient's left eye showed a small optic disc and an intact neural rim.

open-angle glaucoma.[5] Similar studies demonstrating that certain structural changes can precede the observation of a glaucoma endpoint have also been performed with scanning laser polarimetry[6] and time-domain OCT.[7]

Figure 1 illustrates the left eye of a 60-year-old woman of African ancestry with ocular hypertension and a family history of glaucoma. Her untreated IOP is 28 mm Hg, and the central corneal thickness is 571 µm. The optic disc is small but physiologic with an intact neural rim; however, there is a suggestion of reduced inferior RNFL reflectance on the color photograph. As illustrated in Figure 2, SAP and frequency doubling technology (FDT) perimetry are normal. Fourier-domain OCT demonstrates a significant reduction in inferior RNFL thickness on the nerve head map and RNFL thickness map (Figure 3). Despite an increased corneal thickness, this patient has a moderately advanced risk for progression to glaucoma based upon her elevated IOP, young age, family history, and baseline reduction in RNFL thickness. The patient was started on IOP-lowering therapy.

DETECTING EARLY GLAUCOMA

The significant advances in hardware and software platforms for glaucoma imaging should not mislead a clinician to think that glaucoma diagnosis can be solely machine-based at the current time. Rather, the imaging information should be considered complementary to other clinical measures. Yet, some data suggest that imaging and expert assessment of optic disc photographs are similar in their ability to identify early glaucoma,[8] and it is clear that imaging does offer some very attractive advantages. Given the variability of clinician drawings and recordings of optic disc measures, imaging may elevate the assessment of the optic nerve by the general clinician to the level of a fellowship-trained expert. Fourier-domain OCT imaging enables the clinician to objectively evaluate the peripapillary RNFL, which, unlike the optic nerve, cannot be easily visualized or measured and has been demonstrated to change early in the course of the disease.[9,10] RNFL abnormalities often exist in eyes with early glaucoma with normal SAP. Finally, Fourier-domain OCT enables the clinician to compare patients to a population of age-matched normals, thus facilitating one's ability to identify abnormal structural features.

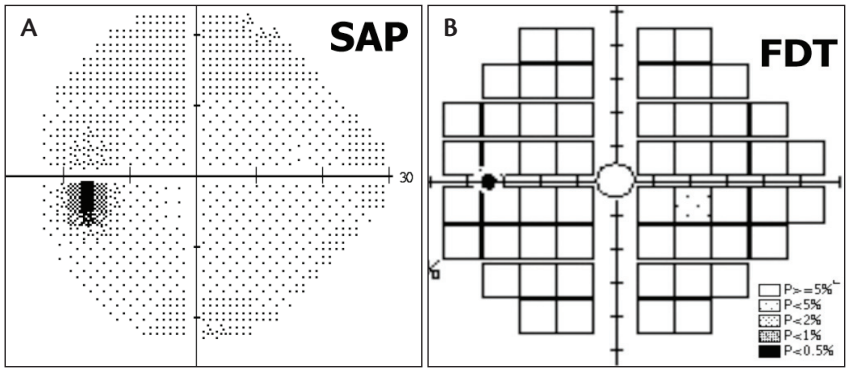

Figure 2. SAP (A) and FDT (B) showed normal visual fields in the patient's left eye.

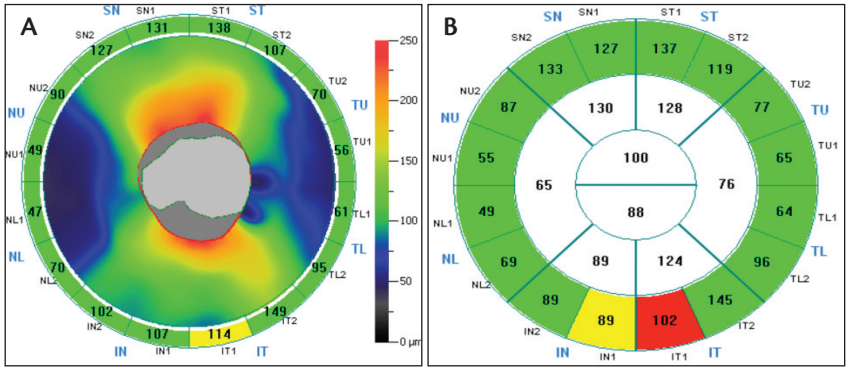

Figure 3. Fourier-domain OCT demonstrated a significant reduction in RNFL thickness on the optic nerve head (A) and RNFL thickness (B) maps.

