Optical Coherence in Glaucoma

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The first retinal imaging was performed in 1989 by David Huang. The first prototype ophthalmic OCT was placed at the New England Eye Center in 1994. In 2002, OCT 3 (Stratus OCT), became commercially available which was then considered the "gold standard" for retinal imaging till the advent of Fourier domain OCT or SD-OCT, or hsHR-OCT in 2006.

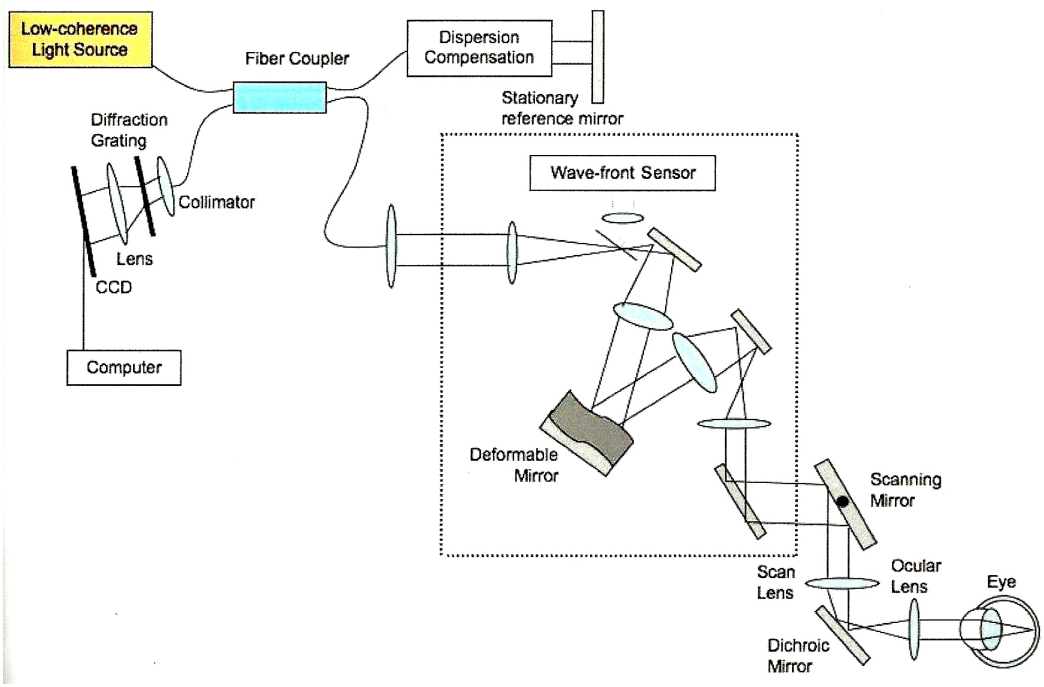
In 1991, Huang and his coworkers first demonstrated using a prototype OCT with 15μm axial resolution in science, its role in imaging a human retina. They were able to compare OCT images with histology of the retina. in 1993, Fercher and associates were successful in presenting the first in vivo OCT images, and in 1995 it was Huang and his coworkers again who produced the first images of retinal disease. Retinal images were presented using an OCT with improved axial resolution of 10μm the prototype instrument was a modification of slit-lamp bio microscope and would enable simultaneous OCT imaging. Using this system, they demonstrated imaging of both the foveal contour and optic nerve head in vivo.

The spatial location of reflected light was determined by the light wavelengths instead of echo time delay which was the milestone in the evolution of OCT. Using Fourier transformation, the OCT has evolved from TD-OCT to SD-OCT. The TD-OCT used the position of a moving reference mirror which was used to encode the location of each reflection in the time information, whereas SD-OCT which has a stationary reference mirror, gives the required information using a spectrometer. By this way, we get more infromation increase in the number of scans within a short duration, making SD-OCT, a very useful tool clinically for both the anterior and the posterior segment.

In 2001, Wojtkowski and colleagues presented the first in vivo SD-OCT scans and gave the technical details of the method. The data capture was rapid, however as the processing of images took 30 minutes to obtain, the clinical use of this technology was impractical at that period of time. The SD-OCT ophthalmic scans had a dramatic improvement with this technology in which each 500X500-pixel image could be processed in only 20 seconds. US Food and Drug Administration (FDA) has approved to use SD-OCT devices for clinical purposes, for its much faster acquisition speed, 3D data that can be acquitted and a good resolution of the structures. Faster machines are used for the research purpose with better axial resolution are now available through not used clinically.

Besides observing the structural anatomy of retina and other tissues, role of OCT has now been extended to monitor the physiological and pathological function of tissue characteristics. Doppler OCT methods similar to Doppler ultrasound are being used in Retinal blood flow studies which are in their initial stages, to look at flow both quantitatively. Assessment of blood oxygenation in retinal arteries and vein was done by Kagemann and colleagues using the spectral data of SD-OCT. the role of OCT to study the retinal functions was emphasized by three published studies demonstrating "optophysiology", in which following exposure of light to retina, OCT analyzed the layers of the retina in vivo.

