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Image analysis of optic nerve disease

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Abstract

Existing methodologies for imaging the optic nerve head surface topography and measuring the retinal nerve fibre layer thickness include confocal scanning laser ophthalmoscopy (Heidelberg retinal tomograph), optical coherence tomography, and scanning laser polarimetry. For cross-sectional screening of patient populations, all three approaches have achieved sensitivities and specificities within the 60–80th percentile in various studies, with occasional specificities greater than 90% in select populations. Nevertheless, these methods are not likely to provide useful assistance for the experienced examiner at their present level of performance. For longitudinal change detection in individual patients, strategies for clinically specific change detection have been rigorously evaluated for confocal scanning laser tomography only. While these initial studies are encouraging, applying these algorithms in larger numbers of patients is now necessary. Future directions for these technologies are likely to include ultra-high resolution optical coherence tomography, the use of neural network/machine learning classifiers to improve clinical decision-making, and the ability to evaluate the susceptibility of individual optic nerve heads to potential damage from a given level of intraocular pressure or systemic blood pressure.

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Scope of this lecture

Optic nerve head surface and nerve fibre layer (NFL) assessment

This lecture will concentrate on the existing methodologies for imaging the optic nerve head (ONH) surface topography and retinal nerve fibre layer (RNFL) thickness within the peripapillary retina and within the macula. While a variety of technologies exist for measuring blood flow within the superficial layers of the optic nerve head, they do not yet have wide clinical application and are not discussed in this report.

Definition of terms

There are at present two principal tasks for these imaging systems. First, cross-sectional screening, in which an eye is imaged initially with the intention of detecting the presence of glaucomatous optic nerve damage. Second, longitudinal change detection, in which an eye that is already known to be at risk is imaged on multiple occasions over time with the intention of detecting change or progressive damage.

Current instruments

Heidelberg retinal tomograph

The Heidelberg retinal tomograph (HRT) is a confocal scanning laser ophthalmoscope (CSLO) that uses a 670 nm diode laser to obtain a series of two-dimensional optical section images of the ONH and peripapillary retina. A three-dimensional topographic image of the ONH surface is then built from the series of 16–64 serial optical sections, when algorithms are used to find the surface at each of 256×256 (HRT I) or 384×384 (HRT II) pixels over a 10 or 15° field of view. The HRT II automatically captures three consecutive 15° images and from these generates a mean topographic image.

To process images, the optic disc margin (anterior scleral canal opening) is defined by a contour line placed around the inner margin of the peripapillary scleral ring. The standard reference plane for volumetric parameter calculation is then automatically determined as 50 μm posterior to the mean peripapillary retinal height along the contour line between 350 and 356°; however, the reference plane

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Disclosure: I use a Heidelberg Retinal Tomograph in my clinic (purchased) and research laboratory (donated) to detect the onset and progression of glaucomatous optic nerve head damage. I am not a paid speaker for any of the instrument companies. I do have an intellectual (but no financial) interest in their development.

definition can be modified. Magnification is automatically adjusted by using the patients' keratometry readings and the power of the correction lens used to acquire the images.

For stereometric parameters, the mean coefficient of variation has been reported to be between 3 and 5% for both glaucoma and normal subjects.[1] The mean standard deviation for individual pixels has been reported to be approximately 30 μm in glaucoma eyes and 25 μm in normal eyes.[2,3] Individual pixel variability varies by region, being related to the steepness of the surface, and is highest at the edge of the optic disc cup and along vessels. The quality and variability of the images are associated with pupil size and density of nuclear and posterior subcapsular cataracts.[4,5] In addition, HRT measurements are influenced by acute changes in intraocular pressure[6,7] and even the cardiac cycle.[8]

Current limitations of the technology include the need to outline the anterior scleral canal opening and a reference plane and stereometric parameters that are dependent upon this delineation. While improvements in image acquisition have been built into the HRT II, the quality of the image still depends on the ability of the technician and requires training, experience, and dedication. Experienced technicians can acquire acceptable images in as many as 90% of eyes. Advanced cataract, corneal opacities, and nystagmus can prevent adequate imaging. Better automated quality control assessment at the time of image acquisition would warn the operator that new or additional images are necessary to ensure good data.