Figure 4 illustrates a 54-year-old man with early open-angle glaucoma. The right optic nerve shows thinning of the inferior neural rim. Figure 5 demonstrates a normal SAP and a superior nasal defect on FDT perimetry. Fourier-domain OCT imaging of the RNFL and macular region was performed. The ganglion cell complex map demonstrates significant atrophy in the inferior macular region, and the nerve head map demonstrates thinning of the superior and inferior RNFL thickness (Figure 6).

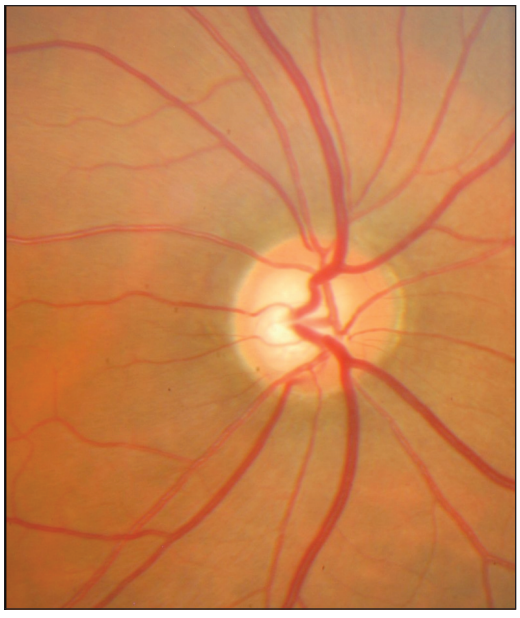

Figure 4. A fundus photograph of the patient's right eye showed thinning of the inferior neural rim.

DETECTING GLAUCOMA PROGRESSION

There are few studies involving the role of imaging in human glaucoma progression detection, hampered in part by rapidly evolving changes in technology that disrupt longitudinal studies. Progressive RNFL thinning measured with OCT[11] and optic nerve cupping measured with CSLO[12] have been reported in experimental models involving nonhuman primates. Many studies have identified greater changes in imaging-derived measures than SAP,[13,14] but the specificity of such changes remains to be validated. Medeiros and colleagues have recently reported that the GDx VCC (Carl Zeiss Meditec, Inc., Dublin, CA) was able to identify longitudinal RNFL loss in eyes that showed progression in optic disc stereophotographs and/or visual fields.[15] Given that Fourier-domain OCT is a relatively young technology, longer follow-up intervals are required in order to determine if the changes identified using this technology predict the subsequent development of visual field progression.

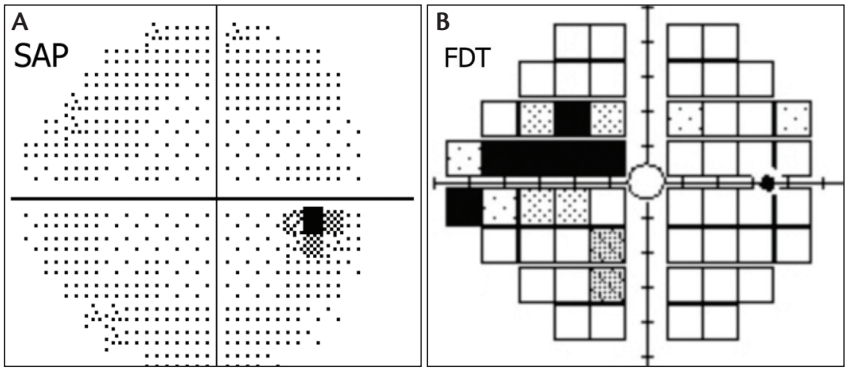

Figure 5. The patient had normal visual fields with SAP (A) and a superior nasal defect with FDT (B).