Optical coherence tomography technology has evolved substantially over a relatively short span of time, from Time Domain to the Spectral



Schematics of spectral domain optical coherence tomography

Domain OCT, which takes much less time that allow researchers to identify properties of the retinal tissue beyond structure. This shows the rapid evolution of the OCT which is becoming an inevitable tool in the field of Ophthalmology.

OCT TECHNIQUES

Spectral domain OCT uses similar hardware as Time domain OCT with a few modifications. The basic principles of OCT and ultrasound are similar with exception of OCT using light as its medium while ultrasound uses sound. The SD OCT uses spectrometer to analyze the reflected light. The above methods results in a creation of three dimensional images based on measuring the echo time delay and intensity of reflection and back scattered light or sound. The A-Scan is the image of the variations in the optical reflectance through the depth of the tissue depicted along a point by the OCT whereas B-Scan is the cross sectional image of these single axial scans through the tissue which are gathered linearly across the tissue. 3D data set is then constructed based on the collection of parallel B-scans. S umming all the pixels in each given scan A and presenting to 3D data cube produces an OCT fundus image.

Advantage of OCT fundus image is that it has actual OCT topographic data but the SLO or fundus photograph has an upper edge in faster acquisition and minimal movement artifact. The difference in the medium makes OCT have much higher axial resolution compared to ultrasound. Time domain OCT uses an axial resolution of 10 µm whereas for an spectral domain OCT it is 5 to 7 µm. Ultrasound uses an axial resolution of 150 µm at a frequency of 10 MHZ. with higher frequencies of ultrasound, higher axial resolutions can be achieved. Anterior segment OCT uses an ultrasound frequency of approximately 60 MHZ and axial resolution of approximately 40 to 20 µm and poor depth of penetration 4 to 3 mm. Light being the medium in OCT has the advantage of non-contact while ultrasound requires a medium like water to pass the sound waves between transmitter and tissue. Hence, ultrasound is more useful in detecting the axial length and the anterior segment, whereas OCT is more useful technique to detect in detail the structures in the retina and anterior segment. Though OCT and ultrasound creates images using principles of reflection, the methods for detecting these reflections is however

different for both. The speed of light being much faster than sound, the time delay in reflections from different layers being in the order of femtoseconds cannot be measured directly. Hence the principle of low- coherence interferometry is used in OCT to measure the delay in time corresponding to distances between structures. A laser with broad bandwidth or a source of super luminescent diode source is used and the beam travels to a beam splitter. This beam is split into two, one goes to a mirror at a known position on a reference arm while the other to sample arm and gets scattered and reflected from the tissue structure. The light beams from reference and sample arms travel back to the beam splitter and recombine forming a constructive interference pattern. This pattern is then sensed by a photo detector. The resolution of the interferometer is defined by the width, of the signal envelope and is based on the coherence length of the light used. The coherence length is in turn dependent on the bandwidth, the broader the bandwidth, the lower the coherence light. Finer resolution can be obtained when the light of shorter coherence wavelength is used.

In TD-OCT, the reference mirror is placed at a known distance and the position is altered for each axial scan to allow imaging of the depths of the tissue. Each pixel in the A-scan presents the reflection intensity at that position. This reflection intensity is converted to a log scale because it varies widely up to 45dB approximately. Initially, the OCT system was based on the principle of Michelson interferometer. TD-OCT uses a fiber-optics system. SD-OCT and TD-OCT has similar principle; however, the signal acquisition is better in SD-OCT as Compared to TD-OCT. The TD-OCT has a moving reference mirror, whereas it is kept stationary in SD-OCT. The interference pattern in SD-OCT is split by a grating into its frequency components, simultaneously these components are then detected by the charged –couple device (CCD). This device has group of arranged photo detectors, each photo detectors individually responds only to a specific frequency range.

These frequencies specifically correspond to certain depth within the tissue after Fourier transform of received signal allowing simultaneous gathering of all points along each A-scan and thus increasing the scan speed. Like TD-OCT, B scan be obtained by using Ascan along the transverse plane. SD-OCT is also called as fourier domain OCT because of encoding of distances in the Fourier transform of the frequencies of light reflected. The advantage of SD-OCT over TD-OCT is that it takes 40, 000 axial scans per second as against TD-OCT which takes only 400 axial scans per second. The speed restriction of TD-OCT is because it uses a moving reference mirror to calculate the time taken by the light to be reflected.

