Imaging for Diabetic Macular Edema

An overview of the retina module of the Heidelberg Retina Tomograph 3.

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Imaging techniques used in assessing retinal anatomy have evolved from photography to stereophotography to fluorescein angiography, and now include several laser-based imaging devices. Various retinal diseases, such as diabetic macular edema (DME), age-related macular degeneration (AMD), and vascular occlusive disease, lead to swelling within the retina and subsequent vision loss. Quantifying these changes is important for diagnosis and follow-up. In addition, accurate and reproducible measurements are essential to determine whether therapeutic interventions are causing anatomical improvement. The Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, Vista, CA) is a confocal scanning laser ophthalmoscope (SLO) platform that obtains topographic images of ocular anatomy. DME is a principal application under investigation using the retina module of the HRT. This article summarizes the basics of the HRT retina module and report pertinent applications for diabetic retinal disease.

RETINA IMAGING TECHNOLOGY

The Heidelberg Retina Tomograph 3 (HRT 3) utilizes confocal scanning laser technology to capture images of the cornea, optic nerve, and retina. Images of the retina are obtained with a rapid scanning class I 670-nm diode laser to acquire and analyze 3-D images of the posterior segment. The laser beam is emitted and travels through a confocal pinhole before being focused on a single point on the retina. The beam is redirected in the x-axis and y-axis along a plane of focus perpendicular to the optical axis (z-axis), using two oscillating mirrors to obtain a 15° x 15° image. The reflected light is separated from the incident beam, deflected by a beam splitter and passed through a confocal imaging aperture (diaphragm) to reach a luminance detector. Point images are combined digitally to produce a 2-D image (Figure 1).

Light that is deeper or shallower than this focal plane is suppressed to provide an optical section of the retina corresponding to a specific focal plane or depth. Therefore, the 2-D image acquired at a focal plane carries only information of the object layer located at that focal plane. By automatically shifting the confocal aperture, optical sections of up to 64 at focal planes (depths) can be obtained to create a 3-D image (Figure 2).

THE RETINA MODULE TECHNOLOGY

The field of view over the macula scan is 15° x 15°, approximately 4.5 x 4.5 mm, and the tissue around the fovea is scanned to a depth between 1 and 4 mm, which is automatically adjusted based on the thickness of the tissue. The image produced has a transverse optical resolution of 10 µm/pixel. The 2-D digital image obtained per optical section has a resolution of up to 384 x 384 pixels. Z-axis penetration may achieve depth resolution up to 64 pixels, and analysis of Z-profile signal width reliably quantifies macular thickening. Three series acquisitions are obtained for each study, with typical intermeasurement variability of less than 30 µm. The data is analyzed and presented to the clinician for interpretation.

Figure 1. Graphic representation of the confocal scanning laser ophthalmoscopy.
RESULTS

Three algorithms are used to analyze data obtained with the HRT3 retina module: the Retinal Edema Index, the Retina Thickness Map, and the Reflectance Image.

**The Retinal Edema Index.** The edema index map (retinal edema index) is a grayscale image that reveals areas of relative macular thickening. Distortion of normal reflectivity due to topographic surface abnormalities results in a “stretched” signal that can be converted to retinal edema index values. Detection of macular surface irregularity using HRT3 prior to clinical detection of macular edema is a valuable potential application (Figure 3).

The edema map is divided into a nine-zone grid using three concentric circles with radii of 500 µm, 1000 µm, and 1500 µm, divided into quadrants. Each zone is analyzed separately and an edema index for that zone is determined (Figure 3). The position of the nine-zone grid can be manually adjusted, and the new position is used automatically for all additional analyses of the same patient in order to minimize variability. Normal edema index values are 1.10 ± 0.30 arbitrary units (au). Values between 1.50 au and 1.80 au are considered borderline and greater than 1.80 au is outside normal limits.

**The Retinal Thickness Map.** The retinal thickness map gives absolute micrometer measurements of the thickness of the nine zones around the fovea. Unlike the edema index, which uses just the vitreoretinal interface, the retinal thickness function localizes both the internal limiting membrane (vitreoretinal interface) and the retinal pigment epithelium, and produces two signal peaks. The difference between the peaks is used to obtain the value of the retinal thickness for each of the nine zones (Figure 4).

Retinal thickness values in microns are shown for each of the nine zones. Simulated color topography allows for qualitative assessment. The retinal thickness map also calculates retinal volume in cubic millimeters for each of the 9 zones (Figure 5).

In addition to the 2-D thickness map shown above, an interactive 3-D retinal thickness map can be produced. This interactive 3-D image provides a 3-D view of the retina allowing physicians to easily see where thickening has occurred.

**Reflectance Image.** The reflectance image or map is a false color image that resembles a retinal photograph. It captures the differences in the surface appearance of the retina. It enables the interpretation of both the retina index and retinal thickness in light of visible anatomical fundus abnormalities. It also allows estimation of study quality based on clarity and brightness of the image obtained (Figure 6).