CONCLUSION

Fourier-domain OCT is an important tool for evaluating patients with ocular hypertension and early glaucoma. By quantifying glaucomatous structural changes in the optic nerve and the RNFL, this technology provides information that will enable the clinician to document and stage glaucomatous structural damage, facilitate risk assessment, and assist with early glaucoma diagnosis and monitoring. ■

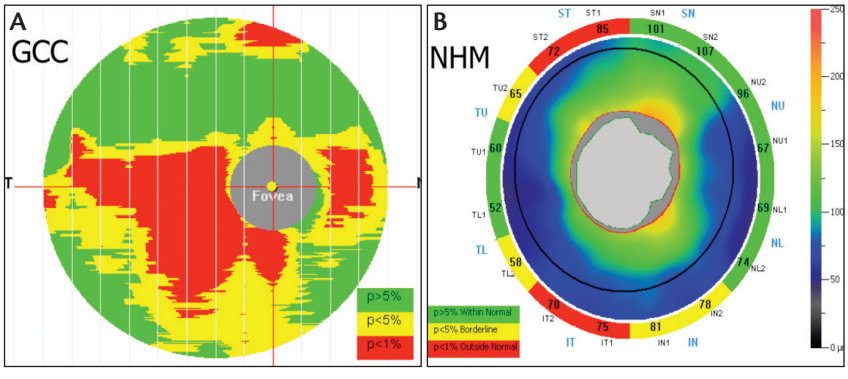

Figure 6. Imaging with the RTVue showed significant atrophy of the inferior macular region (A) and thinning of the superior and inferior RNFL (B).

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The Growing and Evolving Role of SLT in Primary Open-Angle Glaucoma

Advancing laser trabeculoplasty in the treatment algorithm simplifies glaucoma therapy.

BY MARK A. LATINA, MD

The availability of new technologies that detect glaucoma early and allow for expedient treatment may provide ophthalmologists with an unprecedented opportunity to initiate effective therapy before the disease significantly affects patients' vision. Traditionally, first-line treatment consists of monotherapy with a prostaglandin analogue. If this approach fails to lower the IOP, ophthalmologists proceed to adjunctive therapy with as many as three additional drugs before they consider surgical intervention.

Studies suggest, however, that selective laser trabeculoplasty (SLT) is a viable alternative to first-line medical therapy. This article describes how I am using this in-office laser procedure to overcome obstacles to adherence,[1-3] reduce patients' dependence on topical medications,[4-7] and dampen diurnal fluctuations in IOP.[8-10]

Figure 1. The Lumenis Selecta Duet laser.

TECHNOLOGY

During SLT, surgeons use a frequency-doubled Q-switched laser (Lumenis Selecta Duet; Lumenis, Inc., Santa Clara, CA) (Figure 1). This laser has a longer wavelength (532 vs 488 to 514 nm) and emits a larger spot (400 vs 50 µm) than that used for argon laser trabeculoplasty (ALT) (Figure 2). In addition, SLT's pulse duration of 3 nanoseconds is shorter than the thermal relaxation time of melanin and thus does not cause any collateral thermal damage to the trabecular meshwork[11] (Figure 3).

Because SLT does not damage the trabecular meshwork, it is not associated with the formation of peripheral anterior synechiae, and clinicians can perform the procedure on eyes that were previously treated with ALT.[12] Furthermore, SLT can theoretically be repeated in the same eye,[13] and the treatment does not preclude future surgery in or around Schlemm's canal.

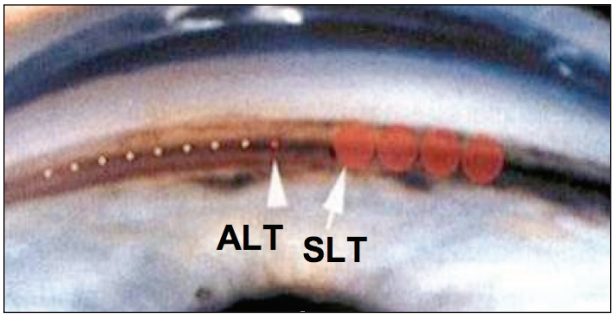

Figure 2. Comparison of ALT and SLT spot sizes.

REASONS FOR EARLY SLT

Simplification of the glaucoma treatment regimen is paramount to improving our patients' adherence and the overall success of treatment. I use SLT as first- and second-line therapy in my practice, because I believe it

(Courtesy of Theresa R. Kramer, MD, and Robert J. Noecker, MD, MBA.)