The beam waist size defines the transverse resolution fundamentally by projecting the beam as well as any aberrations in the eye. Scan density which is dependent on Ascan sampling rate is sometimes incorrectly interpreted as transverse resolution. The resolution of TD-OCT depends on the number of A-scan that were taken. Arbitrarily the scan time increases with increase in the number of a scan taken. The transverse resolution is higher with better scan density in a long duration scan but is highly susceptible to artifacts is reduced with shorter-Duration scans. As said earlier SD-OCT devices are approximately 100 times faster than the conventional TD-OCT.

3D data can be constructed based on these set of B-scans acquired on a faster rate. With the faster speed of the scan, images can be improved with lessser artifacts. 3D images can be further worked upon and processed for visualization and to acquire further quantitative and qualitative data. Graphically these images can be displayed as either grayscale or false color images. With grayscale there is better interpretation and smaller details can be picked up easily. As it is easier for the human eye to differentiate multiple colors rather than various shades of gray, use of false color imaging in OCT makes it easier to identify the tissue structures. But this carries the disadvantages of inducing artifacts. False color imaging shows

highly reflective structures in bright colors like red and white with the intensity as high as ~50dB while darker colors like blue and black represents low reflectivity structures with intensity as low as ~95dB and green represents intermediate reflectivity.

OCT data can often be compared to histological sections. To find out the pathology and identify the inter visit variabilities observed to detect any progression, automated segmentation techniques are important. Segmentation is possible using SD-OCT through which we can analyze and determine the inner retinal complex which includes RNFL, retinal ganglion cell layer (RGCL), and inner plexiform layer. Three steps are involved in segmentation which includes smoothing, edge detection, and error correction. OCT has a normative database in its printouts. This makes it easier for the clinicians to interpret the data of the patients and to correlate whether the data is normal or outside normal limits. So segmentation is vital in glaucoma. Segmentation helps in the quantitative analysis of the RNFL thickness, in this the highly reflective layers appear in hot colours like red. Since RNFL thinning is noticed in the pre-clinical stage of glaucoma, before any field defect would appear, measuring the RNFL thickness is very important. So analyzing the RNFL quadrant wise and clock hour wise may give a more valuable information than just measuring the average thickness. Schuman and colleagues defined the 3.4mm circumpapillary RNLF thickness scan as the standard for TD-OCT glaucoma assessment in the earlier periods.

OCT IN GLAUCOMA:

Since the diagnosis of glaucoma in its early stages may be very critical and is more subjective, we need an objective method to diagnose glaucoma. Optical Coherence Tomography is a robust technology in glaucoma providing objective, high resolution images. The clinical signs of glaucoma include polar notching, more often seen in the inferior and superior poles of the optic nerve head, disc hemorrhages, asymmetric cupping of more than 0.2 between the two eyes, asymmetric appearance of the neuroretinal rim. The diagnosis of Glaucoma is made when there is a loss of neural rim with its corresponding visual field defects. The visual field defects observed in glaucoma are generalized depression, paracentral scotoma, arcuate scotoma, nasal step of Ronne, a double arcuate scotoma, as the disease progresses can result in a temporal or a central island of vision. The proposed risk factors of glaucoma include high intraocular pressure (IOP), thin corneas, heredity, old age, high myopia, diabetes, hypertension and cardiovascular diseases. Loss of retinal ganglion cells is the finding in glaucoma leading to exposure of the lamina cribrosa and is often associated with transsynaptic degeneration in the lateral geniculate nucleus and beyond as well. TD-OCT used a 3.4mm circumpapillary scans to image the RNFL.

The retinal segmentation helps us to analyse the course of the disease and its progression by comparing the Retinal nerve fiber layer thickness in glaucomatous eyes with the normative data base. Intertest reproducibility was less for average RNFL thickness and can be improved in a well dilated pupil. Better imaging with finer details of the retinal layers and the nerve fiber layer thickness can be obtained with Fourier domain OCT (~2 to 3µm) due to its high resolution than the conventional TD-OCT that increases the reliability of the test. The newer softwares in SD OCT has helped better detection and progression analysis in glaucoma. Commercially available OCT's like the Cirrus HD-OCT has improved software package like Ganglion Cell Analysis and Optic Nerve Head Progression Analysis for glaucoma. It also includes the Guided Progression Analysis which detects the RNFL changes over time, it creates a report, where the average RNFL thickness based on 4 visits is analysed in a linear regression pattern against the follow up duration and this change is expressed in µm/year. The spectralis OCT has softwares to reduce motion artifacts and improve repeatability results like the TruTrak and Noise Reduction OCT signal and

newer software like Posterior Pole Asymmetry Analysis which plots asymmetry in the RNFL thickness along the posterior pole across the horizontal hemisphere and between the two eyes. 3D data sets can be created with newer OCT's like 3D OCT-1000 (Topcon) and Cirrus HD-OCT. Since the OCT scans a larger area and in depth we get better information about the retinal ganglion cell defects. Functional data in glaucoma can obtained using SD-OCT to measure physiological parameters like the retinal blood flow in glaucoma and the oxygenation which is still in its research stage. The pathology of glaucoma can be assessed by Optophysiology for functional assessment of glaucoma.