Optical coherence tomography

Optical coherence tomography (OCT) uses the principles of low-coherence interferometry to obtain high resolution, cross-sectional images of the human retina, peripapillary NFL, and ONH. In a manner analogous to B-scan ultrasonography, OCT utilises light echoes from the scanned tissue to discriminate retinal layers due to the differences in time delay of echoes from various components of the retina. The light source of the OCT is a short coherence length superluminescent diode in a near-infrared wavelength (840 nm). Axial reflectance profiles (A-scans) are measured *vs* depth. Tomographic images are constructed from a series of A-scans. The scan rate used is 128–512 lateral pixel retinal tomograms with a depth of 2–3 mm captured within 1 s. The *in vivo* resolution of the Stratus OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA) is 8–10 μm and the OCT 2000 is 10–12 μm.

OCT is capable of scanning the peripapillary retina, ONH and macular region. The peripapillary scan is a continuous circular scan centred on the ONH with a default diameter of 3.4 mm. Macular and ONH scans are composed of six radial scans in a spoke-like pattern centred on the ONH or the fovea at 30° intervals. Interpolation is used to fill the gaps between the scans. For macular scans, the vitreoretinal interface and the retinal pigment epithelium are utilised to define the inner and outer retinal boundaries, respectively.

For ONH scans, the disc margin is defined as the end of the retinal pigment epithelium (RPE)/choriocapillaris layer. A straight line connects the edges of the RPE/choriocapillaris, and a parallel line is constructed 150 μm anteriorly. Structures below this line are defined as the disc cup and above this line as the neuroretinal rim. Additional OCT details can be found in the cited references.[9–13]

OCT RNFL measurements show good reproducibility, with intraclass coefficients of approximately 0.55[14,15] and coefficients of variation of approximately 10%. OCT RNFL thickness measurements increase after trabeculectomy-induced IOP reduction in glaucomatous eyes. OCT RNFL measurements are not affected by refraction changes within $\pm$5.0 D.[16] In the presence of substantial media or lenticular opacities, scanning with OCT can be difficult. While it has been suggested that no pupillary dilation is required in patients with a pupil diameter $>$2 mm, there are no available studies reporting the percentage of patients (with or without media opacities) who require pupillary dilation for good OCT images, nor are there data as to the percentage of glaucoma patients in whom satisfactory results can be obtained.

Scanning laser polarimetry

Scanning laser polarimetry (SLP) estimates the thickness of the peripapillary retinal NFL based on the retardation of polarised light. Owing to their parallel architecture, the axonal microtubules of the NFL demonstrate form birefringence, which generates a net retardation of light that is proportional to the NFL's thickness (approximately 1° of retardation per 7.4 μm of thickness).[17]

To acquire an image, a polarised laser beam scans the peripapillary retina circumferentially around the scleral canal opening. The backscattered light (which double-passes the RNFL) is captured and analysed. The amount of retardation is calculated per pixel and displayed in a retardation map of the scanned area. As the cornea, lens, and sclera also demonstrate form birefringence, their retardation needs to be compensated (neutralised) to isolate that due to RNFL retardation.[18–26] Older versions of the instrument (NFL Analyzer, I and II, GDx and GDx Access) all employed a uniform, fixed compensation in which both axis and magnitude reflected median values

of the general population. In the current version of the instrument (GDx-VCC), custom anterior segment birefringence compensation (ASBC) is employed, which utilises an initial scan of the patient's macula to perform patient-specific compensation.[19]