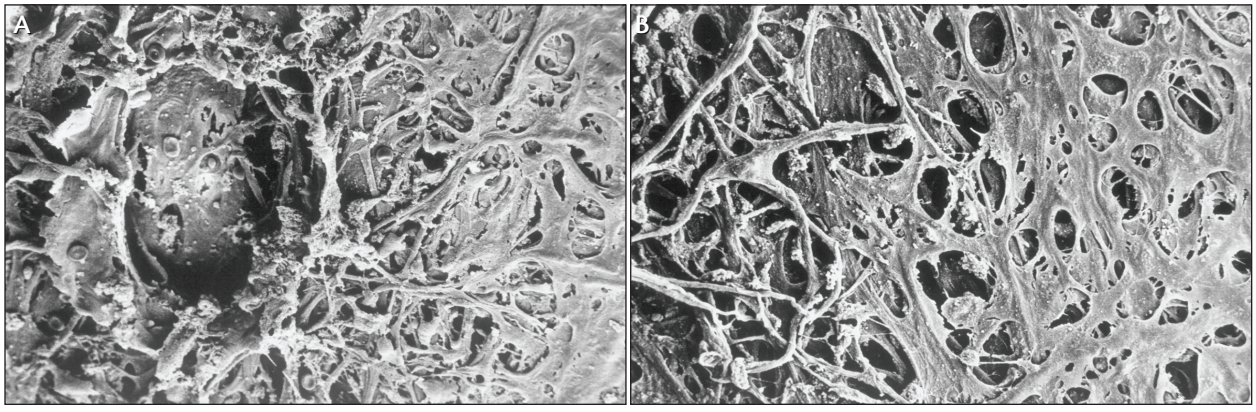

Figure 3. Scanning electron micrographs of cadaveric eyes treated with ALT (A) and SLT (B).

streamlines the treatment of glaucoma in several crucial ways.

Primary Therapy

Nordstrom et al showed that the percentage of patients who adhered to glaucoma therapy decreased from between 50% and 75% with monotherapy to 32% with multiple medications.[1] These bleak statistics are supported by data from the National Community Pharmacists Association and Pharmacists for the Protection of Patient Care. In a telephone survey, 75% of the respondents admitted to behaviors that affected their adherence to therapy, 33% did not fill a prescription, and almost 25% took less than the recommended dosage.[2] Even patients who initially adhere to therapy tend to lapse, with 50% of them discontinuing their eye drops after only 6 months.[3]

Studies have shown that first-line therapy with SLT lowers IOP as effectively as topical medications. In a prospective, randomized clinical trial, a similar percentage of eyes treated with daily latanoprost (n = 39) and SLT to 360º of the trabecular meshwork (n = 44) had a 20% to 30% decrease in IOP from baseline at 10.3 months' follow-up. The investigators did not observe a statistically significant difference in outcomes between the two groups.[4] McIlraith et al found that, at 12 months, latanoprost and SLT provided a mean reduction in IOP of 30.6% and 31%, respectively.[5] Perhaps the strongest multicenter randomized study was conducted by Katz et al, who found similar reductions in IOP with latanoprost (7.6 mm Hg) and SLT as primary therapy (6.7 mm Hg).[6] Longer-term studies showed that the IOP-lowering effect of primary SLT persisted for as long as 5 years postoperatively.[7,14,15]

I believe that patients can benefit from primary SLT, because they can achieve lower IOPs without having to follow the strict dosing schedule required for successful medical therapy. First-line therapy with SLT is also associated with a lower mean cost of treatment over 5 years ($4,949) compared with medication alone ($6,553) and surgery ($6,386).[16]

Secondary Therapy

In addition to using SLT as primary therapy, I offer this treatment to patients with well-controlled IOPs who are interested in using fewer medications. One study showed that approximately 50% of patients (760 eyes) who used one to three drugs preoperatively maintained low IOPs without any medication after SLT.[14] This effect was most pronounced among patients who used one medication preoperatively (86%); it decreased according to the number of drugs used at baseline (62% for two, 42% for three, and 32% for four preoperative medicines).[10] In a separate study, Francis et al found that 87% of eyes required one fewer medication than at baseline to maintain lower IOPs 12 months after secondary SLT.[17]

Because SLT is essentially an "outflow" treatment that does not depend on medication, I like to complement this procedure with drugs that use different mechanisms of action to decrease the IOP. My colleagues and I found that SLT was more likely to lower IOP by at least 3 mm Hg in patients who used aqueous suppressants versus prostaglandin analogues.[18] These results suggest that prostaglandin analogues and SLT compete for the same therapeutic pathway. I therefore tend to discontinue or taper prostaglandin analogues and pilocarpine (both outflow enhancers) in patients who undergo SLT. On the other hand, I often treat patients who need to achieve a lower IOP after SLT with an aqueous suppressant (eg, a beta-blocker or a carbonic anyhdrase inhibitor).