COMPARISON WITH OTHER RETINAL SCANNING TECHNIQUES

The importance of the edema index in the evaluation of DME has already been established, as changes in the edema index have been shown to correlate with changes in visual function. In the same study, the edema index values were shown to have high reproducibility between measurements. Intraobservation variability has been reduced to less than 15% for macular volume mapping. Further validation of HRT volumetric measurements were performed by Zambarakji and coworkers, who demonstrated a high correlation between three examinations for both intraobserver (P<.001) and interobserver variability (P<.001).

Due to high specificity and good sensitivity of HRT topographic assessment, the HRT retina module has been used as a screening modality for the detection of diabetic maculopathy. Early studies of volumetric mapping using HRT
found a sensitivity of 79% and a specificity of 85% compared to clinical examination. A new scoring system for macular edema by Hudson and colleagues had a specificity of 99% and sensitivity of 67% in hospitalized diabetic patients. In another study, the macula edema maps (MEMs) of HRT II were compared with fundus biomicroscopy. Good agreement in identifying areas with DME was observed, with a Kendall coefficient of concordance of 0.80 (P < .01).

The Retinal Thickness Analyzer (RTA; Thalia/Marco, Jacksonville, FL) is different technique used for the objective assessment of DME. It works on the principal of slit-lamp fundus biomicroscopy, where vertical slits are scanned sequentially across the area of the retina to generate a topographic map of the retinal thickness. Guan and coworkers recently demonstrated that the retina module of HRT 2 offered an improved sensitivity (92%) and a comparable specificity (68%) in the detection of DME compared to the RTA, which had a sensitivity of 57% and a specificity of 71%.

Fluorescein angiography (FA) is a long-established standard for evaluation of DME. In the Early Treatment Diabetic Retinopathy Study, FA was used as key investigative technique for the classification of diabetic retinopathy. Diffuse capillary leakage was one of the risk factors that was closely associated with the severity or progression of diabetic retinopathy in another report on the same study. In both studies, FA complemented clinical examination by revealing subtle changes and identifying perfusion and leakage abnormalities.

In a small series, HRT demonstrated agreement with FA, and was slightly more sensitive than early-generation optical coherence tomography (OCT), for the detection of DME. In another series using FA as the standard for diagnosing DME, HRT was noted to have higher sensitivity but lower specificity than OCT.

DME may be treated with laser, intravitreal steroid injection, intravitreal anti-VEGF injection, and surgery. In one study, injection of triamcinolone acetonide 8 mg resulted in an improvement in vision of 0.43 logMAR units, which corresponded to a 36% reduction in the MEM values on HRT at 6 months (P < .001). In a study of a single injection of bevacizumab 2.5 mg, logMAR visual acuity improved by 0.32 units, while the HRT MEM values significantly decreased by 33.3% (P < .001). This demonstrates that the HRT can also be used to accurately track anatomic improvements from treatment.

OCT has been extensively used to evaluate DME. OCT measures the echo time delay and intensity of reflected 820 nm light beams on the posterior chamber of the eye. Using OCT, high resolution 2-D cross-sectional images of the internal microstructure of the posterior ocular structures are generated, including the retinal nerve fiber layer (RNFL), optic disc, and macula.

The use of OCT in the evaluation of DME focuses on the computation of the retinal thickness/volume of the macula. It has been demonstrated that macular thickness can be quantified with OCT. Hee and coworkers demonstrated that the central macular thickness measured by OCT correlates with visual acuity with a sensitivity greater than that of slit-lamp biomicroscopy. In addition, they commented that even in the absence of fluorescein leakage, there could be increases in retinal thickness and loss of visual acuity.
Another study demonstrated that OCT enabled the clinicians to detect subclinical retinal changes in the absence of clinically significant DME or other signs of diabetic retinopathy.19

Studies comparing OCT with clinical examination for the detection of DME have shown that DME may be more easily and accurately diagnosed with OCT compared to clinical methods.17,20,21 Ozdek and coworkers20 found that there was a 77% agreement between clinical examination and OCT results, which was higher than the agreement between clinical examination and FA. In addition, they found that there was a significant correlation between the retinal thickness and FOVEAL CENTRATION in the smallest circle.

Morphological features in DME may be characterized using OCT, including mild, cystoid, neurosensory detachment, and vitreomacular traction.22

In a review performed by the American Academy of Ophthalmology, there was sufficient level 1 evidence to demonstrate that laser scanning imaging can accurately and reliably quantify macular thickness in patients with diabetic retinopathy.23 HRT appears to be a valuable tool for assessing retinal thickness and volume in DME.

CONCLUSION

DME is a major vision threat and its toll on the population will only increase with the predicted increase in type 2 diabetes. For this reason, physicians may benefit from high-sensitivity and high-reproducibility imaging devices for assessing for DME. Most importantly, such a device should be able to detect early DME, so that it can be used as a screening tool.

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