Optic Nerve Head Imaging

Spectral domain optical coherence tomography, a relatively new a imaging modality can be said as a boon to the posterior segment ophthalmic surgeons as it gives a three dimensional structure of the ONH, through which we can now acquire a 3D isotropic image of the structures to be studied. Isotropic means that the size of each imaged element, or voxel, is the same in all three dimensions. With the advent of this isotropic imaging technology, we can get almost an accurate measurement of the optic nerve head. So this is a very useful technology which takes us one step higher in the treatment and follow up of the patients with glaucoma. However, as a routine, glaucoma management was based on the clinical findings like IOP measurement, ONH imaging and visual field parameters. Due to the narrow band width in SD-OCT, the clinical findings like the properties of the disc such as the colour changes are missed the SD-OCT.

Though SD-OCT provides a detailed information about the ONH parameters, we are not able to assess which of these parameters are more useful in detecting the progression of glaucoma. Since glaucoma is a disease of chronic optic neuropathy, the disease undergoes changes over many years. However, the data provided by SD-OCT may be useful in the evaluation and interpretation. Hence, as elucidated by Burgoyne *et al*, SD-OCT may be used to evaluate the progression of glaucoma.

Circus system software could detect the changes in the optic nerve head margins. Kim et al used two methods to detect optic nerve head margins which are centred each time method and centred once method, and found no difference in the datas. Gabriele et al analyzed no significant difference with the RNFL measurements than the ONH measurements. The present result of 58µm ONH centre location deviation is well within this stability margin.

RNFL Thickness Measurement in Glaucoma

Clinically RNFL defect can be detected using a red-free photograph qualitatively; the quantitative assessment can be done using the two imaging technology OCT and scanning laser polarimetry. RNFL is highly reflective on an OCT. The various RNFL thickness measurement analysis protocol includes RNFL thickness circle scan, fast circle scan, concentric three ring protocol, RNFL map and proportional circles. Circular scan of 1.34mm radius centered on the ONH exhibit maximum reproducibility for RNFL measurement.

The measurement of RNFL thickness is determined by the difference in distance between the vitreoretinal interface and a posterior boundary, based on a predefined reflectivity signal level. In SLP the RNFL thickness is measured based on its birefringence property.

With the advent of SD-OCT, the RNFL thickness measurement reproducibility has considerably improved as quoted by many studies. It gives a statistically significant data as compared to the conventional TD-OCT. This could be because SD-OCT provides the data in 3 dimension and reduces the motion artifact due to the faster imaging technology. Moreover SD-OCT with its high axial resolution can define RNFL boundaries more accurately, which makes it a more powerful tool as compared to the TD-OCT.

The Need for improved imaging in Glaucoma

Better objective screening methods are needed to diagnose glaucoma early in a population hugely affected by this disease. As the damage caused is irreparable, early diagnosis and prompt treatment is warranted. Treatment is aimed at halting the progression and preserving the residual vision. Diagnosis is usually delayed till the advanced stages as in the earlier stages patient is symptomless till prominent central fields are preserved. Diagnostic modalities used till present date like the visual field is subjective based on patients' response and the clinician's interpretation of the result. These modalities can detect glaucomatous damage only after significant nerve tissue is lost (~40% or beyond): Present modifications in the diagnostic methods like the scanning laser polarimetry, confocal scanning laser ophthalmoscopy, and time domain optical coherence tomography (OCT) helps in early and objective assessment of the optic nerve head (ONH) and the retinal nerve fiber layer (RNFL) changes in glaucoma.

These methods have reported structural changes that can be seen before the clinical changes. RNFL changes are seen to be more sensitive than ONH parameters on OCT. Thinning of RNFL seen in glaucoma correlates with the ganglion cell loss indicating glaucomatous pathology. RNFL loss seen in red free photographs can be detected 6 years before the clinical manifestation. Interestingly, Deleon – Ortega *et al*, has quoted that the current modalities that are used to diagnose glaucoma are better in ONH imaging as compared to RNFL imaging. The Ocular Hypertension Treatment Study (OHTS) concluded that the ophthalmologist can diagnose glaucoma based on the serial fundus photographs taken over 5 years time before they developed any field defect. So the early diagnosis is very important to provide apt treatment, but according to the surveys conducted, very few patients were diagnosed early and received prompt treatment.

Longitudinal follow up of glaucoma is essential in detecting the rate of progression of the disease, as glaucoma is a slowly progressing disease. Appropriate treatment can be offered and the vision can be restored if we had a better imaging modality.