Fluctuations in IOP

Data from the Advanced Glaucoma Intervention Study (AGIS) showed that the risk of glaucomatous progression increased by 30% for each 1-mm Hg elevation from the mean IOP. In other words, eyes in which the IOP regularly

deviated from the mean by more than 3 mm Hg experienced a higher rate of progression than those that maintained a steadier pressure.[19] Asrani et al also noted that frequent deviations from the mean IOP was associated with a higher risk of progression,[8] a finding supporting the identification of IOP fluctuation as an independent risk factor for glaucomatous visual loss in the AGIS.

Clinical studies by Lee et al[9] and Prasad et al[10] suggest that laser trabeculoplasty can decrease the range of IOP fluctuation in glaucoma patients. In the latter study, the investigators randomized 41 eyes to receive primary SLT over 180º (n = 19) or 360º (n = 22) of the trabecular meshwork. At 2 years' follow-up, 86% of eyes in the 360º group experienced fluctuations of less than 2 mm Hg. A similar reduction was observed in only 52% of eyes in the 180º group. These data support treating 360º of the angle with SLT, because it provides a greater overall reduction of IOP and dampens fluctuations in pressure.

CONCLUSION

In my experience, SLT is a safe first- and second-line therapy that is cost effective, successfully lowers IOP, reduces patients' dependence on topical medications, and modulates the effect of a major risk factor for glaucomatous progression. ■

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Fourier-Domain OCT and Ocular Blood Flow

A potential new parameter for diagnosing early glaucoma.

BY DAVID HUANG, MD, PHD

In 1991, my colleagues and I at the Massachusetts Institute of Technology developed optical coherence tomography (OCT) to provide cross-sectional imaging of tissue with micrometer-level resolution. Since then, the speed and resolution of OCT has steadily improved. The latest leap in speed was provided by Fourier-domain OCT. This article summarizes how Fourier-domain OCT may improve clinicians' ability to diagnose and manage early glaucoma.

> "Many leading causes of blindness, including diabetic retinopathy and age-related macular degeneration, are related to abnormal retinal blood flow."

VISUALIZING THE RETINA

The difference in speed between Fourier-domain and classic time-domain OCT is like that between a jet airplane and an older-generation propeller plane (Figure 1). The first commercially available retinal scanner to use Fourier-domain technology was the RTVue (Optovue Inc., Fremont, CA). This system's scanning rate was 65 times faster than that of the fastest time-domain OCT system on the market (26,000 vs 400 axial scans per second).

The RTVue's higher scanning rate allows more detailed mapping of the retinal structures affected by glaucoma: the peripapillary nerve fiber layer and the macular ganglion cell complex. This development in turn leads to a more accurate diagnosis of glaucoma and more precise tracking of the disease's progression.

To take OCT beyond structural assessment, my colleagues and I have developed a new scanning protocol that may allow clinicians to use this technology to measure retinal blood flow.[1]

(All images courtesy of David Huang, MD, PhD.)