To acquire images with the GDx-VCC, two imaging trials per eye are run successively, the first to determine ASBC, the second to image the area of interest with adjusted ASBC. Image acquisition takes approximately 0.7 s per trial. Owing to the laser wavelength (820 nm), mild to moderate cataract does not degrade the images.[27,28]

Most literature on SLP pertains to the early versions of the instruments. A new normative database has been collected with the GDx-VCC. The variable ASBC has been demonstrated to generate accurate estimates of corneal polarisation axis and magnitude, both in healthy eyes and in eyes with maculopathy.[19,26] Recent studies have demonstrated that custom ASBC narrows the band of normative data,[20–22] improves the discriminating power for glaucoma detection,[21,22] increases the correlation with structural assessments obtained with optical coherence tomography,[24] and improves the correlation with red-free fundus photographs.[25]

Limitations include the following: Images cannot be obtained in eyes with nystagmus. Eyes with large peripapillary atrophy cannot be reliably imaged. Corneal refractive surgery has been demonstrated to variably affect measurements with fixed ASBC.[29–31] The effectiveness of variable ASBC in eyes following corneal refractive surgery is currently unknown. Macular disease may affect the calculation of ASBC.[26] Some eyes continue to show atypical retardation patterns. Histological validation in human eyes has not been done.

Current performance—Cross-sectional screening

In general, all of the instruments have achieved sensitivities and specificities within the 60–80th percentiles, with occasional studies suggesting that specificity can be pushed to greater than 90% in select populations. At present, this level of performance is unlikely to help the experienced examiner, though the performance of the instruments continues to improve.

HRT

A number of studies have evaluated the diagnostic performance of the HRT in groups of patients already diagnosed and attending glaucoma clinics. In general, three methods have been used: (i) linear discriminant functions;[32,33] (ii) comparison of one (or more) stereometric parameters to normative database (the Moorfields Regression Analysis); (iii) use of computer-assisted classification such as neural networks.[34,35] Each of these methods uses HRT parameters (global or sectorial) as inputs to discriminate between the normal and glaucomatous groups of eyes. In general, sensitivities of 62–87% and specificities from 80 to 96% have been reported.[32,33,36–39] However, in most of these studies, this level of performance was achieved in a population similar to the one used to derive the original discriminant functions. Other studies have suggested that when the same strategy is applied to a new population, the diagnostic precision is not as good.[40,41]

HRT descriminating precision is influenced by disc size, with larger discs more precisely discriminated than smaller discs.[37,41] HRT performance has been compared to stereo optic disc photography. Wollstein *et al*[34] reported that for detection of early glaucoma, the Moorfields Regression Analysis had a higher sensitivity with equal specificity compared to the majority opinion of five clinician observers. However, Greaney *et al*[42] and Zangwill *et al*[39] found that clinicians qualitatively assessing stereo optic disc photographs performed as well as or better than the HRT.

OCT

OCT has been shown to discriminate between healthy and glaucomatous eyes with sensitivities and specificities ranging from 68 to 90%.[42–48] Fair to moderate agreement (Kappa = 0.51–0.73) was found between expert observers for classifying OCT clinical printouts as healthy or glaucomatous with fair sensitivities (76–79%) and specificities (68–81%).[43] Recent studies investigating OCT-measured macular thickness suggest differences between healthy and glaucomatous eyes.[49,50] Some evidence suggests that OCT can detect RNFL thinning in ocular hypertensive eyes prior to the onset of achromatic visual field defects.[47,51]

GDx

The sensitivity and specificity of GDx measurements have only been reported for GDx models with fixed ASBC. Most of these published data relate to Caucasian populations, showing moderate discriminating power between healthy and glaucomatous eyes.[52–64]

Current performance—Longitudinal change detection

Only confocal scanning laser ophthalmoscopy has been seriously applied to the problem of longitudinal change detection, and very encouraging results are now available. Only those studies which report 'clinically specific' change detection strategies (or strategies that

have demonstrated the ability to appropriately detect no change in unchanging normal eyes) are summarised below.