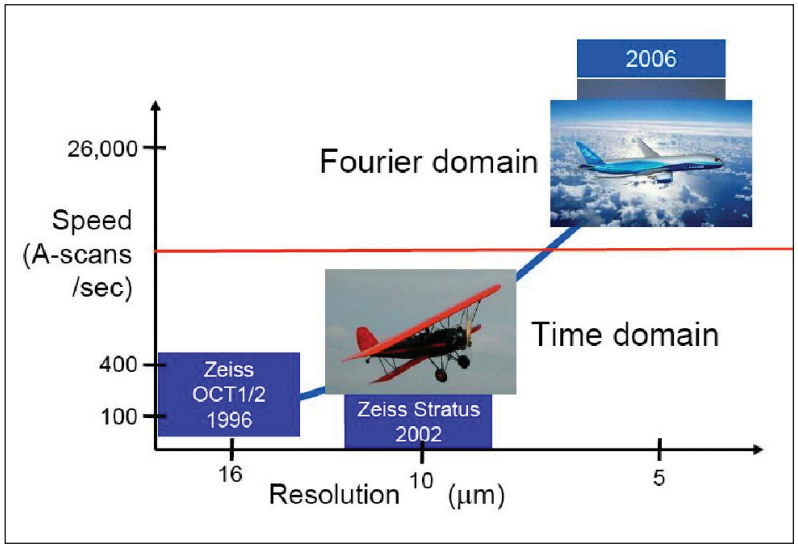

Figure 1. The RTVue has 65 times the scanning speed and twice the resolution of time-domain OCT (Stratus OCT; Carl Zeiss Meditec, Inc., Dublin, CA).

ASSESSING RETINAL CIRCULATION

Studies have shown that many of the leading causes of blindness, including diabetic retinopathy and age-related macular degeneration, are related to abnormal retinal blood flow.[2,3] Unfortunately, current approaches to analyzing this functional parameter (eg, fluorescein angiography, ultrasound, and laser Doppler flowmetry) provide

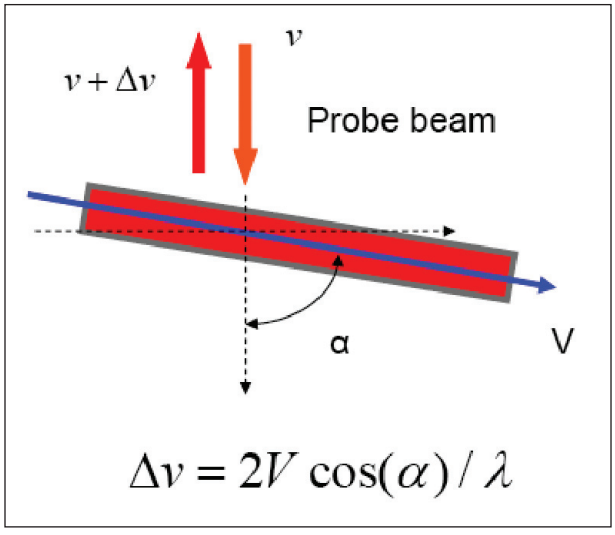

Figure 2. The dual-plane scanning technique measures Doppler shift and the angle of incidence between the OCT beam and the blood vessel. Both of these elements are necessary to calculate total retinal blood flow.

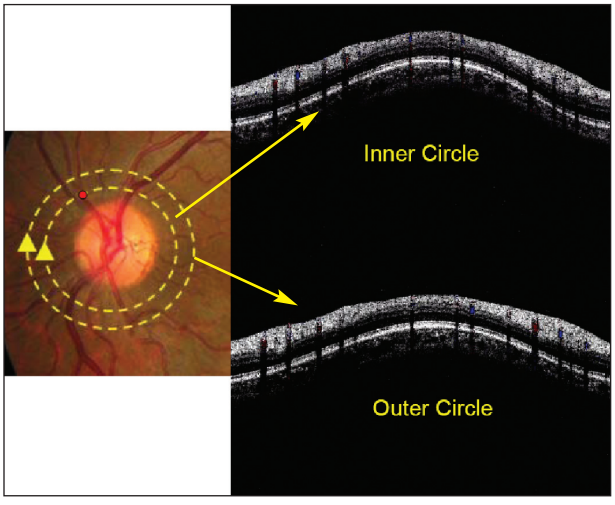

Figure 3. The double circular scan transects all retinal vessels four to six times per second.

limited information. Some investigators have successfully used OCT to visualize retinal circulation,[4,5] but they could not measure the relative angle between the OCT beam and the blood vessel (angle of incidence), which is necessary to calculate total retinal blood flow (Figure 2).

The dual-plane scanning technique my colleagues and I developed for Doppler OCT allows us to capture these missing elements and to measure the volume of blood flowing through the retinal vessels.[1]

First, we sample the retinal blood vessels with a double circular scan around the optic nerve head (Figure 3). The scanning pattern transects all retinal branch vessels four to six times each second, depending on the system used. The relative positions of blood vessels in the two Doppler OCT images are used to calculate the angle between the probe's beam and blood flow. We can then use the detected Doppler frequency shift to determine flow velocity. Next, we compare parallel cross-sectional scans from different sections of the same vessel to establish the direction in which the blood is flowing relative to the reference beam (Figure 4). This step allows us to differentiate between retinal veins and arteries.

Finally, we calculate total retinal blood flow by summing the volume of blood passing through the major retinal veins. We prefer to measure veins because the flow velocity in some arteries can exceed the detection range of Doppler OCT. The repeatability of total retinal blood flow measurement is approximately 10%.[6]

DETECTING ABNORMAL BLOOD FLOW

Using the double circular scan technique, we evaluated retinal circulation in 10 healthy human retinas. The normal total retinal blood flow was 45.6 ±3.8 µL/min and the average venous speed was 19.3 ±2.9 mm/sec.[6] These values were within the range previously established by Doppler flowmetry. The flow speed was independent of vein caliber.

A comparison of blood flow in healthy and glauco-

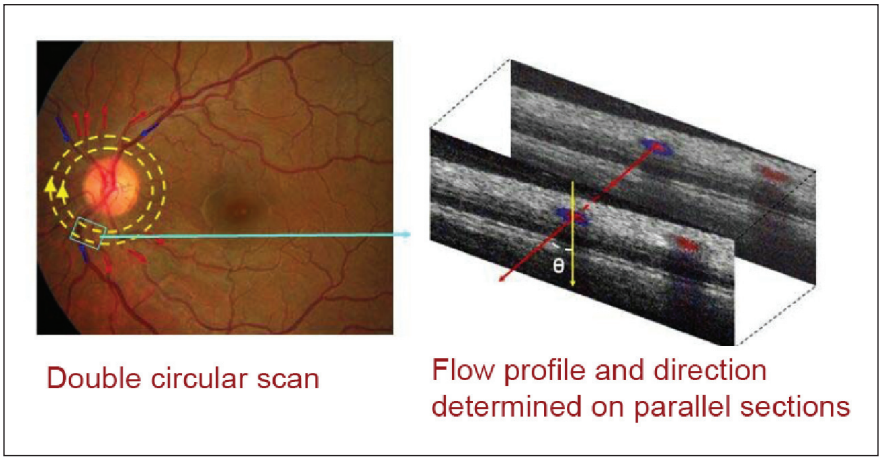

Figure 4. Doppler OCT measures two parallel cross-sections to determine the direction of blood flow relative to the OCT beam.

TABLE. INFORMATION PROVIDED BY IMAGING MODALITIES

	Fourier-Domain OCT	Scanning Laser Tomography (HRT)	Scanning Laser Polarimetry (GDx)
ppNFL thickness	+		+
Macular GCC	+		
Disc and cup	+	+	
Total retinal blood flow	+		
Angle	+		
Cornea	+		

Abbreviations: ppNFL, peripapillary nerve fiber layer; GCC, ganglion cell complex.
Note: HRT (Heidelberg Retina Tomograph; Heidelberg Engineering GmbH, Heidelberg, Germany); GDx (Carl Zeiss Meditec, Inc., Dublin, CA).

matous eyes showed a statistically significant difference between the two groups (40.8 to 52.9 µL/min in healthy controls vs 23.6 to 43.11 µL/min in glaucoma patients).[7] This study also showed a correlation between the decrease in blood flow and the presence of severe visual field defects in glaucomatous eyes.[7] Additional studies with the RTVue detected reduced blood flow in eyes with diabetic retinopathy (32.3 µL/min).[8]

CONCLUSION

Fourier-domain OCT already provides more information about the anatomy of the optic nerve and the retina than other advanced imaging modalities (Table). The addition of blood-flow analysis to this device will increase its utility for detecting early glaucomatous changes in the eye. Furthermore, the clinical assessment of retinal blood flow with Doppler Fourier-domain OCT may help clinicians better understand the role of perfusion in the causation and treatment of glaucoma and other optic neuropathies. ■

The double circular scan technique for Doppler OCT was licensed by the University of Southern California (where the author works) to Optovue, Inc. The technology has been implemented on the RTVue Fourier-domain OCT systems and is undergoing clinical studies at several academic eye centers.

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