HRT

Three clinically specific change detection strategies have been assessed in longitudinally imaged human eyes. A superpixel strategy for ONH surface change detection (which has been incorporated into the existing HRT software) has been described by Chauhan *et al*[65] and used to detect the onset of ONH surface change in 31 of 77 ocular hypertensive (OHT) patients prior to the onset of visual field changes. The technique performed with a 95% specificity within 37 normal eyes, but required a total of three confirmatory tests to achieve that specificity.[66]

Kamal *et al*[67,68] used a segmental strategy to detect change in 13 of 21 OHT visual field converter, 47 of 164 OHT visual field nonconverter and 0 of 21 normal eyes. Tan *et al*[69] detected change in 17 of 20 OHT converters and one in 20 normal eyes by analysing 30° sectors of rim area. However, they too required that change occur in two of three consecutive tests to achieve that specificity.

Additionally, using a similar CSLO (not the HRT) to image monkey eyes, the LSU Experimental Glaucoma Study reported higher sensitivity and specificity for optic disc change detection by CSLO (defined as a significant change in two of three selected CSLO parameters in two consecutive post-laser imaging sessions) as compared to three fellowship-trained glaucoma specialists using stereo photo images of the same eyes.[70,71]

OCT

There are no clinically specific change detection strategies published for OCT.

GDx

There are no clinically specific change detection strategies published for scanning laser polarimetry. Several studies have addressed monitoring progression in glaucoma or other optic neurodegenerative disease using the GDx.[72,73]

Necessary studies

These are by no means inclusive and much needs to be done by all three technologies:

(1) Evaluate screening performance in a population rather than an office-based study population.

(2) Develop contour line- and reference plane-independent screening and progression strategies.

(3) Reduce the number of confirmatory tests required for specific progression detection from the current number of three.

(4) Evaluate the rate of field conversion following change detection.

(5) Compare screening and change detection performance to glaucoma specialists using stereo photos.

(6) Determine the predictive values of each instrument for the onset of standard and BY automated perimetry defects in OHT patients.

(7) Determine if RNFL measurements correlate with histologically determined RNFL thickness in human eyes.

Future directions

High-resolution OCT

Drexler *et al*[74] have introduced ultra-high resolution OCT for macular pathology with an axial image resolution of approximately 3 μm as opposed to 10 μm for standard OCT. Applications for the peripapillary and foveal retinal NFL thickness are actively under study.

Neural network/machine learning classifiers and other postprocessing algorithms

Neural network and machine classifiers utilise multiple parameters (both structural and functional) to improve the sensitivity and specificity of clinical decision making. Brigatti *et al*[75] report the use of several neural network algorithms on a database of 185 eyes of patients with early glaucomatous visual field loss and 54 eyes of age-matched normal control subjects. The information used included automated visual field and structural data (cup/disc ratio, rim area, cup volume, and nerve fibre layer height) from computerised image analysis. A back-propagation network with two intermediate layers assigned an estimated probability of being glaucomatous to each eye and correctly identified 88% of all eyes with 90% sensitivity and 84% specificity. Bowd *et al*[35] used neural networks and linear discriminant functions that employed a variety of HRT data to improve glaucoma detection. Similar strategies are under active investigation for NFL thickness measurements.

ONH susceptibility assessment

The existing strategies for imaging the ONH surface are designed to either detect the presence of disease (cross-sectional screening) or the progression of disease (longitudinal change detection). As we do not have a science of ONH susceptibility, we do not yet have imaging strategies for estimating whether a given optic

nerve head will be susceptible to a given level of intraocular pressure or systemic blood pressure. It bears acknowledging that while we will discuss existing strategies for cross-sectional screening and longitudinal change detection, it is hoped that one day, we will possess not only these strategies for clinical monitoring, but also the equipment and knowledge necessary to assess ONH susceptibility, that is, decide at what level of IOP and blood pressure the connective tissues, glia, and axons of a particular ONH will remain stable.

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